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ORIGINAL PAPER

The implementation of a national paediatric oncology protocol for neuroblastoma in South Africa

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Abstract

Purpose The aim of the World Health Organization-International Paediatric Oncology Society is to improve childhood cancer survival in low- and middle-income countries to 60% by 2030. This can be achieved using standardised evidence-based national treatment protocols for common childhood cancers. The aim of the study was to describe the development and implementation of the SACCSG NB-2017 neuroblastoma (NB) treatment protocol as part of the treatment harmonisation process of the South African Children's Cancer Study Group.

Methods The Consolidated Framework for Implementation Research was used to identify factors that could influence the implementation of the national NB protocol as a health care intervention. The evaluation was done according to five interactive domains for implementation: intervention characteristics, inner setting, outer setting, individual or team characteristics and the implementation process.

Results The protocol was developed over 26 months by 26 physicians involved in childhood cancer management. The process included an organisational phase, a resource identification phase, a development phase and a research ethics approval phase. Challenges included nationalised inertia, variable research ethical approval procedures with delays and uncoordinated clinical trial implementation.

Conclusion The implementation of the national NB protocol demonstrated the complexity of the implementation of a national childhood cancer treatment protocol. However, standardised paediatric cancer treatment protocols based on local expertise and resources in limited settings are feasible.

Keywords South Africa · Neuroblastoma · National protocols · Children · Consolidated Framework for Implementation Research

Abbreviations

ASCT	Autologous Stem Cell Transplantation
CFIR	Consolidated Framework for Implementation Research
HR	High Risk
IR	Intermediate Risk
LMIC	Low- and Middle- Income Country
LR	Low Risk
NB	Neuroblastoma
NHI	National Health Insurance
SACCSG	South African Children's Cancer Study Group
OS	Overall Survival
PI	Principal Investigator
VLR	Very Low Risk

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Introduction

According to both the European Commission (ORPHA number 635: neuroblastoma) [1] and the United States Rare Diseases Act of 2002 [2], childhood malignancies such as neuroblastoma (NB) are rare diseases. Although great clinical and biological advances have been made with regard to paediatric tumours worldwide, the multitude of approaches demand significant human and financial resources [2]. One disadvantage is the isolated development of management

protocols that are not reproducible in other settings due to non-standardisation [2]. A good example of this type of non-standardisation in the management of NB was the development of various different classification systems and treatment approaches by the Children's Oncology Group (COG), the International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) and other paediatric oncology societies in Japan, Australia and New Zealand [3, 4]. In an attempt to improve standardisation, an international collaboration of various NB workgroups led to the establishment of the International Neuroblastoma Risk Group (INRG) and the development of the INRG classification system, based on pooled data from multiple countries. This collaboration initiated larger clinical trials with standardised protocols, which improved statistical significance [5]. The initiative of the INRG and international NB clinical trials is evident in the improved outcomes for high-risk (HR) disease from 5-year overall survival (OS) of 20–57% over the past 20 years [6]. Yet, the inability of low- and middle-income countries (LMICs) to obtain the genetic information required for the INRG classification system used in high-income countries (HICs) limits its use in LMICs.

The South African Children's Cancer Study Group (SACCSG) established a South African Children's Tumour Registry in 1987 [7, 8]. A single NB institutional report by Hesseling et al. in 1990 was available in South Africa prior to the start of the process to develop a national NB treatment protocol [9]. To date, treatment strategies for NB in South Africa have been diverse, based on the experience of individual paediatric oncologists [10]. The treatment of NB was managed according to the available resources and multiple international protocols were used [11]. The SACCSG encouraged the development of a national NB management protocol in 2016, which led to the SACCSG NB-2017 study. The protocol was developed in line with the World Health Organization (WHO)-International Paediatric Oncology Society (SIOP) aim to improve childhood cancer survival in LMICs to 60% by 2030 [12].

The aim of this article is to describe the development and implementation of the SACCSG NB-2017 clinical trial according to a validated implementation research framework. The Consolidated Framework for Implementation Research (CFIR) domains and associated constructs were used for evaluation purposes based on the data gathered during the various phases of the development of the protocol [13]. Based on the CFIR domains and constructs, tables were constructed from e-mails, meeting notes and workshop discussions during the development of the clinical trial [13, 14]. The CFIR was chosen because it allowed for both system-level evaluation and linking of the influence of individual action and behaviour during the implementation process [14, 15]. It allowed for the evaluation of the national governance structures, paediatric oncology units (POUs) and individuals involved [14, 15]. A descriptive overview was used to describe the clinical trial development, implementation process and analysis. An interim evaluation was done to assess preliminary outcomes.

Setting

South Africa has a heterogeneous medical system [16]. Public health care is proportionally funded by the central government in each of the nine provinces. The health authorities within each province determine the financial expenditure for development of medical services in that province. The private health care system is funded on a pay-for-service business model, and private medical insurance plans are available to those who can afford the contribution tariffs [16]. Since the advent of democracy in 1994, the government has introduced several strategies to improve health care and increase access to and affordability of cancer care services and research [17]. One example is the free primary health care for children under 6 years [17, 18]. Access to health care services was being addressed by expanding the health care network to decrease travel distances [18].

Several regulatory processes that support development of national treatment protocols for rare diseases have been developed since 1994 in South Africa. The National Cancer Registry is managed under the umbrella of the National Institute of Communicable Diseases [19]. The National Health Research Ethics Council, established under the National Health Act No 61 of 2003, provides guidance regarding health care research in line with international guidelines [20].

Development of the national neuroblastoma clinical trial

The SACCSG initiated the harmonisation of management for childhood cancers in 2008. The aim was to standardise the management of childhood malignancies across all South African POUs. Individual tumour workgroups lead by a principal investigator were established to develop national treatment protocols. The workgroups consisted of various health care teams involved in the management of childhood malignancies and included paediatric oncologists, surgeons, radio-oncologists as well as laboratory and imaging services from several hospitals. Each workgroup was responsible for evaluation of the adequacy of resources available to the various South African POUs and the evaluation of contemporary clinical trials involving the relevant tumours. The workgroups were then also responsible to develop a standard of care management protocol that could be in all POUs and adapted for the local context [21–23].

A NB workgroup was established in 2016, and initiated the process of developing a treatment protocol. To prepare

for this national clinical trial, a retrospective study was undertaken to evaluate the management of NB between 2000 and 2014 as well as a survey to evaluate available resources for the management of NB in South Africa, which resulted in a publication in 2019 [10]. Protocol development was done via online discussions, document reviews, paediatric oncology meetings and workshops. After finalisation of the management protocol through consensus, research ethics approval was obtained.

Study objectives

The study objectives were as follows:

(1) To describe the development of the SACCSG NB-2017 clinical trial as a future resource for similar projects.
(2) To assess the contributing factors and barriers to the development and implementation of a national paediatric oncology clinical trial.
(3) To describe the alignment of the protocol with clinical practice and evaluate preliminary outcomes.

Methods and analysis

The evaluation was done according to five interactive domains for implementation: intervention characteristics, inner setting, outer setting, individual or team characteristics and the implementation process. The first author (JvH) allocated the themes and described the relevance for the evaluation of the implementation of the trial. The second author (MK) critically evaluated and edited the text, tables, themes and descriptions. The implementation evaluation was completed by consensus between the two authors.

Development of the SACCSG NB-2017 clinical trial

South Africa has 13 public POUs and six private health care POUs, linked to seven universities and situated in seven of the nine provinces. There were fourteen paediatric oncologists who developed the SACCSG NB-2017 clinical trial, including the principal (PI) and co-principal investigator. Four additional clinical contributors also participated—see below.

The first SACCSG NB process of developing protocol consisted of four parts (Fig. 1), namely establishing need and consensus; identifying local health care resources, including medical experts and project managers; facilitating and contributing to the development of the protocol and finally ethics approval. The duration of this process was 26 months (Appendix A).

(1) *Establishing need and national paediatric oncology organisation approval*

The SACCSG application process for national paediatric oncology research involved presentation and approval of the proposed study at an official meeting with a minimum of one representative per South African POU present. The NB protocol was presented at the SACCSG workshop in Durban, South Africa, in September 2016. The presentation included the scope, aims and academic studies associated with the protocol development. The consensus for development served as an invitation for interested physicians to become part of the workgroup tasked with protocol development.

(2) *Establishing resources for protocol development*

Local medical expertise: Each POU identified a physician responsible for local data management, interdisciplinary management and protocol oversight. These physicians became members of the SACCSG NB working group who evaluated the literature and protocol drafts and contributed to ensure feasibility in their local setting. The group also included physicians with an interest in palliative care to develop guidelines for non-curative management.

Sub-disciplinary expertise: Physicians with NB experience in the fields of paediatric surgery, radio-oncology, pathology, laboratory haematology and nuclear medicine were invited. These physicians developed discipline-specific management guidelines, amended protocol drafts and adapted international standards for the local setting. These experts included paediatric surgeons ($n=2$), radio-oncologists ($n=2$), anatomical pathologists ($n=2$), a nuclear physician ($n=1$) and a laboratory haematologist ($n=1$).

Local logistics: During November 2016, a survey was completed by each local hospital investigator. The survey evaluated the resources available for NB management in the respective hospitals (Appendix B) with the aim to develop the prospective protocol (Table 1).

National NB experience: A retrospective study to evaluate the management and outcomes of NB in South Africa between 2000 and 2014 was approved in January 2017 by the University of Kwa-Zulu Natal Biomedics and Research Ethics Council (BREC Ref No. BE572/16) and data collection was commenced, which resulted in a publication in 2019 [10].

International experience: The SACCSG NB working group reviewed the literature for evidence-based NB management from international NB working groups to guide decisions during the protocol development. International experts in NB management were consulted (see "Acknowledgements" section).

Financial resources: The vzw Kinderkankerfonds, Belgium, provided developmental funds [24].

Table 1 Results of the hospital resources survey

Site	Site A	Site B	Site C	Site D	Site E	Site F	Site G	Site H	Site I	Site J	Site K	Site L	Site M
Imaging													
Radiology	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nuclear imaging	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No
mIBG	Variable	Variable	No	Variable	Variable	Variable	Variable	No	Variable	Variable	Variable	No	No
Diagnostics													
Blood tests	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Urine analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
BMAT/Biopsy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pathology	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
FISH	Yes	Yes	No	No	No	No	Yes	No	No	Yes	Yes	No	No
Genetics	No	No	No	No	No	No	No	No	No	No	No	No	No
Treatment													
Chemotherapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Topotecan	No	No	No	No	No	No	No	No	No	No	No	No	No
General surgery	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Paediatric surgery	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No
Thorasic surgery	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Neuro-surgery	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Radiotherapy	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No	No
ASCT service	Yes	Yes	Refer	Refer	Refer	Refer	Refer	Refer	Yes	Yes	Yes	Refer	Refer
Immunotherapy	No	No	No	No	No	No	No	No	No	No	No	No	No
mIBG-therapy	Yes	Yes	No	No	Variable	No	Yes	No	Yes	Yes	Yes	No	No
Supportive care													
AB/Blood/PICU	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Other													
CRA	Variable	Variable	No	No	No	No	Yes	No	Variable	Variable	Variable	No	No
G-CSF	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Propranololss	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Celecoxib	No	No	No	No	No	No	No	No	No	No	No	No	No
Oral MTX	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AB antibiotics, *ASCT* Autologous stem cell transplant, *BMAT* bone marrow aspirate and trephine, *CRA cis*-retinoic acid, *G-CSF* granulocytic colony stimulating factor, *MTX* methotrexate, *PICU* paediatric intensive care unit

(3) *Costs during development*

The development of the management protocol was part of doctorate research. University platforms and logistics were used for project management to limit costs. Group meetings were held on electronic platforms or during academic meetings that were already funded. The development funds were mainly used for the development of the REDCap database and the final protocol approval meeting (Table 2). The inclusion of patients and the data capturing of the management trial was dependent on clinicians.

(4) *Clinical trial initiation and development*

The SACCSG NB-2107 trial aimed to introduce a standardised NB management protocol as a single-arm clinical trial for individual NB risk groups (low-risk, intermediate-risk and high-risk) (Appendix C) across South Africa with the aim of improving overall survival. As the protocol served as an exercise for implementation, the decision by the NB working group was to include only OS and event-free survival (2 years and 5 years) as primary endpoints.

The development was done according to two parallel action plans:

(1) *Tumour-related diagnostic and chemotherapy protocols:*

Diagnostic and evaluation requirements, risk stratification and protocols relating to chemotherapy were collaboratively developed by the paediatric oncology physicians (hospital investigators). The treatment

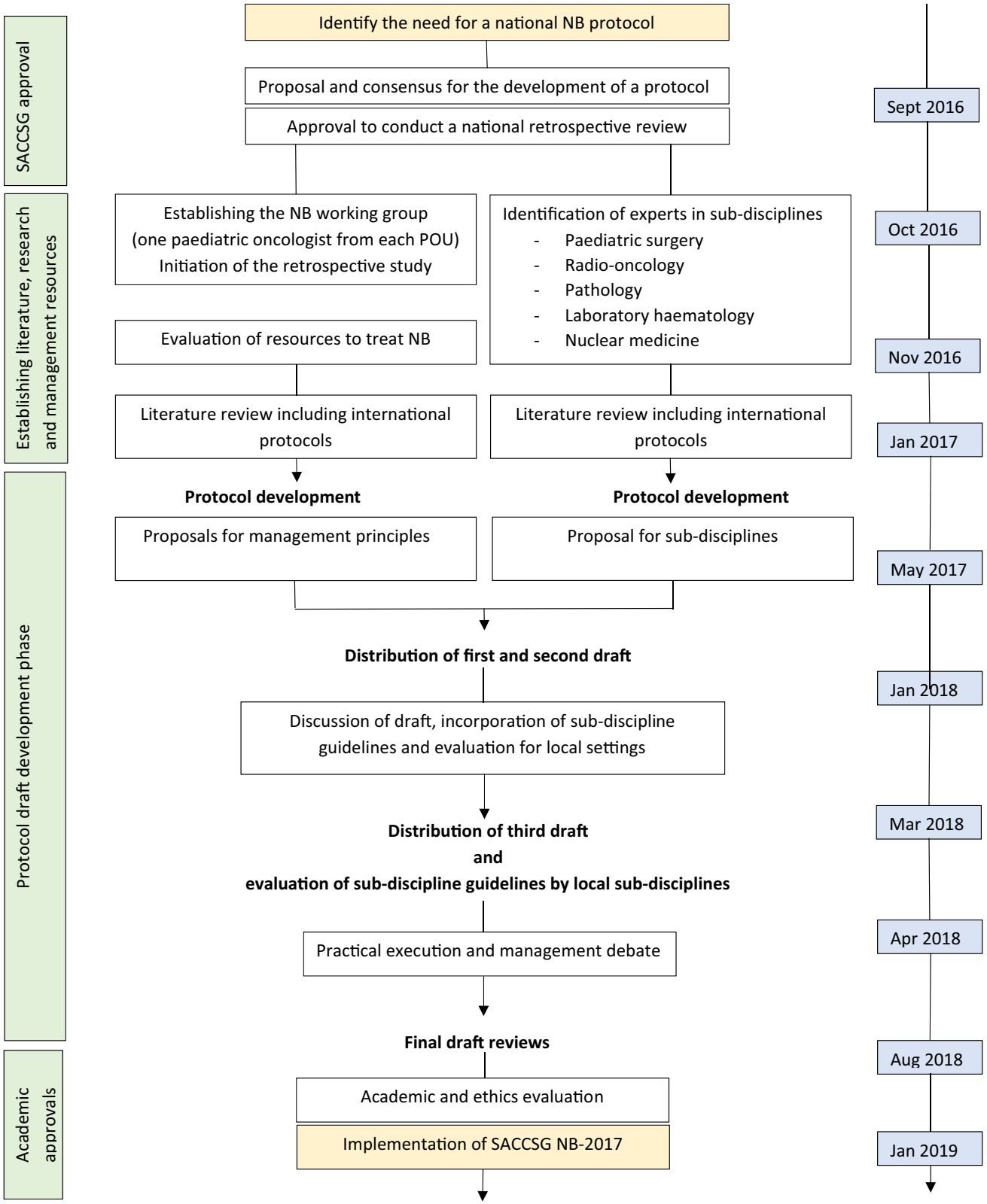

Fig. 1 The protocol and guidelines development process

Table 2 Project development budget and cost limiting measures

Item	Purpose of funds	Budget (US$)
Third meeting: NB working group meeting (Final drafting of the protocol)	Travel expenses Venue hire and expenses For 15 study investigators during 2 days	4,662.00
Protocol documentation	Distribution of protocol on electronic hardware	46.00
REDCap database development	Developer and production fees @ US$ 24/hour	682.00
	Total	**5,390.00**

Cost limiting measures

- University or hospital-based platforms and logistics were used for project management to limit costs
- Group meetings were held on existing electronic platforms or during academic meetings and congresses that were already funded
- Data managing done by hospital investigators and PI

NB neuroblastoma, *PI* Principal investigator, *US* United States (of America)

approaches were adopted by all POUs of the NB working group. The development was done in three stages.

First stage: In May 2017 the management principles were established during the SACCSG protocol development meeting in Stellenbosch (Appendix D). Summaries of the literature review were presented, and recommendations were proposed for the protocol section. It was concluded that the protocol would primarily be a standard of care, curative treatment protocol and would secondarily be supported by recommendations for palliative care. There would be a single treatment arm with no randomisation. Due to the complexity of the pathology, the operational research data and outcome-based indicators should be collected prospectively.

The second stage: In January 2018 an online meeting of SACCSG NB working group was hosted on the web-based Cure4Kids platform (Appendix D). The sections on which consensus had been reached during the first and second draft reviews were discussed, and the completed sub-discipline guidelines were presented. Consensus was not reached on the induction chemotherapy for HR-NB nor on the scope of the autologous stem cell transplant (ASCT) section.

The third stage: In April 2018 the NB working group meeting was held in Johannesburg (Appendix D). The remaining sub-discipline guidelines were presented. Final consensus was reached on all sections after debates on the positive and negative aspects for implementation in the South African setting.

(2) *Associated sub-discipline guidelines*

These were developed by the principal investigator and sub-discipline experts based on literature reviews, expert opinions and practical considerations for the South African setting. Subject to available local health care resources these recommendations were incorporated as guidelines that allowed for adaptation during management.

Consensus decisions were based on four key criteria: established international research evidence, local expertise, availability of resources in all POUs, and financial costs and sustainability. Protocol-specific consensus recommendations can be seen in Supplemental Table S1.

The protocol was developed for all NB-related management aspects independent of risk stratification or funding options. Those with private funding could access advanced treatment options such as ASCT or targeted therapy that are not available in the country. Therefore, the protocol primarily focussed on basic treatment options for all public health care facilities, but also provided guidelines for facilities where advanced treatment options were available.

Ethics reviews and implementation

During this period, all necessary documentation was prepared for academic evaluation and ethics clearance by universities and by governmental (provincial and national) and hospital authorities. Approval of the protocol constituted 42 applications to different regulatory authorities. The duration of the ethics review committee evaluations varied from 1 to 20 months (1 still pending) (range 1–20 months, mean = 5 months, median = 2 months). The total duration for an application (academic and research ethics review) for the POUs varied from 2 to 20 months (still pending) (range 2–20 months, mean = 10 months, median = 12 months) (Table 3).

Contributing factors and barriers to development and implementation of a national paediatric oncology clinical trial

The implementation of the SACCSG NB-2017 clinical trial was an important step in establishing a multidisciplinary,

Table 3 Protocol approvals

Site	Academic approval	Ethics approval	Reciprocal approval	Ethics approval duration	Applicant PI/HI	Duration of process (months)	Hospital approval	Provincial approval	National approval
Governmental institutions									
Site A	Yes	Yes	PI site	1	PI	2	Yes	Yes	Yes
Site B	Yes	Yes	No (initiated after application)	4	Both	9	Yes		
Site C	No	N/A	No	2	PI	5	Yes	Yes	
Site D	No	N/A	No	2	Both	9	Yes		
Site E	No	Yes	Yes	1	PI	1	Yes	Yes	
Site F	No						Yes		
Site G	No	Yes	No	4	PI	12	Yes	Yes	
Site H	No	Yes	No		PI	12	Yes	Yes	
Site I	No	Yes (separate applications)	No	9	HI	14	Yes	Yes	
Site J	No	Yes (separate applications)		8	HI	14	Yes		
Site K	No	Yes	No	2	PI or HI	12	Yes		
Site L	No	Yes	No	2	HI	13	Yes		
Site M	No	Yes	No	20 (pending)	HI	20 (pending)	Yes	Yes	
Subtotal	2	9	1	Mean 5 (1–20) Median 2		Mean 10 (1–20) Median 12	13	7	1
Total	33								
Private institutions									
Site P1	Done in two academic centres	N/A	No	Linked to academic approvals or individual hospital approvals	HI	Linked to academic approval	Yes	Yes	Yes
Site P2		With Site C	No		HI		Yes	Yes	
Site P3		N/A	No		HI		Yes	Yes	
Site P4		N/A	No		HI		Yes	Yes	
Site P5		With Site J	No		HI		Yes	Yes	
Site P6		N/A	No		HI		Yes	Yes	

N/A not applicable; *HI* hospital investigator; *PI* principal investigation

national standardisation of NB management. The latter requires multi-disciplinary involvement in the diagnosis, treatment and continued evaluation of the pathology. These interactions in a resource-strained setting are often challenged by varied experience in management and perceived treatment goals [25]. The CFIR provided an organising framework to identify implementation factors and essential lessons during the development and implementation of the protocol (Supplemental Table S2).

Development and sustainability

A collaborative clinical trial is only possible when each collaborator remains continually responsible for his/her delegated functions through ownership and contribution of local knowledge [25, 26]; therefore, hospital investigators functioned as liaison between the protocol and other disciplines, which prevented unilateral implementation. The prescribed benefits by private medical insurance for treatments and investigations dictate and to a large degree guide the management of treatment in private hospitals. In general health care systems managing fixed budgets are attentive to problems of implementation in order to maximise the health care funds [25, 26].

Individual factors

Historically, POUs in South Africa were self-determining entities. The NB management protocols were based on evidence from international protocols, systematic reviews and clinical practice guidelines [27]. In the national NB protocol, a deviation from known local practices was required to achieve a single standard of care that would be feasible in all POUs regardless of unequal access to resources. In general, established clinical practice is slow to change, referred to as 'clinical inertia' [28], which was present especially

in determining the standard induction chemotherapy for HR-NB. The retrospective review showed numerous induction regimes that were used from 2000 to 2014 [10, 27]. Yet, in the South African context, none proved superior when considering post-induction remission and outcomes. However, the toxicity profile of OPEC/OJEC had a more favourable outcome than the Rapid COJEC protocol and doxorubicin-containing protocols [27].

The interests and priorities of each POU determined their culture or attitude towards the clinical trial and its implementation. A major contributing factor was the lack of time and resources to facilitate implementation and complete administration tasks. The protracted process for state research ethics applications increased the time that lapsed between training on the study procedures and study initiation of the study after approval had been granted. Two sites delayed ethics application by requiring new academic evaluations after an academic evaluation had been done at the PI's site.

External regulatory environment

The National Cancer Strategic Framework for South Africa 2017–2022 does not address the needs of paediatric oncology frameworks [28], nor does it acknowledge paediatric oncology as a discipline independent from adult oncology services. Therefore, development of the SACCSG NB-2017 clinical trial was initiated by the SACCSG and the NB workgroup on the basis that management of NB would be based on international evidence with the available national resources.

Data collection and organization of a data center

Each POU had its own system of data documentation, retrieval and storage. These included files (paper-based) or basic computerised data capture systems, each with its own advantages and disadvantages. The study was commenced with paper-based and Excel-based databases which later was transitioned to REDCap [29], thereby accommodating the challenges associated with transitioning from traditional data systems to online systems. With the PI hosting the database at a single university, access restrictions had to be navigated for the workgroup with university approval needed for each collaborating researcher. Each hospital investigator will be responsible for entering their own patient data, while the PI will oversee data.

Implementation process

No standardised implementation process existed for national paediatric oncology clinical trials in South Africa. Following the national retinoblastoma clinical trial initiated in 2012 [22], the SACCSG NB-2017 clinical trial is one of three newly developed national clinical trials. Due to varying duration of research ethics approvals, a coordinated implementation was not possible. During this period, two additional POUs opened for treating children with malignancies, from which research ethics approval had to be obtained. The movement of evidence-based practices into routine clinical practice demands focussed efforts; therefore, the protocol was based on current POU practices [25, 26]. Yet, linked to resources, a greater number of training sessions in the utilisation of datasets and documentation were needed in order to activate each team.

Resources

The lack of resources in NB management identified were human resources, provision of supportive care and advanced treatment options such as ASCT [25, 26]. A multidisciplinary team representing multiple departments is needed to manage patients with NB. The outcome of a patient is linked to multiple treatment modalities that collectively determine a treatment response. If treatment response is inadequate, surgery is not possible and the variable availability of radiotherapy becomes more important. The inconsistent availability of isotopes for mIBG scans limited this important diagnostic evaluation and treatment modality.

Time was an additional constraint, since South African paediatric oncologists have dual roles as clinician and researcher in addition to numerous other duties, which include both undergraduate and postgraduate education. Some POUs have one clinician who is the proxy hospital researcher for all tumour-specific clinical trials. Research assistants could strengthen the research capacity in POUs.

Challenges

The health systems that currently govern the institutions should adapt to support research initiatives.

Evidence-based, practice-changing clinical trials to improve the system must be prioritised with POUs promoting the implementation of these clinical trials. An efficient balance between clinical duties and research should be supported. Furthermore, ethics committees should contribute to the ease of implementation of quality research.

Introducing new standardised protocols and new technologies such as REDCap for data capturing into an established administrative system necessitates training and increasing the skills of the staff of a POU to initiate and maintain databases [13, 29]. The continued functionality of the data system is reliant on more than a single person to ensure sustained function of the system.

The reliability of the initial data whilst implementing the clinical data system could be limited since only a small

number of participants were enrolled in this study [25, 30]. This was the knock-on effect of the delayed ethics approvals, staggered guidance with initiating enrolment of patients and development of various paper, electronic and online data tools.

As part of the health care system in South Africa, the development of paediatric oncology services faces obstacles that include unequal distribution of resources, increased disease burden of both communicable and non-communicable diseases, limited management and leadership experience to transform the health care system, and limited research support and development to optimise the implementation of national clinical trials [17].

International implementation of paediatric health care initiatives

The components of national childhood malignancy strategies in LMICs include accredited POUs, adequate funding, paediatric cancer registries and a national paediatric oncology governing body [31]. The development of national standards is of the utmost importance. In South Africa, the same challenges of non-standardisation and limited resources were cited in the treatment of Hodgkin lymphoma and retinoblastoma [21, 22]. In contrast to HIV/AIDS and tuberculosis care in South Africa in which improvement of outcomes has been achieved by making treatment available over a wide network, standardised care in childhood cancer relies on early detection and referral to centralised POUs [32–34]. Yet, there are common denominators for childhood cancer, HIV/AIDS and tuberculosis programmes. These include variable needs of patients and medical staff, as well as and an increased need for resources and support during implementation of programmes and research [32, 33].

Increased resources proved beneficial for improved outcomes during the implementation of acute lymphoblastic leukaemia protocols in South America [34]. A national standardised protocol based on available resources in the Dominican Republic improved the 2-year OS for children diagnosed with acute lymphoblastic leukaemia from 40 to 70% by reducing treatment intensity and toxicity [35]. Morocco introduced risk-adapted stratification and treatment guidelines for NB, which has decreased the challenges for the accurate diagnosis and optimal treatment [36].

An evaluation of the protocol in clinical practice and preliminary outcomes

The prospective SACCSG NB-2017 study started recruitment in South Africa in January 2019 with two POUs, respectively, at Tygerberg Hospital (Cape Town) and Inkosi Albert Luthuli Central Hospital-Grey's Hospital (Durban-Pietermaritzburg in Kwa-Zulu Natal). Currently 12 public sector POUs, four private sector POUs and one POU in Namibia are participating in the study.

The original estimated inclusion of patients had been set at 30–40 patients per year, based on the retrospective study data. There are currently only 14 patients included (Table 4).

Table 4 Patients included in the SACCSG NB-2017 study between January 2019 and October 2020

SACCSG NB-2017									
DOD	Sex	Age (mo)	Primary	Stage	MYCN	INRG	Current phase of treatment	Post-induction remission	Outcome
2019	F	67	Neck [R]	4	NA	HR	Completed*	Yes	Alive
2019	F	7	Abd	4	NA	HR	Induction	No	Died
2019	M	19	PS	4	NA	HR	Maintenance	Yes	Alive
2019	M	8	Abd	4	NA	HR	ASCT	Yes	Alive
2019	M	53	Abd	3	NA	IR	Post-treatment	Yes	Alive
2019	M	86	Abd	4	Amp	HR	Palliation	No	Died
2019	M	23	Abd	4	Amp	HR	Palliation	No	Died
2020	F	58	Thx	4	NA	HR	Induction	–	Alive
2020	F	8	Abd	4	NA	IR	Induction	–	Alive
2020	M	76	Abd	4	Amp	HR	Induction	–	Alive
2020	M	26	Abd	4	NA	HR	Induction	–	Alive
2020	M	50	Abd	4	Amp	HR	Induction	–	Alive
2020	F	96	Abd	4	NA	HR	ASCT	Yes	Alive
2020	F	26	Abd	4	T/F	HR	Induction	–	Alive

DOD Date of diagnosis; *mo* months; *INRG* International neuroblastoma risk group; *F* female; *M* male; *Abd* Abdominal; *PS* paraspinal; *Thx* thorax; *NA* not amplified, *Amp* amplified, *HR* high-risk, *IR* intermediate risk, *ASCT* autologous stem cell transplant

*Patient has since relapsed and started relapse treatment

The study is open to include patients across all risk categories, however, at present mainly patients with high-risk disease were enrolled. It is possible that the inclusion of patients are skewed towards the HR-NB group due patients that were not included or that low-risk tumours were not reported.

Results

Patient data results

There was a male predominance with a male to female ratio of 1.3:1, and the median age at diagnosis was 26 months (range 7 months–8 years, mean 43.1 months). The patients had been most frequently diagnosed in the 18–60-months category ($n=7$; 50.0%).

The most common site of the primary tumour was the abdomen ($n=11$; 78.6%). The majority of patients ($n=13$, 92.8%) were diagnosed with stage 4 disease. MYCN was amplified in 69.2% ($n=9/13$) of tumours. The cohort was dominated by patients with HR disease ($n=13$, 92.8%). Three (21.4%) patients have died and one (7.1%) relapsed with a parietal bone lesion. Eight patients completed induction chemotherapy by October 2020 of whom 5 (62.5%) obtained metastatic remission.

Results of the study initiation evaluation

(a) *Personal experience*

Some patients were excluded, because participating POUs have felt that in pre-terminal presentations, the discussion of inclusion into the study was not appropriate. This despite there being a palliative aspect to the study. One hospital investigator felt that including a patient for trial purposes in proximity to a poor prognostic or palliative intent conversation with a parent was difficult to do and might be insensitive to the family.

(b) *Reluctance of medical staff in research participation*

The SACCSG decided that for all national prospective studies, at least one paediatric oncologist from each POU should be part of the working group to lead the study in each hospital. This person would ensure that the local multidisciplinary team adhered to the protocols. The degree of participation from working group members have varied for a number of reasons: (1) NB was not a particular interest (2) Closely linked to the subject matter is the interest to do research. With a limited number of pediatricians in each POU, some have felt they had to take on research responsibilities outside of their clinical interest. (3) One site had difficulty in securing a dedicated hospital investigator due to rotating staff. (4) Some investigators found it difficult to communicate about the recruitment or avoided the subject. (5) Historically POUs developed in autonomous settings with limited co-operative research done on national level. POUs were accustomed to developing local protocols for the management of malignancies and may have found it challenging to adapt to the new trial. (6) Obtaining consent for treatment in South Africa with 11 official languages can be challenging.

(c) *Low level of compliance monitoring*

The responsibility of familiarising oneself with a new national treatment trial paired with the infrequent diagnosis of a patient with NB contributes to low retention of the study protocol. Hospital investigators reported that clinical burdens limited the ability to familiarize themselves with the protocol. This frequency of support by the PI would be beneficial.

(d) *The COVID-19-pandemic*

Since the start of the COVID-19 pandemic, increased pressure rose an already overburdened South African medical system. Academic and administrative responsibilities became secondary to pandemic management. South African COVID-19 control and preventative measures were very strict and protracted [37]. The lockdown commenced on 25 March 2020 and the first de-escalation from level 5 to level 4 occurred on 1 May 2020 [37]. During lockdown interprovincial travel was not permitted except for personal emergencies which had to be approved by governmental institutions [37]. This excluded medical emergencies. The effect on patients needing trans-provincial services is not clear, but the expectation is that delayed diagnoses and relapses will increase. The Kingdom of Lesotho, landlocked by South Africa, mostly refers patients to Bloemfontein, South Africa. NB patients were still permitted to receive their treatment in South Africa, provided supportive documentation for cross-border travel were available, increasing the administrative burden on a POU [37].

Recommendations

The development and approval of a national clinical trial will be facilitated by reciprocal or centralised ethics and academic approvals [38, 39]. The same applies to external regulation of the government as well as hospital and provincial approvals. A homogenous approach to the application systems at universities would provide the first step in simplifying the process.

Acknowledging the need for funding and research support by governmental and non-governmental organisations for national projects should gain greater priority. This would improve establishing national data collection

platforms and contribute to the financial sustainability of health care systems.

The National Department of Health has to implement a strategic policy relating to the care of children with cancer in South Africa. Greater government support and endorsement would highlight the childhood cancer care in South Africa.

Worldwide, health care settings are becoming more dynamic and more resource constrained yet interconnected due to electronic resources and are driven by equally complex political and economic factors [40]. Accordingly, maximising health care outcomes has become a policy requirement internationally [39]. Therefore, even in LMICs, health care systems and health sciences should develop in parallel to meet the service needs [30, 40].

Conclusion

LMICs, such as South Africa, have the capacity to establish a framework for improved clinical care, develop greater research capacity and continued sustainable evaluation of management for better outcomes in NB management. The SACCSG NB-2017 collaborative national clinical trial constitutes the confluence of local experience and multiple incorporated international guidelines. This implementation evaluation can serve as the stimulus for other LMICs to establish NB programmes according to their individual resources.

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Declarations

Conflict of interest The author(s) declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

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