Protocol Compliance and the Use of mHealth to Reduce Pediatric Cancer Treatment Abandonment in Tanzania

by

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Thesis submitted in partial fulfillment of
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ABSTRACT

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Abstract

<u>Background</u>: Low treatment compliance is a well-established barrier to survival for pediatric cancer patients, including those with Burkitt Lymphoma (BL). At Bugando Medical Center in Mwanza, Tanzania, an mHealth application, *mNavigator*, is being used to improve protocol compliance through algorithm-directed BL treatment. With the implementation of *mNavigator* and the rise of mHealth initiatives globally, there is a need to build evidence for the use of mHealth in improving protocol compliance, to encourage the use of mHealth in the pediatric BL context. <u>Methods</u>: A 21-section checklist was created based on the Tanzanian National Guidelines for BL treatment to systematically calculate protocol compliance. All patients <18 years of age diagnosed with BL at Bugando Medical Center in Mwanza, Tanzania from March 2016 to Feb 2021 were included in the evaluation. The patients were separated into a historic and prospective (intervention) cohort based on the introduction of *mNavigator*, in August 2019. The compliance scores were calculated and analyzed for each cohort using StataSE 16. <u>Results and discussion</u>: A total of 82 patients were analyzed in this study, 49 in the historic cohort and 33 in the intervention cohort. There was a significant 9.2% ($p = 0.02$) increase in the total compliance mean after the implementation of *mNavigator* (from 47% in the historic cohort to 56.2% in the intervention cohort). Most notable increases in provider protocol compliance were seen at proper staging at diagnosis and interim evaluation with 39.4% and 45.2% increases, respectively. Significant increases in

provider protocol compliance were observed for every cycle of chemotherapy.

Conclusion: The significant increases in protocol compliance in individual treatment sections and overall treatment after the implementation of *mNavigator* suggest the benefits of including mHealth in pediatric cancer treatment. The study limitations suggested the need for accurate data collection and outcome measurements. Additional studies are required to evaluate the impact of *mNavigator* on treatment outcomes.

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1. Introduction

The global burden of cancer includes over 400,000 newly diagnosed cases among children annually, with LMICs making up over 85% of all pediatric cancer cases. [1–3] Despite the overwhelming majority of children being diagnosed with cancer in LMICs, their survival rates are drastically lower, with rates as low as 5-25% compared to 80% survival rates in high-income settings.[4] These disparities may reflect the many challenges that LMICs face including resource constraints, personal beliefs surrounding cancer, cultural barriers, and suboptimal health systems.[5–9] Some health system challenges include weak infrastructure, inadequate supportive care, and limited equipment and human resources, with the consequences reflected by high cancer mortality rates.[10] In addition to these challenges, the lack of uniform treatment guidelines adapted to local resources makes cancer diagnosis, treatment, and follow-up care a major challenge in these settings.[4] These factors, along with many others, contribute to the complex web of barriers heightened in LMICs, that are responsible for the high treatment abandonment rates and ultimately the disparities in survival rates.

1.1 Treatment Abandonment

One of the main challenges in pediatric cancer treatment is high levels of treatment abandonment, defined as refusal to initiate or failure to complete treatment for 4 or more consecutive weeks, and is directly related to survival.[11–14] Treatment abandonment along with refusal and non-compliance have been outlined by the SIOP (International Society of Paediatric Oncology) working committee on psychosocial issues in pediatric oncology as critical issues responsible for preventable deaths in children with cancer. The report additionally urged health care members to do as much as possible to detect these issues in treatment and prevent them from developing.[15] A concern with treatment abandonment is that the blame and responsibility for abandonment is often placed on the patient and their caregivers. However, there must be a shift from attributing patient-level barriers alone to treatment abandonment and instead investigating health systems issues and evaluating the quality of care, considering the financial, social, political, environmental, health delivery, and quality of care factors responsible for treatment abandonment.[5,16,17]

1.2 Protocol Compliance

Despite the understanding of treatment abandonment as an indisputable barrier to survival, there are very few studies in LMICs evaluating the use of health system strategies to reduce its incidence. This indicates a need to identify the risk factors for non-adherence, including protocol compliance and strategies that may prevent these factors. [18] The use of protocol-driven treatment to improve provider compliance is an evidence driven strategy to reduce treatment abandonment and in turn improve survival. The use of standardized pediatric cancer treatment protocols has been shown to increase survival rates, though the studies are only generalizable to high-income settings.[19,20] In these settings, protocol-driven treatment has improved survival among pediatric cancer patients through guidance in clinical decision-making, uniformity in diagnosis and consistency across providers. [21] When a standardized protocol is available, the implementation of checklists are a simple and cost-effective strategy to further improve protocol compliance through ongoing monitoring and surveillance.[22]

1.3 mHealth

In support of this, the administration of the protocol-driven treatment can be made more efficient using mHealth, through algorithm directed treatment. Success for this strategy has already been documented in improving health outcomes of chronic illnesses through increased patient adherence, and therefore merits further evaluation in the context of pediatric cancer. [23] However, as this is still a fairly novel strategy with insufficient evidence in LMICs, therefore it is important to quantify the success of algorithm driven treatments and create the evaluation tools for provider compliance. This suggests the need for a validated checklist for cancer treatment protocol.

There are many potential advantages of integrating an algorithm directed treatment into cancer care treatment as an alternative to paper-based records, designed using standard treatment protocol. The use of digital records can allow for the simultaneous and ongoing access to patient data that enables task shifting, communication, and coordination between providers.[24–27] The strategy facilitates compliance with clinical best practices in addition to monitoring and surveillance that allows for quality control mechanisms. This can easily be achieved through checklists that can be directly programmed into mHealth applications with convenient data extraction for frequent evaluation and analysis.

1.4 Tanzania & Burkitt Lymphoma

Treatment abandonment is an especially significant issue in Tanzania as its rates are alarmingly higher than other LMICS, with abandonment rates as high as 40% compared to 10-25% in comparable LMICs.[5-8] Fortunately, the implementation of an algorithm-directed mHealth strategy has potential in having a significant impact in Tanzania. The use of mHealth in Tanzania is highly feasible as the national cellular infrastructure is widespread, and continuously expanding. The household cellular ownership was 45% in 2010 and cellular subscription rates were over 76% according to more recent telecom company estimates.[28] The effectiveness of mHealth for pediatric health in Tanzania has already been shown in the implementation of an electronic Integrated Management of Childhood Illnesses protocol that increased compliance by up to 30% compared to the paper-based control. Additionally, the high caregiver acceptability for mobile-based interventions indicate the high feasibility of mHealth interventions for cancer education, patient communication, and care coordination in Tanzania.[29]

An area with urgent need for innovative mHealth strategies in Tanzania is for Burkitt Lymphoma treatment. It is the most commonly diagnosed pediatric cancer in Tanzania and is responsible for many mortalities and morbidities each year.[30] Burkitt lymphoma is a B-cell non-Hodgkin lymphoma (a form of mature B-cell Lymphoma) and is associated with Epstein-Barr virus (EBV) and *Plasmodium falciparum* malaria. This is a concern for children in Tanzania as malaria rates are high in the country in addition to vulnerabilities to EBV infection due to underdeveloped immune systems.[31,32] Despite the excellent prognosis for BL in children, shown by the 90% survival rates in high-income settings, Tanzania suffers from rates as low as 40%.[13,33] This may be due to the low protocol compliance rates, with only 45% of the treatments based on a published pediatric protocol.[13] BL is amenable and highly sensitive to treatment by chemotherapy alone, with excellent prognosis in children, further emphasizing the need to address this disparity in survival.[32,34]

In response to the high rates of Burkitt Lymphoma in Tanzania paired with low rates of protocol compliance, a case management system, *mNavigator*, has been created as a mobile application to address pediatric cancer diagnosis and treatment. It is being implemented at Bugando Medical Center in Tanzania, a regional referral hospital and one of three hospitals treating children with cancer in Tanzania, to increase the accessibility and quality of pediatric cancer care. The application created on CommCare (Dimagi Inc.) uses logic driven algorithm to guide treatment based on the programmed standardized treatment protocol guidelines.[21] The accessibility and algorithm-based guidance of the intervention allows for the consistent and accurate delivery of treatment, filling the gaps in training and resources responsible for inadequate treatment.

With the implementation of this innovative strategy, there is a need to gain evidence for *mNavigator's* role in improving cancer outcomes to encourage its scale-up across the country and integration into policy and national guidelines. The evidence in support of the use of mHealth for treatment and diagnosis is necessary as it is a novel strategy, with most interventions and research geared towards education and communication.[35] Therefore, in addition to the development of mHealth innovations for treatment abandonment, it is equally essential to have an instrument to measure protocol compliance that can evaluate such interventions and identify gaps within treatment delivery. This will ensure that all resources, especially nationally adapted protocol, are being used and allocated most efficiently towards positive health outcomes, in this case treatment adherence, a critical priority in low resource settings.

1.5 Study Goal

The purpose of this study was to assess provider compliance to the recommended Burkitt Lymphoma treatment protocol and to evaluate the effectiveness of the mHealth case management system, *mNavigator*, in improving provider compliance and reducing treatment abandonment at Bugando Medical Center, Tanzania. In addition, the goal of the study was to develop a compliance checklist for BL treatment that can be used as an instrument for ongoing evaluation of provider's compliance to protocol. The study goals will be achieved by 1) Describing protocol compliance in all sections of BL treatment, 2) Comparing protocol compliance by ***mNavigator*** use, and 3) Assessing treatment abandonment by ***mNavigator*** use.

2. Methods

The study was a pre-post interventional study as well as a secondary data analysis using the developed compliance checklist and the *mNavigator* app for data collection. The study design included both a historical cohort before the implementation of *mNavigator*, used as the comparison group, and a prospective (new) cohort as the intervention group with *mNavigator* use.

2.1 Study Hypotheses

The primary hypothesis of this study was that the use of *mNavigator* to guide treatment will increase provider compliance to recommended standard Burkitt Lymphoma treatment protocol. The secondary hypothesis was that the use of *mNavigator* will decrease treatment abandonment in the intervention group compared to the control group. Figure 1 shows the various health systems and individual factors that can lead to treatment abandonment and survival. The pathway from the *Use of Standard Guidelines* to *Treatment Abandonment* to *Survival* supports the rationale for investigating the association between protocol compliance and treatment abandonment to infer on survival outcomes. Treatment abandonment was used over measuring survival as this study did not include enough follow up time to collect survival data for the prospective cohort.

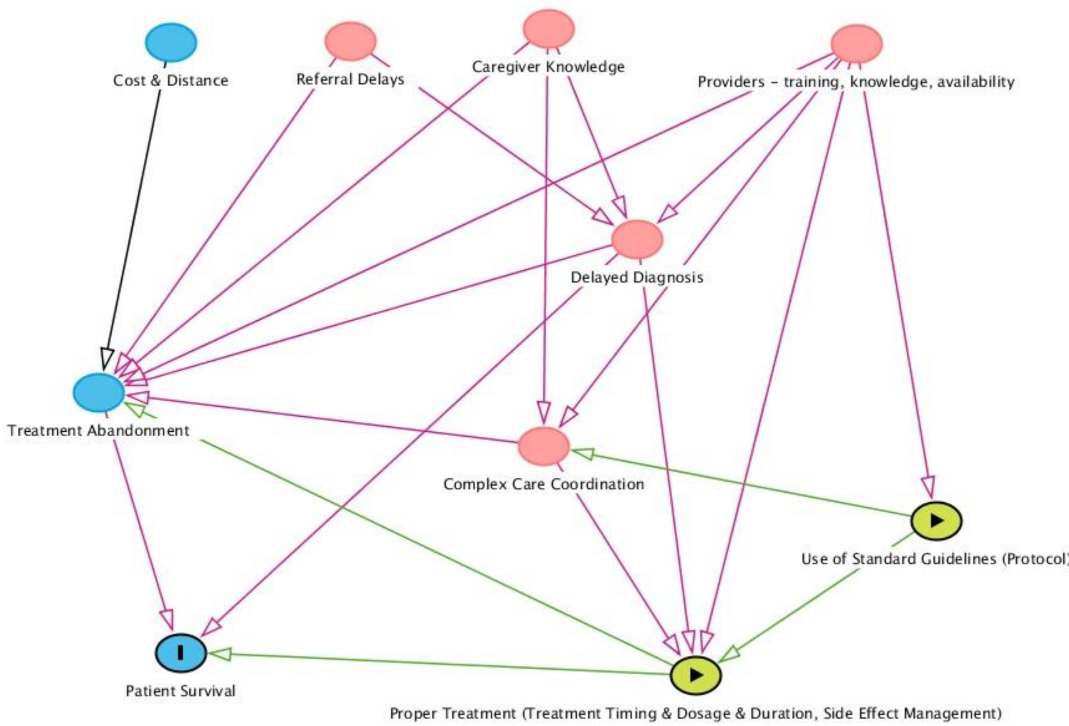

Figure 1: Directed acyclic graph (DAG) of pathways to treatment abandonment and survival

2.2 Study Site

The study took place at the Bugando Medical Centre (BMC) in Mwanza, Tanzania. The African country is a lower-middle income country (LMIC) with a population of approximately 57 million with an under-5 mortality rate of 61.5/1000 live births and under-1 mortality rate of 43.3/1000 live births (IHME, 2017). Mwanza is located on the northern edge of Tanzania along Lake Victoria. It has a population of 2.7 million (UN, 2012) and is projected to continue to rise with urbanization. Bugando Medical Centre is a tertiary referral university teaching hospital with a capacity of 950 beds that serves a population of 19 million, with 300 000 patients a year. It is one of three cancer treatment centers in Tanzania and the only caner referral center in Northern Tanzania.

2.3 Study Sample

The inclusion criteria for the study were children under 18 years old at the time of recruitment with a suspected or known pediatric cancer diagnosis of Burkitt Lymphoma. For prospective patients, there was a screening process to evaluate eligibility, which was be conducted in private before consent and enrollment. No identifying information was collected prior to consent. All patients or caregivers and their children who were suspected or have known diagnosis of Burkitt Lymphoma were asked to participate in the study as long as they met the inclusion criteria. The recruitment was based on the consent of all patients being treated and there was no direct compensation for participation in the study. For historic patients, the patients who met the inclusion criteria had their data retrieved from a clinical database at BMC with the appropriate files extracted, reviewed, and entered into the study. There was no consent process for the historic cohort.

2.4 Compliance Checklist

The compliance checklist was developed through review of the standardized nationally approved Burkitt Lymphoma protocol for Tanzania, creating a workflow of each recommended step during diagnosis, treatment, and follow-up. The goal of the checklist was to include the key steps of treatment, which when not complete, may be associated with increased treatment abandonment. This list from the standard national protocol was then refined with consultation from Dr. Kristin Schroeder to identify the critical steps for decision making, to be included in the final checklist for evaluation of the provider's protocol compliance. Dr. Schroeder, a pediatric oncologist at Duke and at BMC, is one of two oncologists who developed the standardized pediatric oncology protocols in Tanzania, including the national Burkitt Lymphoma guidelines. The final compliance checklist was created on excel and approved by the two Principle Investigators, Dr. Kristin Schroeder and Dr. Lavanya Vasudevan. The checklist consisted of sections that represent the key components of BL treatment with each critical step to be evaluated included within the section. The coding for the checklist involved creating an Excel spreadsheet with 5 columns that include the treatment name, Question ID, Choice ID, Conditions, and Notes. The question and choice IDs included the code that corresponds to the identifiers in *mNavigator* and the conditions were any conditional requirements that had to hold true or exceptions for the compliance of the treatment factor. The notes were for any other concerns or additional information that were useful or points that needed attention. There was a total of 21 sections in the compliance checklist that made up a maximum of 117 total points, with each treatment step under the section a yes/no variable contributing 1 point to the total. The checklist consisted of 4 key diagnostic sections before treatment (laboratory screening, imaging screening, diagnostic pathology, cytology), treatment (on-therapy) evaluation (up to 6 cycles), restaging, end-of-therapy evaluation, and 9 off-therapy sections (for 3, 6, 9, 12, 16, 20, 24, 30, and 36 month visits). The compliance checklist is included under **Appendix A.**

2.5 Exceptions & Eligibility

To ensure that patients did not receive protocol compliance scores of zero for treatment sections that they did not receive, there was an eligibility variable built into the compliance checklist at the beginning of each section. Only patients who were eligible for the section received a percent score for the section, with the scores of ineligible patients left as missing. There were no eligibility requirements for the sections before treatment as all patients enrolled had completed at least one round of chemotherapy. Therefore, eligibility criteria were applied for all cycles, restaging, end of therapy, and off therapy surveillance. For treatment cycles 1-6, patients were eligible for a protocol compliance score if they were alive and did not abandon treatment before the scheduled date of their first day of chemotherapy treatment for the given cycle (day 1 IV date). In addition, for cycles 4 through 6 there was an additional requirement that the patient was “High Risk” at CSF Cytology so that remaining “Low Risk” patients who only required 3 cycles were not included. Exceptions for not providing treatment were included when the reason for not providing treatment on time was due to "chemotherapy availability" or the "weekend/holiday". For restaging, the eligibility was that patients had a positive imaging result in the initial imaging section so that those who did not have positive results did not have to repeat the process. For end of therapy evaluation, patients who were eligible for their last cycle of treatment (either 3 or 6) were made eligible for end of therapy evaluation. For off therapy surveillance, the required date for compliance was calculated based on the scheduled date of their 3-month off therapy surveillance with subsequent months added accordingly (for months 6-36). A week of leniency was added to each scheduled date for off therapy surveillance to allow more patients to be compliant and account for weekends, longer/shorter months, and minor delays. If the patient was alive and did not abandon treatment before the calculated date of surveillance, they were made eligible to receive the respective off-therapy surveillance section score.

The eligibility of prospective patients also had to include whether or not their date of treatment was scheduled before or after the date of data extraction. As the prospective patients have not all completed their full treatment cycles, they were not counted towards compliance scores for cycles/sections that were not yet completed due to their stage of treatment. The eligibility criteria and exceptions included in the checklist are outlined in Table 1 and Table 2, respectively.

Table 1: Eligibility Criteria for Compliance Checklist

Group/Treatment Section	Eligibility
All sections	Alive and did not abandon at the time of treatment
Restaging	Previously positive imaging
Cycles 4-6	High risk cytology
End of Therapy Evaluation	Completed last cycle of treatment
Prospective Cohort	Treatment scheduled before date of data extraction (02/11/2021)

Table 2: Exceptions for Compliance Checklist

Treatment Section	Exceptions
Timely chemotherapy delivery	Chemotherapy unavailable, weekend/holiday
Timely Off therapy visit	One week of leniency from scheduled visit

2.6 Data Collection & mNavigator

The instrument for the data collection in this study was *mNavigator*. The *mNavigator* app was created to allow non-physicians to provide pediatric cancer diagnoses, treatment and follow-up surveillance in low-resource areas. The app is a case management system created on Dimagi Inc.'s CommCare platform, an open-source software, and can be used on computers, tablets, and mobile phones. The *mNavigator* app allows patient navigators to input patient information, case management, decision support, and behavior changes according to the national protocol for Burkitt Lymphoma treatment. Figure 2 shows the interface of the mobile application. The use of the app during treatment is available to all patients at Bugando Medical Center who meet the inclusion criteria and was the method of prospective data collection for the intervention (new) cohort.

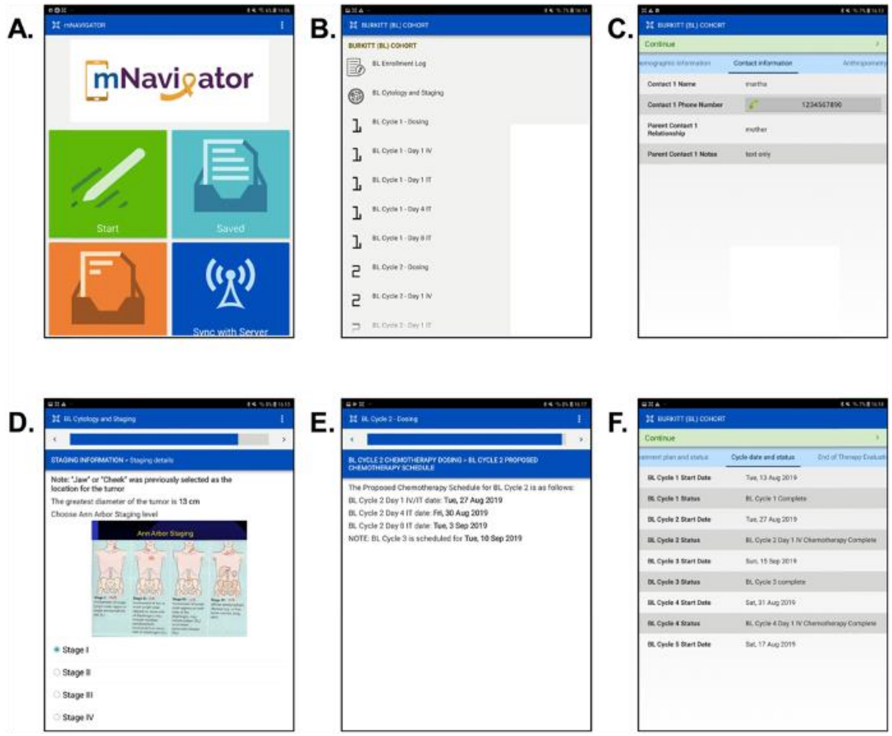

Figure 2: mNavigator user interface. a. mNavigator home screen. b. List of forms built in for Burkitt lymphoma patients. c. Example case detail showing contact information of a fictitious patient. d. Example of data entry question on tumor staging with picture

The historical data for patients prior to the implementation of *mNavigator* was collected through the abstraction of existing paper charts from the BMC clinical database by BMC staff and Duke University medical students. The abstracted data was used to complete medical forms that were then used for the study. The data from the forms were then inputted onto the *mNavigator* app using a tablet, as it was done for prospective patients by the patient navigators at Bugando Medical Center. This was to ensure that the data for historical patients could be extracted from the app the same way was the prospective patients. This ensured consistency and comparability between the historic and prospective data for analysis. The historic cohort were made up of patients who were registered from March 2016 – May 2019, while patients in the new cohort were registered between August 2019 - February 2021. The data from both cohorts on *mNavigator* were exported from the app as a Microsoft Excel spreadsheet for analysis.

2.7 Data Cleaning

After the collection of data, there were many steps that had to be taken to clean the data as there were many duplicates and repeated study IDs. The data was cleaned so that the final dataset would be the most complete with the least amount of missing data for the highest protocol compliance. For duplicates with the same data, the most recent version was kept. For duplicates that differed, the context of the differences had to be examined. If the difference was for whether treatment or imaging was received or not, the patient was classified as compliant if they ever received the specified treatment or imaging. In the case of different test results, if the patient ever received a positive or abnormal result, that is the observation that was kept. This was to ensure that patients with abnormal results would have to receive restaging. For any other differences, the most recent observation was kept. For study IDs that were repeated but corresponded to different individuals, the second repeat was removed by creating a new study ID by increasing the first number in the study ID by 1. For example, if the study ID 20bmc was repeated for a different patient, the repeat would change to 30bmc.

2.8 Analysis

For analysis, the independent variable was the use of the intervention, *mNavigator*. The historic cohort was the comparison group as their treatment was not guided by *mNavgiator*, with the prospective cohort with *mNavigator* use the intervention group. The dependent variables were the protocol compliance percentages for each independent checklist section and a total protocol compliance percentage for the entire treatment. Each section of the checklist had a protocol compliance score that was converted into a percentage based on the maximum score for the respective section, included in the checklist. The scores for each section were added up to calculate a total treatment protocol compliance score, also converted to a percentage. The means of the section and total compliance percentages were calculated for each cohort, historical and prospective. The other dependent variable treatment abandonment, failure to complete treatment, was a dichotomous yes/no variable.

A descriptive analysis was performed for the mean protocol compliance scores of each treatment section as well as the total compliance score for both the historic and new cohorts. The differences in compliance scores and continuous demographics between the two cohorts were analyzed using a Kruskal Wallis test. The differences in the categorical variables of abandonment, death, and other demographics were analyzed using a Fisher's exact test. Non-parametric tests were used as the sample size and distribution of the two cohorts were different. All statistical tests were analyzed using StataSE 16 under a pre-specified significance level of 5%.

2.9 Ethics Approval

This study is a secondary analysis as part of the original protocol, *"A mobile health (mHealth) case management system for reducing pediatric cancer treatment abandonment"* (Pro00094010). The original study has gained Duke IRB approval, Tanzanian National Institute for Medical Research IRB approval, as well as ethical clearance from the Catholic University Health and Allied Sciences and Bugando Medical Center Joint Ethics and Review Committee. The study researcher (Emma Joo) was added to the Duke IRB for the project with no additional IRB or amendments necessary for this study. The original study is funded by the NIH and the Duke Global Health Institute.

3. Results

3.1 Summary

A total of 82 patients who have received treatment from Bugando Medical Center were included in the study, with 49 individuals in the historical cohort and 33 individuals in the prospective cohort. A description of the patient population was conducted by using the registration, enrollment, and cytology forms extracted from *mNavigator*. The age, sex, and risk status of the patients for the full study are outlined by cohort in Table 3.

Table 3: Characteristics of BL patients at enrollment at Bugando Medical Center, Tanzania

	Historical		New		P-value
	Mean (n = 49)	SD	Mean (n= 33)	SD	
Age	6.2	3.6	9	4.5	0.007
	Frequency	Percent	Frequency	Percent	
Sex	N = 49		N = 33		0.353
Male	28	57.1%	23	50.0%	
Female	21	42.9%	10	21.7%	
Risk	N = 44		N = 29		0.002
High Risk	42	95.5%	21	72.4%	
Low Risk	1	4.5%	8	27.6%	

Non-parametric Kruskal Wallis and Fisher's exact tests were conducted to show that sex was not significantly different between the two cohorts, however age and risk status were different, with younger and more high risk patients in the historic cohort.

3.2 Eligibility

The proportion of patients who completed each section of treatment varied from 100% of the original cohort to as low as 42% due variations in eligibility and missing data. Table 4 outlines the eligibility of patients in each section of treatment, which represents the number of patients included in the calculation of the section compliance score, therefore also the dependent variable, mean compliance scores.

Table 4: Eligibility of Enrolled Patients in BL Treatment Sections

Treatment Section	Hist (n)	% Eligible	New (n)	% Eligible
Total Compliance	**49**	**100%**	**33**	**100%**
Lab	49	100%	33	100%
Imaging	44	90%	27	82%
Diagnosis	49	100%	33	100%
Cytology	43	88%	30	91%
Cycle 1	49	100%	27	82%
Cycle 2	32	65%	23	70%
Restaging	30	61%	21	64%
Cycle 3	34	69%	21	64%
Cycle 4	30	61%	20	61%
Cycle 5	25	51%	17	52%
Cycle 6	21	43%	15	45%
End of Therapy	21	43%	15	45%
Off Therapy 3	26	53%	25	76%
Off Therapy 6	26	53%	21	64%
Off Therapy 9	26	53%	20	61%
Off Therapy 12	26	53%	20	61%
Off Therapy 16	27	55%	20	61%
Off Therapy 20	26	53%	20	61%
Off Therapy 24	26	53%	20	61%
Off Therapy 30	26	53%	20	61%
Off Therapy 36	26	53%	21	64%

3.3 Protocol Compliance Scores

The protocol compliance scores were calculated for each individual, with the mean compliance percent presented for each cohort by total and by each treatment section in Table 5.

Table 5: Section and Total Burkitt Lymphoma Protocol Compliance Percentages for Historic and Prospective Cohorts at Bugando Medical Center, Tanzania

Treatment Section	Historical (n = 49)			Prospective (n = 33)			P-value
	Mean	Median	SD	Mean	Median	SD	
Total	47.0%	45.9%	13.3%	56.2%	59.5%	18.4%	0.023
Lab	71.7%	75.0%	16.5%	76.1%	87.5%	22.4%	0.022
Imaging	65.9%	100.0%	47.9%	92.6%	100.0%	26.7%	0.06
Diagnosis	53.1%	100.0%	50.4%	54.5%	100.0%	50.6%	0.91
Cytology	25.6%	0.0%	38.4%	65.0%	50.0%	29.8%	0.0001
Cycle 1	41.1%	37.5%	23.1%	75.0%	75.0%	18.3%	0.0001
Cycle 2	55.3%	53.8%	18.7%	73.9%	84.6%	28.8%	0.002
Restaging	16.7%	0.0%	37.9%	61.9%	100.0%	49.8%	0.006
Cycle 3	56.1%	60.0%	20.8%	72.7%	86.7%	28.6%	0.005
Cycle 4	57.5%	58.3%	18.9%	72.9%	83.3%	22.8%	0.012
Cycle 5	55.1%	57.1%	21.7%	79.8%	78.6%	16.0%	0.0003
Cycle 6	51.6%	50.0%	19.5%	69.4%	75.0%	17.4%	0.005
End of Therapy	35.7%	0.0%	47.8%	73.3%	100.0%	41.7%	0.04
Off Therapy 3	7.7%	0.0%	27.2%	18.7%	0.0%	34.8%	0.24
Off Therapy 6	7.7%	0.0%	27.2%	0.0%	0.0%	0.0%	-
Off Therapy 9	5.1%	0.0%	18.1%	0.0%	0.0%	0.0%	-
Off Therapy 12	3.8%	0.0%	19.6%	0.0%	0.0%	0.0%	-
Off Therapy 16	2.5%	0.0%	12.9%	0.0%	0.0%	0.0%	-
Off Therapy 20	2.6%	0.0%	13.1%	0.0%	0.0%	0.0%	-
Off Therapy 24	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	-

Off Therapy 30	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	-
Off Therapy 36	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	-

The total treatment compliance in the historic group was 47.0% with mean compliance scores in treatment sections ranging from 0% in the off-therapy sections (at 24, 30, 36 months) with the highest mean of 71.7% in the lab section. Restaging had a low mean compliance percentage of 16.7% compared to the sections before and after. Off Therapy Surveillance sections had the lowest scores.

In the intervention cohort, after the implementation of *mNavigator*, the total mean compliance score was 56.2% with mean compliance scores in treatment sections ranging from 0% to 92.6%. There was a drastic 45.2% increase in compliance in the prospective group, after the implementation of *mNavigator* in the restaging section. Similar to the historic cohort, the Off-Therapy Surveillance compliance percentages were the lowest of the treatment sections.

Out of the 14 treatment sections that were comparable, meaning they had non-zero percentages for both historic and new cohorts (including total compliance), 11 sections had an increase in compliance scores that were significantly different. The total compliance means in the two cohorts are compared in Figure 3.

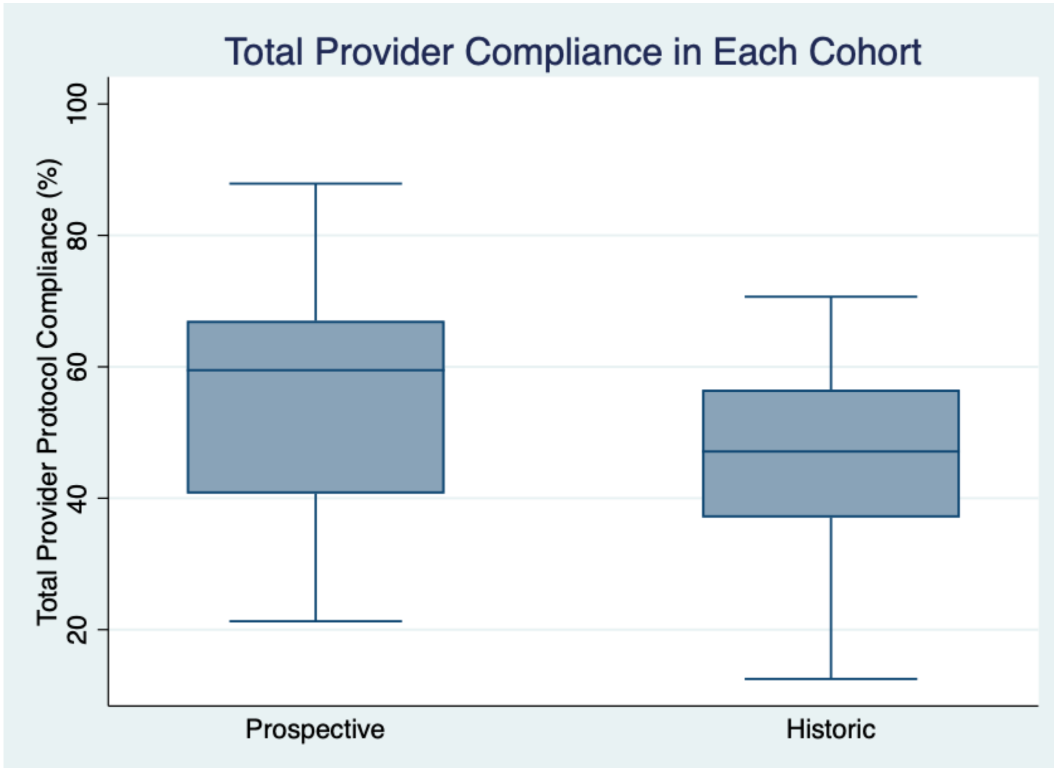

Figure 3: Side-by-side box plot comparison of mean total compliance percentages between historic and prospective BL patients at Bugando Medical Center, Tanzania

There was a 9.2% increase in the mean total compliance mean after the introduction of *mNavigator* in the prospective cohort, compared to the historic cohort. The distribution of the scores was wider in the historic group compared to those in the new cohort. The difference between the historic and new cohorts was statistically significant, with a p-value of 0.02, below the pre-set significance level of 0.05.

3.4 mNavigator Use and Treatment Abandonment

In total, 16 patients abandoned treatment in the full cohort with 12 in the historical cohort and 4 in the intervention cohort. The outcomes of the two cohorts are outlined in Table 4.

Table 6: Comparison of the Proportion of Treatment Abandonment and Death Between the Historic and Prospective Cohort at Bugando Medical Center, Tanzania.

	Historical (N = 49)		New (N = 33)		P-value
	Frequency	Percent	Frequency	Percent	
Abandonment	12	24%	4	12.12%	0.524
Death	8	16.3%	6	18.2%	0.729

The proportion of patients who abandoned care decreased by 11.9 percentage points after the use of *mNavigator*, though the association between historic status and abandonment was not statistically significant (p = 0.52). Additionally, there was no association between historic status and death (p = 0.73).

4. Discussion

4.1 Findings

The protocol compliance scores, presented as percentages for pediatric BL treatment in Tanzania showed a significant increase from the historic cohort to the new cohort. These increases in protocol compliance of up to 45.2% in the intervention group compared to the comparison group build evidence towards the benefits of *mNavigator* use in increasing protocol compliance for pediatric BL treatment at BMC. The significant increases in compliance in the pre-treatment categories, labs and cytology, are especially meaningful as a previous study had stated that less than 55% had a staging evaluation before treatment at BMC, which is essential in determining proper treatment.[13] The 11.9% decrease in treatment abandonment rates after the implementation of *mNavigator* in the intervention cohort, though not statistically significant, also suggest the benefits of mHealth in not only increasing protocol compliance, but also reducing treatment abandonment.

The treatment sections that exhibited the largest increases in protocol compliance were especially meaningful due to their significance for proper treatment and improved outcomes. The 4 largest percentage point increases in protocol compliance were in the cytology, cycle 1, restaging, and end of therapy sections, with increases in the intervention cohort of 39.4%, 33.9%, 45.2%, and 37.6%, respectively.

The protocol compliance increases in cytology, cycle 1, and restaging are indicative of the accurate assignment of the most effective treatment plan for their disease stage. The cytology section is decisive on whether or not the patient is at low or high-risk, which determines whether they will receive 3 cycles of chemotherapy or the full 6 cycles. The increased completion of proper cytology suggested that patients are more likely to be assigned the most optimal number of treatment cycles. This allows for the most effective use of the limited resources available for both the patient and the health system, since children are not receiving extra cycles that they do not require. This reduces the costs of additional medications, reduced trips to the hospital, and conserves the time of personnel to be used for more urgent patients.[5,16] Additionally, the negative side effects with more aggressive chemotherapy drugs and their toxicity, including tumour lysis syndrome, fever, hematologic toxicity, and severe infection from extra treatment cycles are prevented.[32]

The improvement in accurate treatment planning through *mNavigator* use is further supported by the increase in compliance for restaging, which had the highest percentage point increase in protocol compliance in the intervention cohort compared to the historic control cohort (45.2%). The restaging of BL confirms the diagnosis and ensures that the patient is responsive to treatment, allowing for changes in diagnoses and adjustments to treatment if necessary. The protocol compliance for the initial staging of BL was relatively high in the control group (65.9%) with remarkable improvements to almost all patients receiving proper staging (92.6%). The high protocol compliance percentages in the initial staging are however expected as it is recognized by providers as a crucial prerequisite to assessing the patient's prognosis and determining the appropriate treatment. [36] However, the repetition of this process is easier to be overlooked and skipped, explaining the low protocol compliance percentages in the pre-intervention (historic) cohort. Therefore, the dramatic increases in protocol compliance in restaging, as well as the other sections are consistent with the purpose of *mNavigator*. The use of algorithm-directed treatment through mNavigator facilitates the completion of critical treatment steps that may have otherwise been missed and overall, the adherence of best practice treatment.

Furthermore, the 33.9% percentage point increase in the protocol compliance of cycle 1 is meaningful as the chemotherapy of BL is shown to be quite rapid with tumour shrinkage within the first cycle of treatment. Therefore, similar to restaging, the patient's response after the first round of chemotherapy may be used as an indicator of misdiagnosis, inactive drugs, and any other treatment deficiencies, acting as an additional checkpoint for adequate treatment.[34] Adequate treatment plans that meet the patients' specific needs result in effective individualized treatment leading to favourable outcomes.

Lastly, the increase in protocol compliance for End of Therapy is valuable as it is where the surveillance of the patients is initiated with the scheduling of follow-up visits.

The importance of posttreatment surveillance for BL is well documented with its importance in checking for the early detection of recurrence as well as the detection of chemotherapy-related complications including second cancer, cardiac and endocrine toxicity.[37] These posttreatment visits that start at end of therapy evaluation promote better long-term outcomes and increase survival as the risk of relapse is highest and most common during the first 2 years after treatment, with prognosis highly associated with early detection.[34] The benefits to survival from posttreatment surveillance emphasizes the importance of providers initiating follow-up care at the end of therapy, which has improved by 37.6% percentage points through the use of *mNavigator*.[37,38]

The development of the protocol compliance checklist used to calculate the protocol compliance scores was a valuable deliverable from this study. The creation of this instrument has enabled the ongoing evaluation of the quality of Burkitt lymphoma treatment at Bugando Medical Center. The implementation of this checklist in the based on the Tanzanian Burkitt's Lymphoma National Treatment Guidelines is an imperative step in establishing the foundation for surveillance and accountability for providers, promoting consistency and adherence to best practices.[39] The simple incorporation of the checklist also allows for the documentation of improvements over time, comparisons between providers, and differences between different institutions. The assessment of "adherence to clinical guidelines" is part of the provider competence indicator in the Health Service Delivery of Tanzania outlined by the World Bank, with its power in assessing service providers an taking corrective action.[40] The checklist from this study is valuable in its ability to specialize the indicators provided by the World Bank for assessing health service delivery to evaluate the quality of patient care and collect data in the pediatric cancer treatment setting.

4.2 Limitations

There are many limitations to this study given the mix of retrospective and prospective data collection. The first concern is information bias that is a common issue with retrospective data collection. Since the historical data is from patients who received treatment from 2016-2019, data abstraction could have taken place up to 5 years after it was first collected. This time delay along with the inconsistencies in individuals abstracting the data can lead to discrepancies in how the data is inputted into the *mNavigator* app. Information bias is likely in this study as many errors were identified during the data cleaning process, including the repetition of records, spelling errors, and non-standard metrics, among others. The use of historical data also makes it difficult to address missing variables, as contact information may no longer be valid and patients may no longer be reachable, making loss to follow-up difficult to address.

Loss to follow-up is another source of bias as the assumption that loss to follow-up is the same as treatment abandonment may create a construct validity issue. This is because there may be a difference in factors that influence treatment abandonment to factors that influence dropping out of a study. Therefore, the measures of association reported in the study may not be reflective of the actual relationship between protocol compliance and treatment abandonment but may be due to reasons that are related to loss to follow-up in a study, independent from protocol compliance. Additionally, there are multiple factors that can also influence treatment abandonment outside of protocol compliance. This makes it important to identify any other factors that may influence treatment abandonment, specifically patient-centered barriers such as distance from the hospital, economic status, and cancer beliefs. Not accounting for these factors in analysis may overestimate the association between protocol compliance and treatment abandonment when the effects may be due to external factors. If these factors are differential among the two groups, the comparability between the two groups is further weakened. This may have been the reason for the positive association between protocol compliance and treatment abandonment in the historic cohort.

Selection bias may also exist in the study as participants were recruited at a hospital after cancer diagnosis. This may introduce external factors including health seeking behaviour or other personal factors that may invalidate the direct relationship between protocol compliance to treatment abandonment assumed in this study. Additionally, the sampling method and the recruitment from one hospital may select participants that are not representative of the overall target population. Therefore, the results of the study could not be used to make inferences on the total population of pediatric Burkitt lymphoma in Tanzania, which threatens generalizability and the external validity of the study.

As this study was conducted with a short follow-up time given the time and resource constraints, it was not possible to infer on causal relationships between protocol adherence and survival, the main question at hand. Instead, the study used the mediator of treatment abandonment to infer on the effects of protocol compliance on survival. This inference has its limitations as it is assuming that the full effect of protocol compliance on survival goes through the mediator of treatment abandonment or that the effect of protocol compliance on treatment abandonment is proportional to the direct effect of the exposure on survival, both of which are not true. The study also lacks statistical power due to the small sample size due to the time constraints of the study. With 49 historical and 33 prospective participants, it is difficult to reach statistically significant conclusions at the pre-set significance level of 0.05.

4.3 Implications for further research

Future studies should increase the time of follow-up to collect complete data up to 1-year survival outcomes to strengthen the causal inference made between protocol adherence and survival in this given context. Factors that hinder the effectiveness of mHealth outside of protocol compliance should be looked at such as user level differences. Additionally, further research to investigate other pathways from protocol compliance to survival outside the treatment abandonment mediated pathway. This will allow for the measurements of the direct and indirect effects of protocol compliance and other variables affecting Burkitt lymphoma survival, to provide a more accurate foundation for causal inferences. There is also a need to identify the timing of abandonment to understand the parts of treatment most vulnerable to abandonment. Lastly, social factors that affect treatment abandonment for the pediatric BL in Tanzania should be looked at including caregiver demographics, rural/urban location, financial, incurability, and transportation. Many of these patient and individual level barriers may be responsible for the lowest protocol compliance percentages in the posttreatment (off-therapy) surveillance sections in the historic cohort and therefore merit further investigation. The low percentages in the prospective intervention cohort were mainly due to the fact that they have yet to reach that stage of surveillance since they are being followed prospectively.

4.4 Implications for Policy and Practice

The results of this study supporting the effectiveness of *mNavigator* in improving protocol compliance at BMC can be used to inform policy making to strengthen protocol-driven treatment in Tanzania. The case management system can scaled-up to first be implemented in the other two cancer treatment centers in Tanzania outside of BMC, then adapted for use in for other disease settings. This will allow for the integration of *mNavigator* into the Tanzanian health care system for its use in other facilities outside of cancer care. The results of this study also suggest the benefits of building the monitoring and surveillance capacity to evaluate a health system. This is in line with literature supporting the need for consistent and transparent reporting of incomplete treatment in cancer for collaborations to improve outcomes for pediatric patients with a variety of chronic diseases.[16]

5. Conclusion

The potential benefits of mHealth interventions in low-resource settings has been a growing topic of interest. This study has demonstrated the significant increase in protocol compliance after the implementation of *mNavigator*, a mobile case management system, and successfully developed a compliance checklist for ongoing protocol compliance evaluation. The study results create evidence for policies to incorporate mHealth in pediatric cancer treatment. The study limitations suggest the need for accurate data collection and outcome measurements, with further research needed to identify additional factors associated with treatment abandonment as well as the impact of *mNavigator* use on survival. Overall, the development and implementation of *mNavigator* have shown promise in improving the compliance of pediatric Burkitt Lymphoma treatment protocols at Bugando Medical Center, Tanzania. The success of this study gives hope to the future expansion of *mNavigator*, to be adapted for various diseases in low-resource settings and prevent unnecessary mortalities and morbidities globally.

Appendix A: Protocol Compliance Checklist

PRE-TREATMENT	**Question ID**	**Choice ID**	**Condition**	**Exceptions**
Laboratory Screening				
Complete Blood Count				
White Blood Cell (1)	wbc			
Hemoglobin (1)	hgb			

Platelets (1)	plt			
Neutrophil (1)	np			
Renal Function Test				
Creatinine Value (1)	creatinine_value			
Potassium (1)	potassium_value			
Uric Acid Value (1)	uric_acid_value			
Liver Function Test				
Total bilirubin	total_bilirubin_value; direct_bilirubin_value			

OR Direct bilirubin (1)				
Section Total (/8)				
<u>Imaging Screening</u>				
Chest X-ray (1)	cxr_result	normal; abnormal		CXR+ ab us is compliant; Ab US + chest CT is compliant, CXR+ Ab CT is compliant; combination of (CXR or Chest CT) AND (Ab US OR Ab CT)
Ultrasound (1)	ab_ultrasound_result	normal; abnormal		
CT Scan chest or	ct_scan_result	normal; abnormal	if QUESTION ID:	

abdomen (+1)			ct_scan_location = neckchest OR abdomen	
Section Total (/2)				
Diagnostic Pathology				
Diagnosis				
Method of diagnosis? - Trocar biopsy, Excision biopsy, or FNA (1)	method_of_diagnosis	trocar_biopsy; excision_biopsy; fna		

Section Total (/1)				
CSF Cytology				
Was CSF cytology completed -yes (1) or No AND Clinically unstable selected (1)	csf_cytology_completed	yes		OR no (if QUESTION ID: csf_cytology_not_completed_reason = clinically_unstable)
CSF cytology collected prior to treatment start - Yes (1)	csf_cytology_before_chemo	yes		

Section Total (/2)				
TREATMENT COMPLIANCE (BL)				
Cycle 1				
Anthropometric Values				
Height - Recorded (1)	height			
Weight - Recorded (1)	weight			

Treatment				
Were supported medications given as recommended? - Yes (1)	blc1d1_IV_chemotherapy_supportive_medicines_given	yes		
Day 1 Methotrexate given? (1)	blc1d1_IT_methotrexate_given	yes		OR blc1d1_IT_methotrexate_given == "no" & blc1d1_IT_methotrexate_not_given =="chemotherapy_availability"
Day 1 IV given on the correct date? (1)	blc1d1_IV_chemotherapy_date_give	yes		blc1d1_IV_chemotherapy_date_give == "no" & (blc1d1_IV_chemotherapy_not_given == "weekend_holiday" | blc1d1_IV_chemotherapy

				_not_given == "some_chemotherapy_unavailable")
Day 1 IV given in correct dose? (1)	blc1d1_IV_chemotherapy_dose_give	yes		blc1d1_IV_chemotherapy_dose_give == "no" & blc1d1_IV_chemotherapy_dose_not_ == "chemotherapy_availability"
Day 4 Cytarabine given? (1)	blc1d4_IT_Cytarabine_given	yes		blc1d4_IT_Cytarabine_given == "no" & blc1d4_IT_cytarabine_not_given_r == "chemotherapy_availability"
Day 8 Methotrexate given? (1)	blc1d8_IT_methotrexate_given	yes		blc1d8_IT_methotrexate_given == "no" & blc1d8_IT_methotrexate_not_given

				=="chemotherapy_availability"
Section Total (/8)				
<u>Cycle 2</u>				
Complete Blood Count				
White Blood Cell (1)	wbc			
Hemoglobin (1)	hgb			
Platelets (1)	plt			

Neutrophil (1)	np			
Renal Function Test				
Creatinine Value (1)	creatinine_value			
Uric Acid Value (1)	uric_acid_value			
Liver Function Test				
Direct bilirubin (1)	direct_bilirubin_value			
Treatment				
Were supported	blc2d1_IV_chemotherapy_supportive_medicines_given	yes		

medications given as recommended? - Yes (1)				
Day 1 Methotrexate given? (1)	blc2d1_IT_methotrexate_given	yes		OR blc2d1_IT_methotrexate_given == "no" & blc2d1_IT_methotrexate_not_given =="chemotherapy_availability"
Day 1 IV given on the correct date? (1)	blc2d1_IV_chemotherapy_date_give	yes		blc2d1_IV_chemotherapy_date_give == "no" & (blc2d1_IV_chemotherapy_not_given == "weekend_holiday" | blc2d1_IV_chemotherapy_not_given == "some_chemotherapy_unavailable")

Day 1 IV given in correct dose? (1)	blc2d1_IV_chemotherapy_dose_give	yes		blc2d1_IV_chemotherapy_dose_give == "no" & blc2d1_IV_chemotherapy_dose_not_ == "chemotherapy_availability"
Day 4 Cytarabine given? (1)	blc2d4_IT_Cytarabine_given	yes		blc2d4_IT_Cytarabine_given == "no" & blc2d4_IT_cytarabine_not_given_r == "chemotherapy_availability"
Day 8 Methotrexate given? (1)	blc2d8_IT_methotrexate_given	yes		blc2d8_IT_methotrexate_given == "no" & blc2d8_IT_methotrexate_not_given =="chemotherapy_availability"

Section Total (/13)				
<u>Restaging</u>				
If previously positive, was imaging repeated with Chest X-ray - Yes (1)	cxr_results	normal; abnormal	IF QUESTION ID: cxr_result = abnormal	OR if ct_scan_location = neckchest AND ct_scan_result = abnormal (both from initial imaging)
If previously positive, was imaging repeated with Abdominal	ultrasound_result (AND ultrasound_location = abdominal)	normal; abnormal	IF QUESTION ID: ultrasound_location = abdominal AND IF QUESTION ID:	OR if ct_scan_location = abdomen AND ct_scan_result = abnormal (both from initial imaging)

Ultrasound? - Yes (1)			ab_ultrasound_result = abnormal	
Section total (/2)				
Cycle 3				
Response Evaluation				
Any (1)	blc3_result_of_response_eval	complete_response; partial_response; stable_disease; progressive_disease		

Complete Blood Count				
White Blood Cell (1)	wbc			
Hemoglobin (1)	hgb			
Platelets (1)	plt			
Neutrophil (1)	np			
Renal Function Test				
Creatinine Value (1)	creatinine_value			

Liver Function Test				
Total bilirubin OR Direct bilirubin (1)	direct_bilirubin_value			
Anthropometric Values				
Height - Recorded (1)	height			
Weight - Recorded (1)	weight			
Treatment				

Were supported medications given as recommended? - Yes (1)	blc3d1_IV_chemotherapy_supportive_medicines_given	yes		
Day 1 Methotrexate given? (1)	blc3d1_IT_methotrexate_given	yes		OR blc3d1_IT_methotrexate_given == "no" & blc3d1_IT_methotrexate_not_given =="chemotherapy_availability"
Day 1 IV given on the correct date? (1)	blc3d1_IV_chemotherapy_date_give	yes		blc3d1_IV_chemotherapy_date_give == "no" & (blc3d1_IV_chemotherapy_not_given == "weekend_holiday" | blc3d1_IV_chemotherapy_not_given ==

				"some_chemotherapy_unavailable")
Day 1 IV given in correct dose? (1)	blc3d1_IV_chemotherapy_dose_give	yes		blc3d1_IV_chemotherapy_dose_give == "no" & blc3d1_IV_chemotherapy_dose_not_ == "chemotherapy_availability"
Day 4 Cytarabine given? (1)	blc3d4_IT_Cytarabine_given	yes		blc3d4_IT_Cytarabine_given == "no" & blc3d4_IT_cytarabine_not_given_r == "chemotherapy_availability"
Day 8 Methotrexate given? (1)	blc3d8_IT_methotrexate_given	yes		blc3d8_IT_methotrexate_given == "no" & blc3d8_IT_methotrexate_not_given =="chemotherapy_availability"

Section Total (/15)				
Cycle 4				
Complete Blood Count				
White Blood Cell (1)	wbc			
Hemoglobin (1)	hgb			
Platelets (1)	plt			
Neutrophil (1)	np			

Renal Function Test				
Creatinine Value (1)	creatinine_value			
Liver Function Test				
Total bilirubin OR Direct bilirubin (1)	direct_bilirubin_value			
Treatment				
Were supported medications given as recommen	blc4d1_IV_chemotherapy_supportive_medicines_given	yes		

ded? - Yes (1)				
Day 1 Methotrexate given? (1)	blc4d1_IT_methotrexate_given	yes		OR blc4d1_IT_methotrexate_given == "no" & blc4d1_IT_methotrexate_not_given =="chemotherapy_availability"
Day 1 IV given on the correct date? (1)	blc4d1_IV_chemotherapy_date_give	yes		blc4d1_IV_chemotherapy_date_give == "no" & (blc4d1_IV_chemotherapy_not_given == "weekend_holiday" | blc4d1_IV_chemotherapy_not_given == "some_chemotherapy_unavailable")
Day 1 IV given in	blc4d1_IV_chemotherapy_dose_give	yes		blc4d1_IV_chemotherapy_dose_give == "no" & blc4d1_IV_chemotherapy

correct dose? (1)				_dose_not_ == "chemotherapy_availability"
Day 4 Cytarabine given? (1)	blc4d4_IT_Cytarabine_given	yes		blc4d4_IT_Cytarabine_given == "no" & blc4d4_IT_cytarabine_not_given_r == "chemotherapy_availability"
Day 8 Methotrexate given? (1)	blc4d8_IT_methotrexate_given	yes		blc4d8_IT_methotrexate_given == "no" & blc4d8_IT_methotrexate_not_given =="chemotherapy_availability"
Section Total (/12)				
<u>Cycle 5</u>				

Complete Blood Count				
White Blood Cell (1)	wbc			
Hemoglobin (1)	hgb			
Platelets (1)	plt			
Neutrophil (1)	np			
Renal Function Test				
Creatinine Value (1)	creatinine_value			

Liver Function Test				
Total bilirubin OR Direct bilirubin (1)	direct_bilirubin_value			
Anthropometric Values				
Height - Recorded (1)	height			
Weight - Recorded (1)	weight			
Treatment				

Were supported medications given as recommended? - Yes (1)	blc5d1_IV_chemotherapy_supportive_medicines_given	yes		
Day 1 Methotrexate given? (1)	blc5d1_IT_methotrexate_given	yes		OR blc5d1_IT_methotrexate_given == "no" & blc5d1_IT_methotrexate_not_given =="chemotherapy_availability"
Day 1 IV given on the correct date? (1)	blc5d1_IV_chemotherapy_date_give	yes		blc5d1_IV_chemotherapy_date_give == "no" & (blc5d1_IV_chemotherapy_not_given == "weekend_holiday" | blc5d1_IV_chemotherapy_not_given ==

				"some_chemotherapy_unavailable")
Day 1 IV given in correct dose? (1)	blc5d1_IV_chemotherapy_dose_give	yes		blc5d1_IV_chemotherapy_dose_give == "no" & blc5d1_IV_chemotherapy_dose_not_ == "chemotherapy_availability"
Day 4 Cytarabine given? (1)	blc5d4_IT_Cytarabine_given	yes		blc5d4_IT_Cytarabine_given == "no" & blc5d4_IT_cytarabine_not_given_r == "chemotherapy_availability"
Day 8 Methotrexate given? (1)	blc5d8_IT_methotrexate_given	yes		blc5d8_IT_methotrexate_given == "no" & blc5d8_IT_methotrexate_not_given =="chemotherapy_availability"

Section Total (/14)				
<u>Cycle 6</u>				
Complete Blood Count				
White Blood Cell (1)	wbc			
Hemoglobin (1)	hgb			
Platelets (1)	plt			
Neutrophil (1)	np			

Renal Function Test				
Creatinine Value (1)	creatinine_value			
Liver Function Test				
Direct bilirubin (1)	direct_bilirubin_value			
Treatment				
Were supported medications given as recommended? - Yes (1)	blc6d1_IV_chemotherapy_supportive_medicines_given	yes		

Day 1 Methotrexate given? (1)	blc6d1_IT_methotrexate_given	yes		OR blc6d1_IT_methotrexate_given == "no" & blc6d1_IT_methotrexate_not_given =="chemotherapy_availability"
Day 1 IV given on the correct date? (1)	blc6d1_IV_chemotherapy_date_give	yes		blc6d1_IV_chemotherapy_date_give == "no" & (blc6d1_IV_chemotherapy_not_given == "weekend_holiday" | blc6d1_IV_chemotherapy_not_given == "some_chemotherapy_unavailable")
Day 1 IV given in correct dose? (1)	blc6d1_IV_chemotherapy_dose_give	yes		blc6d1_IV_chemotherapy_dose_give == "no" & blc6d1_IV_chemotherapy_dose_not_ ==

				"chemotherapy_availability"
Day 4 Cytarabine given? (1)	blc6d4_IT_Cytarabine_given	yes		blc6d4_IT_Cytarabine_given == "no" & blc6d4_IT_cytarabine_not_given_r == "chemotherapy_availability"
Day 8 Methotrexate given? (1)	blc6d8_IT_methotrexate_given	yes		blc6d8_IT_methotrexate_given == "no" & blc6d8_IT_methotrexate_not_given =="chemotherapy_availability"
Section Total (/12)				
END OF THERAPY				

EVALUATION				
Chest X-ray? - Yes (1)	eot_cxr_result	normal; abnormal		
Abdominal Ultrasound? - Yes (1)	eot_ab_ultrasound_result	normal; abnormal		
Section total (/2)				
OFF THERAPY EVALUATION				
3-Months				

Attended 3 mo visit - Yes (1)	ots_month	three_months		
Chest X-ray done? - Yes (1)	ots_cxr	yes		
Abdominal Ultrasound Done? - Yes (1)	ots_ab_ultrasound	yes		
Section total (/3)				
6-Months				
Attended 6 mo visit - Yes (1)	ots_month	six_months		

Chest X-ray done? - Yes (1)	ots_cxr	yes		
Abdominal Ultrasound Done? - Yes (1)	ots_ab_ultrasound	yes		
Section total (/3)				
9-Months				
Attended 9 mo visit - Yes (1)	ots_month	nine_months		
Chest X-ray done? - Yes (1)	ots_cxr	yes		

Abdominal Ultrasound Done? - Yes (1)	ots_ab_ultrasound	yes		
Section total (/3)				
12-months				
Attended 12 mo visit -Yes (1)	ots_month	twelve_months		
Chest X-ray done? - Yes (1)	ots_cxr	yes		
Abdominal Ultrasound Done? - Yes (1)	ots_ab_ultrasound	yes		

Section total (/3)				
16-months				
Attended 16 mo visit -Yes (1)	ots_month	sixteen_months		
Chest X-ray done? - Yes (1)	ots_cxr	yes		
Abdominal Ultrasound Done? - Yes (1)	ots_ab_ultrasound	yes		
Section total (/3)				

20-months				
Attended 20 mo visit -Yes (1)	ots_month	twenty_months		
Chest X-ray done? - Yes (1)	ots_cxr	yes		
Abdominal Ultrasound Done? - Yes (1)	ots_ab_ultrasound	yes		
Section total (/3)				
24-months				

Attended 24 mo visit -Yes (1)	ots_month	twenty_four_ months		
Chest X-ray done? - Yes (1)	ots_cxr	yes		
Abdominal Ultrasound Done? - Yes (1)	ots_ab_ultrasound	yes		
Section total (/3)				
30-months				
Attended 30 mo visit -Yes (1)	ots_month	thirty_months		

Chest X-ray done? - Yes (1)	ots_cxr	yes		
Abdominal Ultrasound Done? - Yes (1)	ots_ab_ultrasound	yes		
Section total (/3)				
36-months				
Attended 36 mo visit -Yes (1)	ots_month	thirty_six_months		
Chest X-ray done? - Yes (1)	ots_cxr	yes		

Abdominal Ultrasound Done? - Yes (1)	ots_ab_ultrasound	yes		
Section total (/3)				
Checklist Total = Low Risk Total (/79) or High Risk Total (/117)	12 pre-tx, 29 post-tx; low-risk tx (+ rstg) = 38; high-risk tx (+ rtsg) = 76			

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