Capstone Practicum Report (20%)

Implementation of the Hunger 2 regimen for acute lymphoblastic leukaemia in the Butaro Cancer Centre of Excellence: toxicity and interim outcomes

By

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DECLARATION

I, Grace Dugan, hereby declare that the practicum capstone thesis has been written by me without any external unauthorized help, that it has been neither presented to any institution for evaluation nor previously published in its entirety or in parts. Any parts, words, or ideas in the thesis, however limited, that are quoted from or based on other sources, have been acknowledged as such without exception.

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DEDICATION

This project is dedicated to the memory of the children and teenagers who died of ALL while under my care at Butaro Hospital.

ACKNOWLEDGEMENT

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ABSTRACT

Background

Outcomes in acute lymphoblastic leukaemia (ALL) in low income countries are poor, with only 20-50% of patients successfully treated. Many of the failures are due to relapsed disease but mortality from complications of therapy is also increased. Hunger et al. have proposed regimens of graduated intensity for ALL in resource-limited centres so that capacity for managing toxicity, particularly neutropenic fever can be built over time without excessive treatment-related deaths (Hunger, Sung, & Howard, 2009).

The Butaro Cancer Center of Excellence (BCCOE) is located in a Rwandan district hospital with limited antibiotics, no microbiology and no intensive care. The centre began treating ALL in 2012 with the Hunger 1 regimen; few deaths from toxicity were experienced but the cure rate was unacceptably low (Rubagumya, Xu, et al., 2017). In October 2016 the centre transitioned to using the Hunger 2 regimen, which is more intense and incorporates a delayed intensification phase.

Objective

The objective was to assess the toxicity and interim outcomes at 24 weeks of the first 25 patients treated with the Hunger 2 regimen for ALL at BCCOE in Rwanda starting from October 2016.

Methods

The sample included all patients, both adult and paediatric, with a pathology-confirmed diagnosis of ALL, from October 2016 to September 2017, who were treated with the Hunger 2 regimen. Patients who received previous treatment with chemotherapy were excluded.

A retrospective cohort study design was used, with patient status at week 24 as the key outcome variable, as well as survival of episodes of neutropenic fever. Routine data was collected by manual chart review.

Results

Twenty-four patients had a bone marrow diagnosis of ALL during the study period, but only 17 of those survived to start treatment with the Hunger 2 regimen. The cohort included a high

proportion of patients with high-risk features such as older age, T-cell subtype and white blood count (WBC) greater than 50,000 at presentation.

Most treatment delays were caused by neutropenia and thrombocytopenia, with negligible delays due to medication stockouts or social factors. There was a high use of red blood cell and platelet transfusions during the induction phase.

Patients had a median of one episode of neutropenic fever. Median time to antibiotics was 10.5 hours. Identified infections included malaria, pyoderma, pneumonia and enterocolitis.. The most common antibiotics used were ceftriaxone and ceftazidime. All episodes resolved with no patient deaths.

The majority of patients (63%) who commenced treatment achieved remission and were still alive and in treatment at week 24. Two patients failed induction, one patient died during induction, another patient abandoned treatment and another transferred out.

Conclusion

This study suggests that neutropenic fever may be less of a limiting factor in ALL treatment in resource-poor settings than has been supposed, as all patients survived this complication despite limited resources. The high number of deaths prior to treatment was surprising; this may be due to delayed presentation but deserves further study. The ability to report on ultimate outcomes of the treatment and associations with risk factors was limited by the short duration of follow-up and small cohort size.

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CHAPTER ONE: INTRODUCTION

Background

A child who develops ALL, the most common cancer of childhood, in a high-income country has a greater than 90% chance of surviving their disease and growing to adulthood; a child with the same disease in one of the sub-Saharan African countries where paediatric cancer care is scarce to non-existent has a life-ending illness (Bonaventure et al., 2017). The reasons for this inequity are manifold – not simply a lack of access to a drug or a diagnostic test, but the absence of a whole system of treatment and care. Even in high-income countries, the excellent outcomes for ALL are hard-won; treatment is intensive, and lasts for over two years (Inaba, Greaves, & Mullighan, 2013). An unavoidable side effect of treatment is profound immune suppression which puts patients at risk of severe and life-threatening infections, and requires a high level of supportive care. Replicating this system in low-income countries presents an enormous challenge.

In 2012 the Butaro Cancer Centre of Excellence (BCCOE) opened in northern Rwanda and began providing care for adults and children with ALL. The centre is a partnership between the Rwandan Ministry of Health and Partners in Health/Inshuti Mu Buzima, a non-governmental organization with a mission to provide "a preferential option to the poor" and with experience in HIV scale-up in Rwanda (Stulac et al., 2015). The centre is based in a rural district hospital and uses a task-shifted model of care, with general practitioners, paediatricians and internists providing care using treatment protocols and with remote technical support from cancer centres in the USA (Rubagumya, Greenberg, et al., 2017).

While every patient who arrives at BCCOE with ALL is theoretically curable, treating this cancer has challenged the centre. From the beginning, the treatment protocol used was based on a strategy proposed by Hunger, Sung and Howard (2009) that had never been implemented elsewhere. This strategy aims to address the challenge of providing high-toxicity, myelosuppressive treatment in a low-income country hospital; it involves using a series of regimens of gradually increasing intensity, referred to as Hunger 1, Hunger 2, Hunger 3 and Hunger 4 regimen. The approach is for a new centre to start with the low-intensity Hunger 1 regimen, treat at least 25 patients and then assess outcomes. If there is no more than one death due to the toxicity of treatment, it demonstrates that the centre is able to provide an adequate

level of care and can advance to the next step, using the reduced-intensity regimen Hunger 2. The same process of treating 25 patients and then assessing outcomes is repeated, with the same benchmark of no more than one treatment-related death, and if the centre passes this metric, step three involves using the Hunger 2, 3 and 4 regimens according to the risk profile of the patient (Hunger et al., 2009). Hunger, Sung and Howard estimate that patients treated with the Hunger 1 regimen should have a cure rate of 50-55% (2009). The experience at BCCOE however was quite different, with only 22% of patients alive and in care at 2 years of follow up (Rubagumya, Xu, et al., 2017). The reasons for this are unknown, but may include more patients with high-risk features, delayed presentation, delays to diagnosis, treatment quality, and challenges with supportive care in the initial stages of treatment. Treatment toxicity, however, was not a major contributor to failure; of the 30 deaths in the cohort examined, only one was attributed to treatment (Rubagumya, Xu, et al., 2017). Following review of this data, the decision was made to implement the Hunger 2 regimen for all cases of ALL treated at BCCOE.

There are no published reports of the use of the Hunger 2 regimen in low-income countries, and the overall question of how ALL should be managed in this context deserves further analysis. Of the factors which may limit treatment success – reliable access to chemotherapy, access to quality diagnostics, access to blood products, the challenge of adherence, and management of life-threatening treatment complications such as neutropenic fever – which are the most important? And how can they be individually addressed to give patients in low-income countries such as Rwanda the best chance of cure? By examining the experience at BCCOE with the Hunger 2 regimen, with a particular focus on the management of neutropenic fever, this report contributes to the literature addressing these questions.

Problem Statement

The Hunger 2 regimen for ALL while decreasing the risk of leukemic relapse may result in unacceptable levels of toxicity in a low-resource environment such as the Butaro Cancer Centre of Excellence.

SMART Practicum Objective

To assess the toxicity and interim outcomes at 24 weeks of the first 25 patients treated with the Hunger 2 regimen for acute lymphoblastic leukaemia (ALL) at the Butaro Cancer Centre of Excellence in Rwanda starting from October 2016.

Setting and Beneficiaries

The setting is Butaro Hospital, a district hospital located a rural area in Burera District in the Northern Province of Rwanda. Rwanda is a low-income country which has made significant gains in health and economic development since it was engulfed in violence and genocide in the early 1990s (Stulac et al., 2015; Tapela et al., 2016). It has a widely used community-based health insurance scheme, a network of health centres providing primary care, district hospitals and three tertiary hospitals (Tapela et al., 2016). Prior to the opening of the BCCOE, however, there was essentially no cancer treatment available in the country (Stulac et al., 2015). BCCOE currently serves patients from every district of Rwanda and also receives referrals from Burundi and eastern Democratic Republic of Congo, where cancer services are limited (Stulac et al., 2015).

Beneficiaries of this study include individuals with ALL in Rwanda and these neighbouring areas. Patients in other low- and middle-income countries are also potential beneficiaries, as sharing the experience of our implementation of this treatment can inform practitioners, program managers and policy-makers in other countries.

Layout of Capstone Report

Chapter One introduces the report. Chapter Two summarises the relevant literature on ALL treatment in low- and middle-income countries, including a basic introduction to the disease and its standard treatment, challenges in treatment in low- and middle-income countries and suggested strategies to address them. It also describes the literature on neutropenic fever, the most common and serious toxic effect of ALL treatment, including its standard treatment, recent developments, and the impact of neutropenic fever on patient care in ALL in low- and middle-income countries. Chapter Three describes the design of the study, data collection and analysis, as well as relevant ethical issues. Chapter Four presents the results of the study in tables and narrative format. Chapter Five discusses the implications of the study in relation to the literature,

including a comparison of risk factors in the patient cohort, treatment outcomes and a discussion of the high proportion of patients who died prior to commencement of treatment and possible causes for this. The impact of treatment toxicity on the patient cohort is discussed, including the management of neutropenic fever and the absence of mortality caused by this complication. The difficulty of treating neutropenic fever in the absence of a microbiology lab is described, as well as the challenges posed to antibiotic stewardship. Finally, the limitations of the study are discussed. Chapter Six concludes the report with recommendations for both the program at BCCOE and other cancer centres in low- and middle-income countries and proposes directions for future research.

CHAPTER TWO: LITERATURE REVIEW

Acute lymphoblastic leukaemia (ALL)

ALL is a haematological malignancy which occurs in both adults and children, most commonly between the ages of two to five (Pui, Robison, & Look, 2008). The risk of ALL during childhood (up to age 15) is 1 in 2000, making it the most common cancer of this age group (Inaba et al., 2013; Pui & Evans, 2006). Twin studies have shown that the majority of cases of ALL can be traced back to prenatal genetic changes in haematopoietic cells, which usually require further events postnatally to lead to the creation of malignant cells (Eden, 2010). Many risk factors have been proposed for these changes but the only ones for which strong evidence exists are ionizing radiation and certain chemicals such as benzene and some chemotherapy agents (Eden, 2010) (Inaba et al., 2013).

Treatment of ALL

Untreated, ALL is universally fatal. However, treatment advances over the last 40 years have led to high cure rates (Bonaventure et al., 2017). Treatment typically involves a long regimen of chemotherapy, with an induction phase which aims to rapidly reduce the burden of leukaemic cells, and restore normal blood cell production, followed by a consolidation phase, sometimes one or more intensified phases, then a long maintenance phase of up to two years, which aims to rid the body of residual leukaemic cells (Pui & Evans, 2006). Cases which fail to respond to first-line therapy can be switched to more intense therapy or bone marrow transplantation (Pui & Evans, 2006). A component of most regimens is central nervous system chemotherapy, which is administered directly into the cerebrospinal fluid via a lumbar puncture. This has been shown to significantly reduce the risk of relapse in the central nervous system (Pui & Evans, 2006). Cranial radiotherapy has also been used but has significant toxicities and is thus recommended in the highest risk cases only (Pui & Evans, 2006).

Risk stratification and prognosis

A key element in improving ALL patient outcomes has been stratifying patients according to their projected outcome, and choosing treatment regimens according to risk stratum (Pui et al., 2008). Risk strata have been defined based on studies that have indicated that age below one year

or over 10 years, T-cell immunophenotype and initial white blood cell count above 50,000 are all factors which put patients at an increased risk of treatment failure and relapse (Inaba et al., 2013). Early response to treatment has also been used to stratify patients into different regimens. Measures of response to treatment which have been shown to be prognostic include repeat bone marrow biopsies at 15 and 29 days of treatment, examined either morphologically or by polymerase chain reaction (PCR) or flow cytometry (Connor et al., 2017; A. Gupta, Kapoor, Jain, & Bajpai, 2015; Teachey & Hunger, 2013). Certain genetic changes have also been used more recently to further define prognosis (Teachey & Hunger, 2013).

Outcomes in high-income and low- and middle-income countries

ALL treatment and outcomes in low- and middle-income countries differ enormously from those in high-income countries. A recent comparison of nearly 90,000 children with leukaemia in cancer registries from 53 countries showed huge inequities in survival rates, which range from 10.6% in China compared with 86.8% in Austria during the period 1995-1999 (Bonaventure et al., 2017). This gap was described as having narrowed in 2005-2009 with the lowest survival rate being 52.4% in Colombia compared with the highest, 91.6% in Germany; however, the analysis excluded registries judged to have poor quality data and included only one sub-Saharan African country (Bonaventure et al., 2017). Furthermore, it has been reported elsewhere that only 11% of Africa is covered by cancer registries (Gopal et al., 2012). An example possibly more representative of sub-Saharan Africa would be a cancer centre in Tanzania which achieved a one-year survival rate for children with leukaemia of just 5% as recently as 2005, improving to a 2-year estimated event-free survival of 33% in 2010 (Kersten, Scanlan, DuBois, & Matthay, 2013).

Challenges to providing ALL treatment in Sub-Saharan Africa

Resources to diagnose, treat and support patients with ALL are severely limited in the region; there are few pathologists, equipment is limited and vital tests such as immunohistochemistry are often not available (Gopal et al., 2012). Chemotherapy agents are expensive and patients require high quality supportive care in order to survive initial disease and also the toxic effects of treatment (Gopal et al., 2012). Blood products, broad-spectrum antibiotics and antifungals are key adjuncts to the treatments discussed above, and some of the most important drugs may not be

stocked in low- and middle-income country pharmacies (Gopal et al., 2012). Due to all of these challenges, a multi-pronged strategy has been proposed as a way forward, involving increased awareness and advocacy, greater global investment, translational research in improved diagnostics and treatment, greater access to palliative care and family support (Gopal et al., 2012; Lehmann, El-Haddad, & Barr, 2016).

Treatment strategies in low- and middle-income countries

Given the demanding and resource-intensive nature of treatment, some researchers have proposed graduated or stratified treatment strategies depending on the level of healthcare resources or experience of a centre in managing ALL. The Asian Oncology Summit suggested a strategy of stratifying countries or regions according to their healthcare expenditure per capita and then issuing a set of guidelines appropriate for each level (Yeoh et al., 2013). They suggest that a country might step up its level of treatment as it advances economically, rather than according to the expertise of the centre or the needs of the population. Hunger, Sung and Howard (2009) suggested a different centre-specific approach that aims to initially treat ALL with a low-intensity/low toxicity regimen similar to that used in high-income countries in the early 1980s and switching to progressively stronger regimens as the experience of the centre and its capacity to manage toxic side effects improves. The first regimen, "Hunger 1," is a 30-month program of chemotherapy involving a one month Induction Phase, a one month Consolidation Phase, and a Maintenance Phase for 28 months (Hunger et al., 2009). This low-intensity treatment is not likely to result in high cure rates, but it also has low toxicity and is thus less likely to cause treatment-related deaths. It is suggested that once a centre can demonstrate use of this regimen with fewer than 1 in 25 treatment-related deaths, the centre can step up the Hunger 2 and then the Hunger 3 and 4 regimens (Hunger et al., 2009). Like the Hunger 1 regimen, Hunger 2 involves an Induction and Consolidation Phase, and also introduces a Delayed Intensification phase involving strong chemotherapy agents such as doxorubicin, cyclophosphamide and cytarabine, followed by a maintenance phase to make up a total of 30 months of treatment (see Table 1). The Hunger 3 and Hunger 4 regimens incorporate additional chemotherapy agents for more intense treatments necessary for patients with high-risk features, and are comparable to protocols in use in high-income countries (Hunger et al., 2009).

In terms of delivery of treatment, task shifting to generalist doctors, along with protocol-based treatment and ongoing mentorship from off-site oncologists has been described at BCCOE as a way of addressing the extreme shortage of oncologists in low-income countries (Rubagumya, Greenberg, et al., 2017). Implementation of a twinning arrangement between an established cancer centre and a low-income country centre has been shown to reduce abandonment and treatment-related mortality in ALL in other settings (Suarez et al., 2015). Given the many unanswered questions in global cancer delivery, and the necessity of adapting treatment practices from other contexts, the importance of implementation science has been emphasized (Shulman, Mpunga, Tapela, & Wagner, 2014; Tapela et al., 2016).

ALL treatment at BCCOE

BCCOE used the Hunger 1 Regimen for treatment of all ALL cases from 2012 to 2016. An analysis of the first 42 patients showed very poor results in terms of treatment success, with an event-free survival of only 22% at 2 years (Rubagumya, Xu, et al., 2017). This is in contrast to the expected cure rate of 55% predicted by Hunger. The reasons for this are unknown, though the data showed some challenges with stockouts and delays in treatment which could have influenced outcomes. In addition, Hunger et al may have underestimated the risk of relapse with this minimalist approach. However it was demonstrated that the toxicity of this regimen was very low in the district hospital setting, with only one treatment-related death in 42 patients (Rubagumya, Xu, et al., 2017). A comprehensive description of the resources involved in treatment is also included.

Neutropenic fever as the major complication of treatment in ALL

Infection is a significant cause of morbidity and mortality in patients receiving chemotherapy, and often fever may be the first or only manifestation of infection (Klastersky & Paesmans, 2013). Immunosuppression is quantified by a low neutrophil count, and in these cases infections can be rapidly progressing and life-threatening (Klastersky & Paesmans, 2013). Due to these factors, the practice of giving prompt empirical antibiotic treatment for neutropenic fever has been widely accepted since the 1980s, often recommended with the addition of empirical antifungal treatment if fever does not resolve within four days (Gea-Banacloche, 2013; Klastersky & Paesmans, 2013). The goal of treatment within one hour has been recommended,

based on evidence from treatment of sepsis, meningitis and pneumonia (Klastersky & Paesmans, 2013). Reviews have shown, however, that even in high income country centres, treatment within one hour is rarely achieved (Klastersky & Paesmans, 2013; Perron, Emara, & Ahmed, 2014). Studies have shown an association between delayed antibiotics and length of stay, but not mortality (Butts et al., 2017; Klastersky & Paesmans, 2013; Ko et al., 2015; Perron et al., 2014).

More recent research has focused on more conservative and risk stratified treatment of neutropenic fever. It has been shown that the empirical administration of vancomycin and aminoglycosides has no added benefit, and that these medications should be reserved for cases with an identified pathogen (Gea-Banacloche, 2013; Lehrnbecher et al., 2017). The empirical use of antifungal treatment is also being questioned by experts in light of poor evidence for efficacy (Gea-Banacloche, 2013; Lehrnbecher et al., 2017). In adults, the Multinational Association for Supportive Care in Cancer (MASCC) risk index score provides a validated method to stratify between high risk and low risk neutropenic fever, with low risk cases able to be treated as an outpatient with oral antibiotics (Bergstrom, Nagalla, & Gupta, 2018). The MASCC criteria uses risk factors such as age and comorbidities as well as clinical signs of illness severity to stratify cases of neutropenic fever (Klastersky & Paesmans, 2013) The adoption of this practice in high income country cancer centres has not been consistent (Bergstrom et al., 2018).

In low- and middle-income country cancer centres, neutropenic fever has been associated with a significant mortality, with 9% reported in Tunisia (Masmoudi, Khanfir, Maalej-Mezghan, Hammami, & Frikha, 2015), 13% in Turkey (Duzenli Kar, Ozdemir, & Bor, 2018) and 5.5-6% India, (Krishnamani, Gandhi, Sadashivudu, & Raghunadharao, 2017; Noronha et al., 2014; Oberoi, Das, Trehan, Ray, & Bansal, 2017). For comparison, in high-income country centres only 0-4% of neutropenic fever episodes result in death (Hann, Viscoli, Paesmans, Gaya, & Glauser, 1997; Miedema et al., 2016). In ALL this high rate of infection-related death contributes to elevated treatment-related mortality, which has been reported from 11-20% of patients compared to 1-3% in high-income countries (S. Gupta et al., 2011). A study in Central America of 1670 children with ALL showed a treatment-related mortality of 9.3%, with 59% of deaths occurring in the induction phase, and 64% of deaths attributed to infection (S. Gupta et al., 2011).

Table 1: Comparison between Hunger 1 & Hunger 2 regimens (Hunger, et al., 2009)

Hunger 1	Hunger 2
Induction (4 weeks) Prednisone, IT methotrexate, vincristine, L-asparaginase	**Induction (4 weeks)** Prednisone, IT methotrexate, vincristine, L-asparaginase
Bone marrow biopsy at Day 29 determines whether patient is in remission	
Consolidation (4 weeks) IT methotrexate, 6-mercaptopurine, vincristine	**Consolidation (4 weeks)** IT methotrexate, 6-mercaptopurine, vincristine
Maintenance (continued for a total treatment duration of 2.5 years) IT methotrexate, oral methotrexate, 6-mercaptopurine, vincristine, dexamethasone	**Interim Maintenance (8 weeks)** IT methotrexate, oral methotrexate, 6-mercaptopurine, vincristine, dexamethasone
	Delayed Intensification (8 weeks) IT methotrexate, vincristine, L-asparaginase, dexamethasone, doxorubicin, cyclophosphamide, cytarabine
	Maintenance (continued for a total treatment duration of 2.5 years) IT methotrexate, oral methotrexate, 6-mercaptopurine, vincristine, dexamethasone

CHAPTER THREE: METHODS

Setting

The Butaro Cancer Centre of Excellence (BCCOE) is a collaboration of the Rwandan Ministry of Health and Partners In Health/Inshuti Mu Buzima, with the support of academic and technical partners in the United States including the Dana-Farber Cancer Institute, the Brigham and Women's Hospital, University of Pennsylvania and the Dartmouth-Hitchcock Cancer Centre. Diagnosis, staging, chemotherapy and follow-up are provided at Butaro District Hospital, a Rwandan public district hospital supported by Partners In Health/Inshuti Mu Buzima. Patients are referred elsewhere for some operations and a limited number of patients are have support for radiotherapy in Nairobi Hospital as there are no in-country radiation facilities. BCCOE has been operating since 2012 and has treated over 6000 patients including both adults and children.

Design

A retrospective cohort study design was used, with patient status (remission, deceased, failed induction, relapsed, lost to follow up, transferred out) at week 24 the key outcome variable, as well as survival of episodes of neutropenic fever.

Sample

The sample included the first 24 patients, both adult and paediatric, with a pathology-confirmed diagnosis of acute lymphoblastic leukaemia after 1 October 2016, and who commenced treatment on the Hunger 2 regimen. Patients who received previous treatment with chemotherapy were excluded.

Data collection tools

Routine clinical data was collected by manual chart and input directly into an Excel spreadsheet for data analysis, according to a data collection guide prepared by the principle investigator (PI) with the support of Oncology Research Associate.

Data collectors

Data collection was performed by a medical student from the University of Pennsylvania and the PI during September 2017 and January 2018.

Data management

Routine clinical data was collected through manual chart review and input directly into a Microsoft Excel spreadsheet to use for data analysis.

Data analysis

Frequencies and percent were reported for categorical variables and medians and interquartile ranges were reported for continuous variables. Descriptive statistics were used to present demographic variables, baseline clinical characteristics and treatment details. Bi- and multi-variate analysis was conducted to determine if certain risk factors are associated with clinical outcomes, with p-value set at 0.05. Analysis was conducted using Excel and STATA version 13.

Ethical considerations

The collection of data was approved by the Inshuti Mu Buzima Research Committee under an umbrella protocol which is approved the Rwandan National Ethics Committee. As the study involved only retrospective review of routinely collected clinical data, individual patient consent was not required.

Data collection was performed by personnel with existing professional and/or legal obligations to protect confidentiality. Data was de-identified by the Oncology Research Associate prior to analysis, and all copies of data containing identifying information will be destroyed at the conclusion of the study. Only data collectors and the oncology research associate will have access to raw data during the collection phase. Once the data has been de-identified the oncology research associate will hold the key and the data will be stored on Partners In Health/Inshuti Mu Buzima servers.

CHAPTER FOUR: RESULTS

Twenty-four patients were eligible for inclusion in the study based on a bone marrow biopsy demonstrating ALL (Figure 1, Table 8). A third of the cohort were in the low-risk age group of 1-9 years old (33%), and 38% of patients were over 15 years of age (Table 2). There were no infants. A majority of patients were male (62%). One third of cases were T-cell subtype, and half of patients had a white blood count (WBC) greater than 50,000 at presentation.

During the period of diagnostic work-up, a quarter of the patients died (25%). Another patient who was discharged while results were pending did not return for treatment. Of patients who survived to the start of treatment, the majority (70%) completed the induction phase and achieved remission, as diagnosed by repeat bone marrow biopsy showing less than five percent leukemic blasts. Patients whose bone marrow biopsies were inconclusive continued treatment along with those in remission. A large majority of patients who continued treatment completed the delayed intensification phase or were still alive on treatment at the end of the study period (93%).

Patients had grossly abnormal WBC, haemoglobin levels and platelet counts at presentation, and there was a trend towards more abnormal results among the patients who died before being able to start treatment. This were compared using t-test for haemoglobin and Wilcoxon Ranksum test for WBC and platelet count with no significant difference detected (Table 3).

Patients presented a median of two months after the start of symptoms, with the most common symptoms being fever, weight loss, weakness and fatigue and lymphadenopathy (Table 4). Common examination findings were lymphadenopathy, splenomegaly and hepatomegaly. A quarter of patients were malnourished as measured by height-for-weight (for under 5 years) or BMI-for-age (above 5 years), but only one patient had severe acute malnutrition.

On average, patients waited two weeks from arrival at BCCOE to start treatment (Table 5). During 24 weeks of treatment, patients experienced a median of 13 days of delay. The majority of delays in treatment were caused by patient-related factors of neutropenia (59%) or thrombocytopenia (24%). There were minimal delays caused by social problems or medication stockouts. Patients required a median of three transfusions of red blood cells and two transfusions of platelets during the period of diagnosis and induction. After the induction phase, far fewer blood products were used (Table 6).

Patients had a median of one episode of neutropenic fever after achieving remission (Table 7). These episodes were spread nearly evenly between the consolidation and delayed intensification phases. Antibiotics were administered a median of 10.5 hours after fever was identified. Blood cultures were not performed as microbiology analysis is not available but clinically identified sources of infection included pyoderma, pneumonia and enterocolitis. Nearly half of episodes (47%) had no clinically identified source of infection. Two episodes were associated with malaria diagnosed by blood smear microscopy. The median number of anti-infective agents used during an episode of neutropenic fever was three, with the most common agents being ceftriaxone and ceftazidime. Patients with malaria were treated with artesunate followed by artemether/lumafantrine. One patient received oxygen therapy. All episodes of neutropenic fever resolved with no patient deaths.

There was a trend towards improved treatment outcomes in the younger age group, with 83% of 1-to-9-year-olds achieving remission compared to 67% of 10-to-14-year-olds and only 25% of those over 15 years (Table 9). There was also a trend towards improved outcomes in females, with almost twice the proportion of females achieving remission compared to males (86% versus 44%). There were no deaths among females who started treatment. The majority of treated patients had T-cell immunophenotype, and a greater proportion of these (78%) achieved remission compared to patients with B-cell immunophenotype (43%), though the small sample size means that statistical significance was not achieved. There was no obvious difference in outcome between patients with higher or lower WBC at presentation.

Figure 1: Overview of results

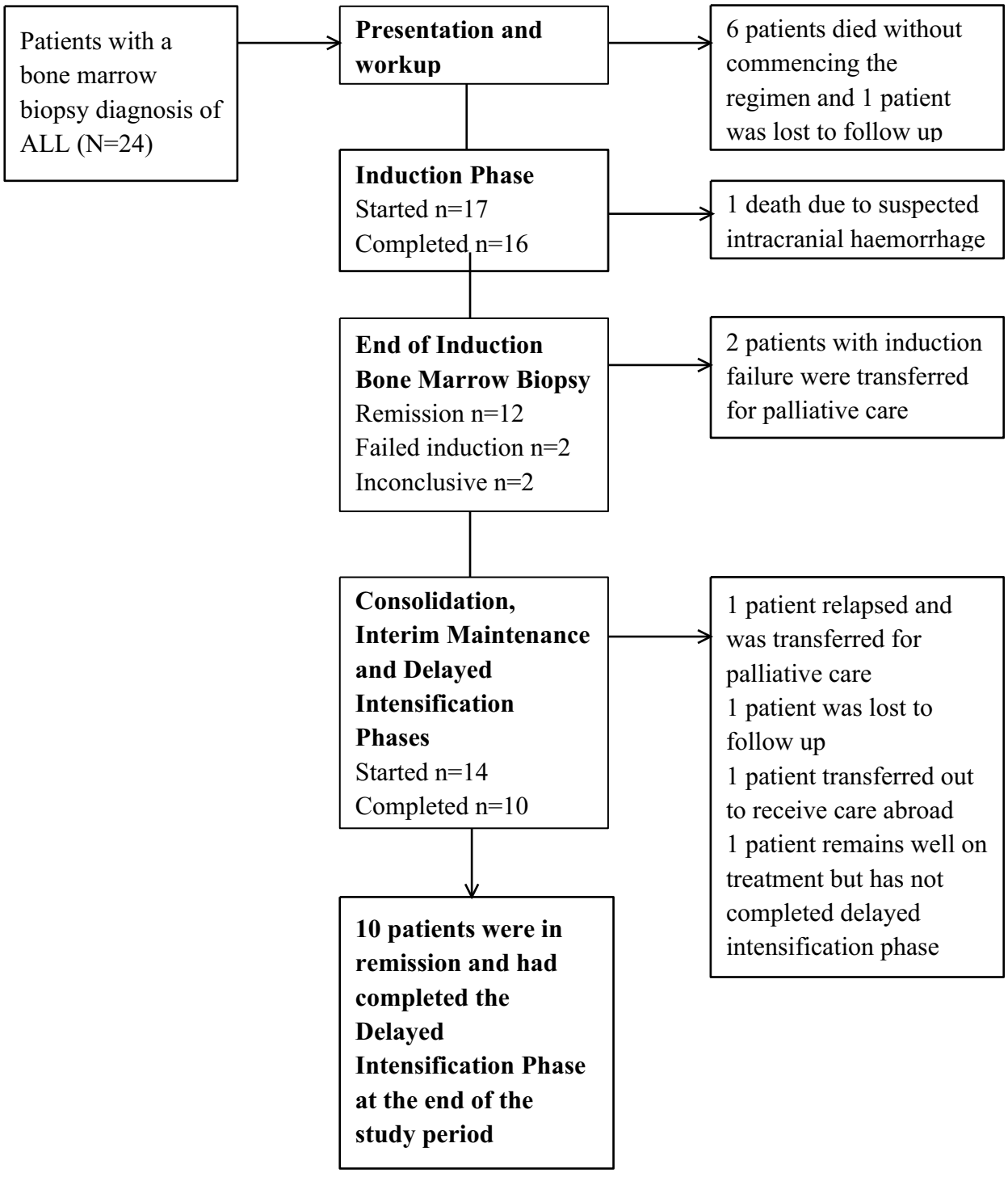

Table 2: Patient characteristics (N=24)	**% (n)**
Age	
<1	0% (0)
1-9	33% (8)
10-14	29% (7)
>15	38% (9)
Sex	
Male	62% (15)
Female	38% (9)
Subtype	
B-cell	66% (16)
T-cell	33% (8)
Leukocytosis	
White blood cells >50	50% (12)

Table 3: Laboratory results on arrival at BCCOE comparing patients who started treatment vs those who died or were lost to follow up before starting treatment

	Treated N=17	**Never treated N=7**	**All N=24**	
	Median (IQR)	Median (IQR)	Median (IQR)	p-value
White blood cell count	45.5 (19-87)	79.5 (48-357)	55.47 (21.99-91.5)	0.1721
Haemoglobin	6.7 (6.2-7.4)	4.9 (4.4-8.1)	6.5 (4.95-7.5)	0.1513
Platelet count	26 (8-56)	11 (3-62)	22 (7-59)	0.4267

Table 4: Presentation

Duration of symptoms (months)	Median 2 (range 1-12)
Presenting symptoms (N=24)	% (n)
Fever	88% (21)
Weight loss	75% (18)
Weakness/fatigue	63% (15)
Lymphadenopathy	54% (13)
Bleeding/bruising	46% (11)
Bone/joint/muscle pain	46% (11)
Examination findings (N=22)	
Lymphadenopathy	86% (19)
Splenomegaly	64% (14)
Hepatomegaly	32% (7)
Malnutrition (N=20)	
Severe Acute	5% (1)
Moderate Acute	20% (4)

Table 5: Treatment delays	Median (IQR)
Days from intake to start of treatment	14 (9-22) (N=17)
Days of delay during treatment	13 (3.5-20.5) (N=16)
Cause of delays (N=17)	% (n)
Neutropenia	59% (10)
Thrombocytopenia	24% (4)
Delay in lab results	6% (1)
Hepatotoxicity	6% (1)
Malaria	6% (1)
Error	12% (2)
Stockout of cytarabine	6% (1)
Social cause	6% (1)

Table 6: Use of blood products (N=17)	**Transfusions Median (range)**	**Patients receiving blood products % (n)**
Intake to end of induction		
Red blood cells	3 (0-5)	88% (15)
Platelets	2 (0-8)	53% (9)
End of induction to end of delayed intensification		
Red blood cells	0 (0-5)	47% (8)
Platelets	0 (0-4)	18% (3)

Table 7: Neutropenic fever

Episodes of neutropenic fever while in remission	Median 1 (range 0-3) (N=16)
Phase of neutropenic fever episode	**% (n) (N=16)**
Consolidation	43% (7)
Interim maintenance	7% (1)
Delayed intensification	50% (8)
Absolute neutrophil count during episode	**Median (IQR) (N=15)**
Initial	0.34 (0.09 – 0.63)
Nadir	0.23 (0.03 – 0.51)
Identified possible focus of infection	% (n) (N=15)
Unknown	47% (7)
Malaria	13% (2)
Mucositis	7% (1)
Enterocolitis	7% (1)
Gingivitis/fungal skin infection (same patient episode)	7% (1)
Perianal skin abscess	7% (1)
Pneumonia	7% (1)
Number of anti-infective agents used per episode	Median 3 (IQR 1-4)
Number of times anti-infective used	% (n) (N=15)
Ceftriaxone	87% (13)
Ceftazidime	27% (4)
Piperacillin/tazobactam	13% (2)
Fluconazole (oral)	40% (6)
Acyclovir (oral)	27% (4)
Metronidazole	20% (3)
Gentamicin	13% (2)
Artesunate followed by artemether/lumafantrine	13% (2)
Ampicillin	7% (1)
Cloxacillin	7% (1)
Use of oxygen therapy	7% (1)
Time from fever to antibiotics (hours)	Median 10.5 (IQR 4.9-19.5) N = 13
Outcome of episode	% (n) (N=16)
Recovery	100% (16)
Death	0% (0)

Table 8: Patient status at end of delayed intensification phase	**% (n) N=16***
Remission	63% (10)
Deceased	6% (1)
LTFU	6% (1)
Failed induction	13% (2)
Relapsed	6% (1)
Transferred out	6% (1)

*Excluding patients who did not receive treatment and 1 patient in remission who had not completed delayed intensification phase

Table 9: Patient status at end of delayed intensification phase, by age, sex, subtype and WBC at presentation (N=16)

	Remission % (n)	Deceased % (n)	LTFU % (n)	Failed Induction % (n)	Relapsed % (n)	Transferred out % (n)
Age						
1-9 (N=6)	83% (5)	0% (0)	0% (0)	0% (0)	17% (1)	0% (0)
10-14 (N=6)	67% (4)	17% (1)	0% (0)	17% (1)	0% (0)	0% (0)
>15 (N=4)	25% (1)	0% (0)	25% (1)	25% (1)	0% (0)	25% (1)
Sex						
Male (N=9)	44% (4)	11% (1)	0% (0)	22% (2)	11% (1)	11% (1)
Female (N=7)	86% (6)	0% (0)	14% (1)	0% (0)	0% (0)	0% (0)
Subtype						
B-cell (N=7)	43% (3)	0% (0)	14% (1)	29% (2)	0% (0)	14% (1)
T-cell (N=9)	78% (7)	11% (1)	0% (0)	0% (0)	11% (1)	0% (0)
WBC at presentation						
<50 (N=9)	56% (5)	11% (1)	0% (0)	11% (1)	11% (1)	11% (1)
50-100 (N=4)	75% (3)	0% (0)	25% (1)	0% (0)	0% (0)	0% (0)
>100 (N=3)	67% (2)	0% (0)	0% (0)	33% (1)	0% (0)	0% (0)

CHAPTER FIVE: DISCUSSION

The cohort included a large proportion of patients with known high-risk features for whom a reduced-intensity regimen may not be appropriate. Risk factors for poor outcome include age >10, WBC >50 and T-cell subtype. In Lebanon excellent results have been achieved in ALL treatment, with event-free survival of 78%, with a patient cohort with 78% in the 1-9 age group, 78% with WBC <50,000, and 86% B-cell immunophenotype, which is dramatically different from those treated at BCCOE (Muwakkit et al., 2012). A cohort in Tanzania also had lower presenting WBC of 36.2 and 69% of patients in the low risk age group; in the Central American study median WBC was 9.6 and median age 6.3 (S. Gupta et al., 2011; Kersten et al., 2013). Other risk factors such as central nervous system involvement were not able to be assessed at BCCOE due to laboratory limitations, and cranial irradiation is not available. Extra intrathecal chemotherapy doses at day 15 and day 22 of induction were used for all patients, recommended for central nervous system disease in the Hunger protocol, given the inability to determine patient-specific involvement. Treatment outcomes will not be able to be determined until patients have completed the regimen, or ideally until 5 years of follow up have been achieved; in the interim, we have focused on treatment-related morbidity and mortality, a competing cause of therapeutic failure.

The period of greatest danger for this patient cohort was after arriving at BCCOE but before initiation of treatment; the large proportion of deaths in this period was a surprise and warrants further investigation. Most studies report results beginning with chemotherapy administration but given the high mortality seen prior to therapy initiation this may be an important area of future focus for implementation science. In a large study in Central America, 6.8% of patients who were diagnosed with ALL did not start chemotherapy, but it is not clear whether this was due to death or loss-to-follow-up (S. Gupta et al., 2011). In Tanzania, only 7% of patients died before starting treatment (Kersten, Scanlan, DuBois, & Matthay, 2013). Deaths in the induction period are likely to be of similar causes as deaths prior to commencement of treatment. Our rate of induction deaths (6%) was similar to that seen in Central America, higher than the 1% seen in Lebanon, but lower than Tanzania where 23% of patients either died in induction or failed to achieve remission (S. Gupta et al., 2011; Kersten et al., 2013; Muwakkit et al., 2012). One possible contributor deaths early in treatment is delayed diagnosis and referral. Research at

Kigali University Teaching Hospital, the major source of referrals for BCCOE, has shown that in paediatric cancer, there is a median of 36.5 days of patient-related delay, 23 days of health provider delay, 12 days of system-related delay and 19 days of diagnostic delay totaling nearly 3 months of delay (Kanyamuhunga, 2017). These delays may result in worsening disease status which can be responsible for the grossly deranged blood counts seen at presentation. This is consistent with the high requirements for blood products during induction, which was far higher than those used in the Lebanese cohort (Muwakkit et al., 2012). The overall picture is of patients who are critically ill on arrival at the centre and sometimes cannot be stabilized in the context of a resource-limited district hospital.

Despite the challenging nature of treatment, the rate of abandonment of treatment (6%) was low, even lower than other paediatric cohorts at BCCOE, which range from 10-13% (Rubagumya, Xu, et al., 2017; Shyirambere et al., 2016). The single case of loss-to-follow-up was associated with an unplanned pregnancy; follow up for the full duration of treatment may reveal other cases. A systematic review of abandonment in paediatric acute leukaemia in middle-income countries showed rates of 1-49% in ALL (S. Gupta et al., 2013). Abandonment was significantly more common in lower than in upper middle-income countries, but the huge variability between centres was not explained by the cost of treatment, the country's gross national income or health expenditure by capita (S. Gupta et al., 2013). Good treatment adherence at BCCOE has been attributed to social supports and subsidized chemotherapy but this has not been investigated conclusively (Shyirambere et al., 2016).

Consistent with the goal in using graduated-intensity approaches there were no deaths related to treatment toxicity. Despite a median time-to-antibiotics of over 10 hours, and no ability to identify bacterial pathogens, all patients recovered from neutropenic fever. This is in contrast to other studies of neutropenic fever in low- and middle-income country settings which show mortality rates of 5-13%, and deaths from toxicity in up to 29% of ALL cases (Duzenli Kar et al., 2018; Kersten et al., 2013; Krishnamani et al., 2017; Masmoudi et al., 2015; Noronha et al., 2014; Oberoi et al., 2017). The rationale behind the graduated intensity regimens of proposed by Hunger, Sung and Howards (2009) is that increasing intensity of chemotherapy regimens require a higher skill level of health-care workers which is expected to increase over time. The delayed intensification phase, the only difference between the Hunger 1 and 2 regimens, accounted for 50% of episodes of neutropenic fever, suggesting that the change in regimen creates an increase

in quantity rather than necessarily an increase in the complexity or difficulty of management of toxicity.

All but one case of neutropenic fever occurred in the inpatient setting. In this context, it is less surprising that the time-to-antibiotics of 10.5 hours led to good outcomes. Studies in high-income countries of neutropenic fever are often using a time-to-antibiotics from emergency department triage, without evaluating the symptom-to-door interval (Ko et al., 2015; Perron et al., 2014). Keeping patients admitted in the ward during the majority of the delayed intensification phase may have been protective at BCCOE. In India, symptom-to-door interval in ALL patients with neutropenic fever has been reported as a median of 24 hours, but not found to be significantly associated with poor outcomes (Oberoi et al., 2017; Oberoi, Trehan, Marwaha, & Bansal, 2013).

Most low- and middle-income centres which have published reports on ALL treatment have access to microbiology investigations, with the exception of the Tanzanian cohort (Kersten et al., 2013). While the use of empirical antibiotics is standard of care in neutropenic fever for the first 24-48 hours, microbial cultures would ideally guide more directed therapy when their results become available. Wholly empirical therapy represents challenges both in treatment and in antibiotic stewardship. Several patients at BCCOE were treated with more than 3 different agents in one neutropenic fever episode, suggesting that the treatment may have been changed following a lack of initial response. The WHO Model List of Essential Medicines recommends intravenous amoxicillin/clavulanate or ciprofloxacin for low risk and piperacillin/tazobactam for high risk neutropenic fever as empirical treatment, with vancomycin, meropenem and amikacin and second choices, but of these only ciprofloxacin is consistently available at BCCOE (World Health Organization, 2017). Ceftriaxone, the most commonly used antibiotic in our cohort, is included in a “watch group” for agents to be prioritized for antibiotic stewardship and reserved for specific indications (World Health Organization, 2017). While treatment was successful in all cases, the use of empirical antibiotics in this population risks generating resistant organisms which could spread within the facility, especially given infection control challenges such as an open ward and patients sharing beds.

Comparisons between the earlier cohort of ALL patients studied by Rubagumya et al (2017) and our cohort are revealing. In the earlier cohort, almost 50% of patients had died by six months, compared to 24% of our patients. The differences between the Hunger 1 and Hunger 2 regimens

are minimal until month 4 of treatment, so it is likely that improvements in supportive care and treatment quality contributed to this change rather than the regimen itself. The most important cause of treatment delay in our cohort was neutropenia, compared to thrombocytopenia in the Hunger 1 cohort, which caused delays in 54% of those patients (Rubagumya, Xu, et al., 2017). Increased neutropenia in the Hunger 2 cohort is likely due to stronger chemotherapy used in the delayed intensification phase; a decrease in delays due to thrombocytopenia suggests access to platelet transfusions has improved. Delay due to medication stockout has decreased from 38% of patients to 6%, which was a single episode of cytarabine stockout (Rubagumya, Xu, et al., 2017). Taken together, these findings suggest that treatment quality and supportive care have improved over time.

The study is limited by the small sample size which makes it difficult to determine associations between risk factors and outcomes and to generalize about baseline features such as immunophenotype. The short duration of the study also limits the ability to determine treatment outcomes and 5-year-event-free survival which are the standardized measures in the literature.

CHAPTER SIX: CONCLUSION AND RECOMMENDATION

ALL remains one of the most common but challenging malignancies to treat in resource-poor environments. This study contributes to the literature by describing the treatment of 17 patients with a reduced-intensity regimen in the context of an implementation-science approach to cancer care. The two most surprising findings in the study were the high proportion of patients who died shortly after arrival at the hospital before being able to start treatment, and the absence of deaths in 18 episodes of neutropenic fever resulting from a regimen of increased intensity.

The literature on treatment of ALL in low- and middle-income countries reveals a great deal of heterogeneity in treatment-related mortality, abandonment and ultimate outcomes. This suggests that the findings from individual programs may not be generalizable, and that the outcomes in each setting are due to an interaction between population, disease, health-system and program factors. Studying the successful aspects of different programs may help to develop a tool-kit of clinical and programmatic approaches to solve whichever problems are most relevant.

In the context of BCCOE, our patient population has multiple risk factors for poor outcomes such as older age, T-cell immunophenotype and a high WBC at presentation; this suggests that low-intensity and reduced-intensity regimens may fail to provide acceptable cure rates. As treatment toxicity has not been a significant problem, upgrading to step three of the Hunger strategy would be an appropriate and necessary step in order to provide patients with a reasonable chance of cure; this has in fact occurred and a new protocol has been approved as of March 2018 incorporating Hunger 2, 3 and 4 regimens to be given to patients according to risk stratification. In light of our experience with toxicity and with very poor outcomes with the Hunger 1 regimen, new ALL treatment programs in similar settings could consider skipping Step 1 of the Hunger protocol and using the Hunger 2 regimen from the start.

Further research should follow this cohort to the end of their treatment and five years of follow-up to determine the outcome of treatment and associations with demographic, disease and treatment factors. Priority should also be given to studying the patients who died before being able to start treatment in order to determine patterns in cause of death and association with risk factors. This could inform life-saving programmatic changes.

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Capstone practicum final report grading scheme

Area	Max score	Score
The Problem Statement Does the Problem Statement describe specifically what the problem is, which issues the capstone will explore, and why they need to be explored?	4	4
Objectives Is the overall objective of the project SMART and clearly stated, providing a clear indication of the expected contribution of the project to the specific organization/institute where the project is conducted? - If included, do specific/secondary objectives clearly outline the steps through which the overall objective will be achieved?	4	4
Background and Justification Does the Background to the Study provide a description of: (i) The significant and topical background issues (historical, current) pertaining to the study; (ii) why the project is being undertaken; and (iii)previous work related to the study? It is expected that the Justification of the project should provide a quick sketch of the proposed solution or study approach and briefly explain how it differs from other works – and within this context, it should make a strong case for why the project is needed, how the results of the study would fill this need and be beneficial; and why it is significant.	4	4
Layout of the Thesis Brief description of each of the chapters of the entire thesis	2	1.75
Literature review To what level and extent has the candidate reviewed, analyzed, and synthesized relevant previous works? Has the candidate: ● reviewed and documented the results of other studies that are closely related to the present study? ● demonstrated that s/he has a comprehensive understanding of the field of study and that he/she is aware of important recent substantive, methodological and theoretical developments in the field of study? ● identified the limitations of past/current research approaches and explained how s/he will build on the strengths of past studies while overcoming their limitations? ● identified potential outcomes of the study and discussed the importance of each?	4 4 4 4	4 3.5 3.9 3.5
Methodology **Project Design and Method**		

● Does the candidate identify which study design had been adopted/used (if any), and then describe, discuss and justify the choice, relevance, and implementation of the intervention?	2	2
Measures ● What type of data/Indicators has the project measured?	2	1.9
Implementation ● Does the data collection method appear to be appropriate? ● Was the data collection tool clearly described? ● intervention appear to be addressing the root cause (if intervention is applicable)?	1 2 1	1 2 0.5
Data analysis ● Appropriate analysis method(s), statistical or coding method(s) (if applicable) described with sufficient detail.	3	3
Results ● Does the candidate present relevant results, without interpretation? ● Are the results obtained using the analysis methods described previously in the report? ● Does the candidate use appropriate tables/figures if applicable?	2 1 1	2 1 1
Discussion ● Does the candidate interpret the results rather than simply restating them? ● Does candidate discuss the factors contributing to the results (success/failure of intervention, if applicable)? ● Does the candidate relate the results to the literature? ● Does the candidate discuss the challenges encountered and steps taken to overcome them? ● Does the candidate discuss the limitations of the project?	1 1 1 1 1	1 1 1 .9 1
Conclusion Does the candidate provide a clear summary of the project, and does the candidate provide recommendations for follow up and future studies?	5	4.75
Adherence to the Guidelines for Writing Capstone Project Thesis The candidate strictly adheres to the guidelines provided for preparing the capstone document. Document is prepared with appropriate structure, format and layout (size 12 font, double-spaced, 1-inch margins); text is well developed and coherent; language and style are clear and appropriate; sources and citation style are correct; and references are high quality and relevant.	5	3
Total	60	55.7 (93.7 %)