Enabling Intensity-Modulated Radiation Therapy
on Older Generation Accelerators and Co-60 Units in Low- and Middle-income Countries

Abstract

Radiation therapy is one of three major modalities beside surgery and chemotherapy to treat cancer. In all treatments it is the goal to destroy the cancer and save surrounding tissue and organs, especially those crucial to survival and the quality of life. Often a compromise must be invoked between these two goals. This is especially true for head and neck cancers that are nestled among critical organs that if harmed in treatment, greatly affect the wellbeing and quality of life of the patient. This is called the toxicity of the treatment. To achieve the best possible compromise between cancer eradication and limiting toxicity the radiation beam is modulated in intensity to provide high radiation intensity to the tumor while curbing the beam intensity to surrounding tissue. This technique developed over the last two decades in the US is called intensity modulated radiation therapy (IMRT) and has matured to involved highly sophisticated hardware (multi-leaf-compensator (MLC-IMRT) married to advanced accelerators and combined with equally complex software that allows to fully control the equipment by computer. This kind of sophistication requires a dedicated infrastructure, prolonged training and demands a high price tag.

The medical system in middle and low income countries (MLICs) often lack all three requirements, infrastructure, training and wealth to acquire state of the art cancer treatment systems. At the radiation oncology department at UNC PI Chang developed a decade ago a compensator-IMRT system that in many way rivals the state of the art scheme currently employed in the US but at a fraction of the cost. Chang’s compensator system was clinically approved and used for treating complicated cancers for more than a decade at UNC. Moreover it was developed to be employed with accelerators that are currently being widely used in LMICs. Chang and collaborators also developed a treatment planning system that allows for compensator-IMRT planning and for quality assurance.

Here we propose to modify the UNC compensator-IMRT system for use in LMICs, especially Brazil and India. We intend to transfer the modified radiation treatment system to the intended medical centers in Brazil and India who have agreed to collaborate with us. In this 2-phase proposal we will demonstrate the feasibility of the technology transfer to developing countries (phase 1) and establish the sustainability of the technology and viability of business plan in developing countries (phase 2).
SPECIFIC AIMS

The goal of this proposal is to offer low- and middle income countries (LMICs) an economical viable alternative to deliver advanced radiation therapy treatment currently delivered in the US and other developed countries by modern technologies that cost millions of dollars. We will modify a low-cost compensator-IMRT technology that we have previously developed and clinical implemented in our institution. We will transfer this technology to LMICs to significantly reduce the high treatment toxicity and improve treatment efficacy for head and neck and other cancers. In the UH2 phase of the project we will focus on the technology feasibility demonstration and transfer. In the UH3 phase we will focus on the establishment of the transferred technology in LMICs and the development of a sustainable business plan for widespread application of the transferred technology.

UH2 Phase (2 YEARS)

AIM1: Preparation of compensator-IMRT technology for LMIC application
  AIM 1.1: Modeling Co-60 irradiator in treatment planning system PLUNC
  AIM 1.2: Modification/simplification of PLUNC for LMIC application
  AIM 1.3: Modification and verification the compensator fabrication process
  AIM 1.4: End-to-end test on the compensator-IMRT program

AIM2: Training of LMIC test site (Brazil) personnel on compensator-IMRT
  AIM 2.1: Training of PLUNC and IMRT treatment planning
  AIM 2.2: Training of compensator fabrication process and IMRT QA

AIM 3: Transfer, Installation and testing the compensator-IMRT technology at the LMIC test site (Brazil)
  AIM 3.1: Installation and testing the compensator fabrication device and fabrication process
  AIM 3.2: End to end test on compensator-IMRT program at test site
  AIM 3.3: Evaluation of the compensator-IMRT program and identifying modifications for sustainability at the test site

AIM 4: Initiation of compensator-IMRT clinical trial at the test site (Brazil)
  AIM 4.1 Pilot clinical use of compensator-IMRT
  AIM 4.2: Compensator-IMRT clinical trial design

AIM 5: Regulatory approval for compensator-IMRT commercialization in Brazil

UH3 Phase (3 YEARS)

AIM 1: Sustainability enhancement of the compensator-IMRT technology in LMIC settings
  AIM 1.1 Compensator materials
  AIM 1.2 Milling machines
  AIM 1.3 Compensator-IMRT QA
  AIM 1.4 Compensator-IMRT treatment planning system and interface

AIM 2: Feasibility demonstration of LMIC compensator-IMRT technology local hub (Brazil)

AIM 3: Business plan development and execution for compensator-IMRT technology application in test site country (Brazil)

AIM 4: Transferring compensator-IMRT technology to a new test site (India)

Aim 5: Development training and education/support infrastructure in LMICs
I. RESEARCH STRATEGY

Cancer is a leading cause of global mortality, which is increasingly pronounced in LMICs with extremely limited health care resources compared to the standard of HICs (high income countries). Cancer patients in LMICs have significantly worse survival than cancer patients in HICs and the disparity is expected to continue to increase [2]. The disparity, however, doesn’t not stop at survival rate; cancer patients in LMICs are also likely to suffer a great deal more while living with the disease. This is largely due to the fact that cancer patients in LMICs do not have access to the advanced medical technologies and procedures that are known to work. Developed countries have the advanced technologies for earlier detection, more accurate diagnosis, and better treatment for many cancers but they are simply out of reach for most cancer patients living in LMICs. In this proposal we aim to significantly reduce treatment toxicity and improve treatment therapeutic ratio for neck and neck cancer patients in LMICs by modifying and transferring a low-cost advanced radiation therapy technology that we have developed and clinically proven at the University of North Carolina. The cost-effective technology was developed by our group years ago using the previous generation equipment we no longer use but that is still widely used in LMICs. We target head and neck cancers because our technology and its alternative modern technology have been proven in the US to reduce severe treatment toxicity and thus open room for better cure for head and neck cancers.

A. Background and Significance

A1. Head and neck Cancers

Head and neck cancers are serious diseases that can be life threatening and debilitating. Every year there are estimated 550,000 new cases of head and neck cancers diagnosed in the world and almost 2/3 of them occur in developing or LMICs[3]. In some LMICs such as Brazil and India, head and neck cancer account for more than 30% of all cancer cases and is the leading cancer site in males and 3rd most common site for females ([4] The high cancer rate is believed to be closely associated with the higher use of tobacco and alcohol, endemic viruses (e.g. Epstein Barr Virus and Human Immunodeficiency virus), and consumption of betel nut (Asia). Unfortunately tobacco/alcohol/betel nut cessation programs have not been effective in LMICs and prevention of viral infection can be costly and difficult. Early detection has a great potential impact but it can be extremely challenging to develop suitable early detection technologies and implementation systems that are feasible for large-scale application in LMICs[5]. The reality is that in LMICs the prevalence of head and neck cancers at later stages are and will continue to be disproportionately higher with poorer survival in LMICs than developed countries[6]. It has been a global effort led by World Health Organization (WHO) to reduce the large gap between cancer[5, 7]. Head and neck cancers have been listed as major cancers of research priorities in a review paper by Sankaranarayanan and Boffetta titled Research on cancer prevention, detection and management in low- and medium-income countries [1] and cancer treatment is ranked as high as prevention and early detection for its role in cancer control (Table 1).

Head and neck cancer themselves cause significant symptoms that adversely affect quality of life. In addition the standard multimodality treatment (i.e. surgery, radiation, and chemotherapy) for head and neck cancer is associated with acute and chronic toxicities rates of up to 40 to 50%[8, 9].

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<th>Table 1. Cancer control measures and research priorities for major cancers in LMIC</th>
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<td>Cancer site</td>
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Head and neck (H&N) cancers are in close proximity to vital anatomic structures that are involved in important physiological and social functions. The tumors are located in the sinonasal area, pharynx (nasopharynx, oropharynx, hypopharynx, larynx), and oral cavity that are near many critical/vital structures (brain, spinal cord, salivary glands, etc.). These anatomic regions and surrounding vital structures are essential for basic physiological functions (eating, swallowing) and critical for personal appearance, expression (talking), and social interactions. Because of the close proximity of these tumors to vital anatomy, head and neck cancer treatments often incidentally and unavoidably cause significant toxicity by radiation damage of surrounding organs: e.g. salivary glands (dry mouth), pharyngeal constrictors (difficulty swallowing), optic structures (blindness), brainstem/spinal cord (paralysis). The impact of the treatment toxicity can be debilitating and even life threatening. To the cancer survivors the long-term toxicity can be more devastating than the cancers themselves. For example, dry mouth and difficulties with swallowing are the most common long term toxicities associated with radiation therapy. Dry mouth affects the types of food choices patients can make, increases the incidence of dental cavities and periodontal disease, and affects speech and swallowing. Radiation can also damage the very muscles that are required for swallowing. These toxicities disproportionately affect patients in LMICs because nutritious food supplies and follow-up oncological care are limited.

A2. Radiation Therapy

Radiation therapy is a major treatment modality for head neck and neck cancers in both HICs and LMICs. Radiation is often the curative and definitive treatment (i.e. surgery can be omitted). In fact, in some LMICs radiation is the most utilized treatment for head and neck cancer [4]. The therapeutic efficacy of radiation therapy depends on maximizing the radiation dose to the tumor, and minimizing it to normal tissues/organs [10]. Unfortunately, LMICs utilize older radiation technologies (see below IMRT section) that have limited capabilities at reducing the radiation dose to the non-cancerous normal tissues and organs that are in close proximity to head and neck tumors. In US and other developed countries there are not only advanced medical technologies for cancer treatment there are also adequate means to manage treatment related toxicity during and after treatment. These resources are practically nonexistent in many LMICs as there are not even enough medical resources to simply treat cancer patients. Fang et al [11] reported that economic status remained the most significant variable correlated with head and neck functional impairment and survivors with better economic status reported less severe impairment. Thus, radiation therapy for head and neck cancers in LMICs is associated with higher rate of toxicity than in HICs due to lack of advanced radiation treatment technologies. Furthermore patients in LMICs suffer significantly more from their radiation toxicities because resources for medical management of toxicities are scarce.

A3. Intensity-modulated Radiation Therapy (IMRT)

The holy grail of radiation therapy is tumor eradication with minimum damage to nearby normal tissue. This is especially challenging for head and neck anatomy- the most complex anatomy to deliver safe and effective radiation therapy. The tumors are often large and irregularly-shaped, and closely surrounded by many critical organs. Figure 1 shows a nasopharyngeal carcinoma surrounded by critical normal structures: left and right parotid glands, left and right globes, optic chiasm, brainstem, and spinal cord. IMRT is an advanced radiation therapy technology/approach that maximally focuses radiation to the tumor while sparing nearby normal tissues [12]. Radiation dose distribution of an IMRT treatment is computer-optimized to conform to the tumor and avoid the critical structures. Compared to the conventional treatment IMRT treatment is a superior radiation treatment for effective tumor control and lower treatment toxicity. Clinical benefits of IMRT for head and neck cancers have also been well documented. Feng et al[13] reported that Chemoradiotherapy local and regional control is not compromised by IMRT that reduces Dysphagia (swallowing difficult) in patients with oropharyngeal cancer. Pow et al [14] reported that IMRT was significantly better than conventional radiotherapy in terms of parotid sparing and improved quality of life for early-stage disease. A random controlled trial recently reported by Nutting et al [15] concluded that sparing the parotid glands with IMRT significantly reduces the incidence of xerostomia (dry mouth) and leads to recovery of saliva secretion and improvements in quality of life, and thus strongly supports a role for IMRT in squamous-cell carcinoma of the head and neck.

In the last two decades real and perceived benefits of IMRT and other high-precision targeting treatment technologies have propelled the radiation oncology equipment industry to a unprecedented technical revolution. As a result new generations of treatment planning systems, radiotherapy electronic data management systems,
delivery automation systems, as well as treatment imaging verification systems have been developed and commercialized. Most of them also carry an unprecedentedly high price tag and require an infrastructure/network to run. More than a decade past the radiation therapy technology revolution IMRT has become a basic feature of treatment planning systems and modern accelerators, and IMRT is the standard of care for head and neck cancer treatment in US today.

IMRT has been shown to benefit head and neck cancer patients in LMICs just as it did in HICs to reduce long-term treatment toxicity in severity of dry mouth and difficulties of swallowing and consequential improvements in quality of life [16]. Figure 1 shows an example of a head and neck IMRT dosimetry using our compensator-IMRT technique. The figure shows that the IMRT treatment significantly reduced the dose to nearby critical organs compared to the conventional treatment currently used in many LMICs.

**A3. Modern IMRT technology not suited for LMICs**

The demonstrated clinical benefits of IMRT for head and neck cancer treatments, however, have not been received by most patients form LMICs. The first and enormous obstacle is the cost of purchase the modern medical linear accelerators that is equipped with automated IMRT functions as Varian accelerators shown Figure 2 (left). Such an accelerator generally cost millions of US dollars but the high purchasing price is not the only hurdle. The modern accelerators deliver IMRT treatment through a complex and automated process that controls and monitors the treatment delivery through a treatment record and verify (R&V) system. Although the benefit of the R&V system is beyond IMRT delivery it is another complex and expensive system to purchase and to manage. The workflow of a radiotherapy treatment using the conventional system is manual and simple, which is drastically different from the workflow of an automated IMRT treatment. For instance, conventional treatments use only 2-5 radiation fields/portals per treatment and the accelerator is manually operated by therapists (who operate the treatment machine and deliver daily treatment to cancer patients). An IMRT treatment requires approximately 100 small portals and each is formed from 40-160 individually controlled multileaf collimator (MLC) leaves (see Figure 1 left), which requires delivery automation. MLC accelerators and record & verify system are complex hardware and software that require interconnectivity via a computer network system. The complex and automated IMRT system inevitably creates more room for error and posts new threats for patient safety. For most radiation therapy centers in LMICs the modern accelerator based IMRT system is not only too costly to purchase they also lack the required technical expertise and new infrastructure to sustain the operation. Other hurdles preventing the implementation of the
IMRT in LMICs include the high cost of IMRT-able treatment planning software, lack of training on IMRT planning and on IMRT QA. For these reasons the IMRT technology widely used in US is not suited for LMICs.

**A4. Compensator-IMRT is ideally suited for LMICs.**

Compensator-IMRT technology is ideal for LMIC settings because it utilizes the treatment delivery technologies and the workflow currently used in LMICs[17]. Therefore expensive modern accelerator and record and verify system are not necessary; there is even no need to change the current treatment delivery workflow. An IMRT-compensator is a physical device custom-made for each patient (and for each treatment field) ahead of time and it is inserted into the head of treatment machine as shown in **Figure 2** (right). The workflow of compensator-IMRT delivery is the same as the wedge-field delivery in the conventional radiotherapy. The core of IMRT treatment delivery is intensity-modulation generation. MLC-IMRT technology generates the intensity-modulation by sequentially delivering of a large number of beamlets (segments) formed by MLC of a modern accelerator via automation (**Figure 2 left**). Compensator-IMRT generates the intensity modulation by converting the uniform intensity radiation of an open field to the desired intensity-modulation through the use of compensator (**Figure 2 right**). Compensator-IMRT has been referred as a “poor man’s IMRT” as it does not require millions of dollars but does requires manual labor. We will show in the Preliminary Data section that

**Figure 2** Modern accelerator automated IMRT delivery with multileaf collimator (MLC) system (left images). Radiation intensity modulation is achieved by sequential irradiation of a number of small fields/segments automatically formed by MLC. IMRT can also be delivered by compensator-IMRT approach (right images) on old generation accelerator or Co-60 unit by the use of compensator that generates the intensity modulation by differential attenuation the radiation before it reaches patient.

**Figure 3** is an illustration describing how IMRT compensator works (by Dotdecimal, a commercial vendor). The open field from the radiation source is converted into modulated radiation as specified by dose optimization before the radiation reaches patient.

**Compensator-IMRT is perhaps the “wise man’s IMRT” for LMICs.**

There are currently two types of IMRT-compensator technologies[16]. One is solid-compensator that is manufactured from a solid piece of metal block by industrial grade milling machine (**Figure 2 lower right**). The other is granule-compensator that is made of recyclable metal granules packed in a Styrofoam compensator-mold fabricated by a less powerful milling machine. Both types of compensator work the same way to produce the intensity modulation as illustrated by DotDecimal (a solid compensator vendor Florida, USA) in **Figure 3**. Dr. Chang (PI) has developed a recyclable granule –based compensator-IMRT technology before the MLC-based and compensator-based IMRT technologies became commercially available. The in-house...
developed compensator-IMRT technology was in clinical use for 14 years (1996 to 2010) and treated 1500 patients at UNC. In 9 of the 14 years we used manual compensator-IMRT side-by-side with the automated MLC-IMRT because the former had shorter treatment time[18, 19]. In 2011 we terminated clinical use of compensator-IMRT as it no longer suited our clinic - we had completed the replacement of older generation accelerators with modern accelerators equipped with automated MLC-IMRT and, more importantly, our workflow was changed based on electronic recording and automation.

The benefit of compensator-IMRT over MLC-IMRT is more than cost saving. Our own and others’ studies have shown that compensator-IMRT has superior spatial resolution[18], less accelerator wear and tear (modern MLC accelerators are less robust than the old analog accelerators), no motion-interplay effect for intra-fractional organ motion[20], and even faster IMRT delivery time[21]. However, despite of undeniable benefits compensator-IMRT has not been widely used in US. The seemingly puzzling fact can be explained by reasons that may not be relevant to LMICs. There is a strong financial incentive for accelerator vendors to promote modern accelerators. Different than LMICs where cancer patients often need to compete with each other to be treated in a cancer center, in US nearby cancer centers compete with each other for cancer patients. Buying the newest technologies is a commonly deployed strategy for the competition. Perhaps the most important reason that compensator-IMRT is not widely used in US is its lack of automation. Instead of delivering the entire IMRT treatment sitting down by a computer keyboard at the control console therapists must go in and out of the treatment room and manually exchange compensators between treatment fields many times per treatment. It is obvious which IMRT technology is preferred by therapists. Automation and electronic record have been totally embraced by the practice of radiation oncology in US and the new generation of therapists is only trained on modern accelerators and on automated treatment delivery. However, in LMICs where most radiotherapy technology is one or two decades behind US, compensator-IMRT technology is the perfect solution to start IMRT with minimum cost and minimum change in workflow.

A5. University of North Carolina is the ideal host for the compensator-IMRT technology transfer

To our knowledge we are the only institution that has developed all aspects of a compensator-IMRT technology (treatment planning and compensator fabrication) and implemented its clinical use. We developed the compensator-IMRT using the same accelerator hardware as currently used in the majority of the radiation therapy centers in LMICs. We have also developed a dose optimization algorithm[22], the brain of IMRT technology, and implemented both the compensator-based and MLC-based IMRT in PLanUNC[23] (PLUNC for short), our in-house clinical treatment planning system (TPS). PLUNC is also an open source research and educational tool. We have distributed a research and education version of PLUNC free of charge for public research and education purposes for the past three decades. Under previous NIH funding we have developed special training modules, documentation, and workshops for PLUNC software. Today we have distributed PLUNC code to several hundreds users from all over the world. For this project PLUNC will be used as the IMRT treatment planning system for the UH2 phase. In UH3 phase of the project we will consider commercializing PLUNC for distribution in LMICs as one of the options for compensator-IMRT treatment planning. To successfully transfer a complex clinical technology that is used by medical professionals of diverse technical and medical backgrounds requires a strong education and training component. We have a long history and success in developing education programs in the Department of Radiation Oncology at UNC. We have a comprehensive radiation oncology educational program including a Radiation Oncology Residency Program for physicians, a Medical Physics Residency Program for medical physicists (Chang is the Program Director), a Medical Dosimetry School for dosimetrists, and a Radiation Therapy School for therapists. We have approximately 20 faculty members with a diverse expertise include radiation oncology, therapy physics, cancer biology, medical imaging, nanotechnology for cancer, and research on radiation therapy patient safety and process improvement. The later program was initiated by the Department Chair Dr. Larry Marks and Dr. Bhisham Chera (co-investigator) and it will play an important role for safe and efficient implementation of the transferred compensator-IMRT technology in the LMIC. UNC has a unique combination of expertise in compensator-IMRT hardware and software technology, research development and clinical implementation, and education and safety to successfully transfer the compensator-IMRT technology to LMICs.
A6. Instituto Nacional de Câncer (INCA) (Brazil) is an ideal test site in LMIC for compensator-IMRT

We selected Instituto Nacional de Câncer (INCA), National Institute of Cancer of Brazil as the first test site for the compensator-IMRT technology transfer because of its unique qualifications. In Brazil 90% of its radiation therapy delivery systems (400 total only) cannot deliver MLC-IMRT and thus can benefit from the transferred technology. More than 75% of cancer patients in Brazil are from low economic class that depend on public services[24]. INCA is a major public institution in Brazil that not only has the necessary resources for the technology transfer but it also has the reputation, influence, and commitment to further spread the transferred technology to many smaller cancer treatment centers within Brazil. Approximately 30% of the patients treated in INCA have head and neck cancers and they can benefit from the compensator-IMRT technology. INCA has Co-60 units and the same older model of accelerators we used years ago to develop and clinically use the compensator-IMRT technology at UNC. This coincident makes it possible for us to expedite the UH2 phase of the project. UNC will donate the entire set of compensator-IMRT technology (equipment/material) to the project for feasibility demonstration. We aim to start pilot clinical use within 24 months. Such a feasibility demonstration will not weaken the value of the test for LMIC as a different treatment delivery system (a different brand of accelerator or a different Co-60 unit) only require modification in geometrical parameters of compensator design that can be easily achieved by future compensator device vendors such as Medintec in Brazil. Due to severe budget constraint and the strong desire to offer IMRT Brazil has already started exploring their own compensator-IMRT approach (a student MS thesis work at University of Brazil, an alternative test site in Brazil). They are very excited about the opportunity to be the test site in this project for the compensator-IMRT technology transfer. They have committed to provide full support needed including the efforts of their staff (physicians, physicists, dosimetrists, technicians and residents) to be trained in compensator-IMRT planning, QA tests, and all aspects of compensator fabrication and usage. Because the INCA radiotherapy department is a referral center for public hospitals for the entire region of Midwest Brazil they can become a local training site to expand the tested compensator-IMRT to others radiotherapy centers in the region and beyond.

A7 Cobalt-60 - the oldest radiation therapy unit still widely used in LMIC

Cobalt-60 represents the oldest generation of megavoltage photon radiotherapy machines still in use today (Figure 4). The first Co-60 unit was built and the first patient was treated in 1951 in Canada[25]. The Co-60 unit has a higher energy (average 1.25 MeV) beam than the orthovoltage x-ray machines and it started to replace the x-ray machines in 1960s to reduce skin toxicity. Today in developed countries Co-60 units have largely been replaced by linear accelerators, which are capable of even higher energy and electronic radiation beam generation and control. Although modern Co-60 units are built (Equinox by Best Medical), older generation Cobalt-60 units are still in widespread use in LMICs because these countries lack the fund to purchase, the expertise to run, and the infrastructure to support the newer radiotherapy technologies. Co-60 unit has reliable machinery, simple operation and maintenance that have made it a sustainable and economical viable radiation treatment technology in LMICs. The disadvantages of Co-60 units include the need for high activity radioactive isotope (which poses security concerns), constant background radiation (although low) for therapists, and lack of electronic and computerized control capacities. We believe that compensator-IMRT technology will give a new life to aged Co-60 units. This is supported by an experimental study by Schreiner et al [26] (Figure 5) that demonstrated that Co-60 radiation is capable of high conformal dose distribution comparable to that delivered by modern technologies (TomoTherapy and IMRT). A dose optimization study by Fox et al [27] showed that a modern Co-60 system with MLC functionality can produce similar quality IMRT plans compared to accelerators with 6 MV beam. In this
proposal we aim to enable the 60+ years old Co-60 treatment technology to deliver similar dosimetric quality IMRT treatments as delivered using modern accelerators. The potential value of our proposal is welcomed by international radiotherapy community[27].

A8 There is tremendous business opportunity in LMIC for compensator-IMRT technology

The benefit of IMRT treatments for treatment toxicity reduction and therapeutic ratio improvement for head and neck and other cancers have been studied, published, and publicized for more than a decade since IMRT was clinically used in developed countries[14, 28, 29]. As a result there has been a great demand for cancer centers in LMICs to acquire IMRT technologies and provide IMRT treatment options to their own patients. However, most radiation delivery equipment (for teletherapy) in LMICs is older generation equipment that is not capable of IMRT functionality. The cost to bring the typical IMRT technologies used in the US to under developed countries is prohibitive even if the initial purchase cost is not an issue because no infrastructure is available and resources to sustain the operation are lacking. For instance, in Brazil, there are about 400 Megavoltage units being used clinically. Of the 400 units about two-thirds are in government facilities and one-third in private clinics. Only 10% of these units can deliver IMRT through conventional MLC solutions. 36 of the units are Cobalt units, which are already in the process of being upgraded for compensator-IMRT application due to a recent initiative by Hemingway (sub-contractor PI) on the of Best Medical the vendor of the Co-60 units. The upgrade increases the mechanical accuracy of the Co-60 unit, which is important for the quality of the IMRT treatment delivered by the units. There is a need for at least 1500 more radiation therapy delivery units in Brazil over the coming years. The compensator-IMRT approach and its successful application in the test site INCA can shape the path of the radiation therapy technology update in Brazil to a more economically viable approach. The government of Brazil is the 6th largest economy in the world, with enormous natural resources and energy independence. The fact that both the current President (Breast Cancer) and former President (Head and Neck Cancer) of Brazil have been victims of cancer also makes cancer treatment more of a national issue to resolve.

The tremendous business opportunity is also afforded because of the low cost of implementing the compensator-IMRT technology. The compensator system cost only a small fraction of the MLC-IMRT for the same clinical outcome. Once the compensator-IMRT technology is modified and transferred to the LMIC test site, feasibility demonstrated, and local hub support established (the specific aims of this proposal) we expect many cancer treatment clinics will be interested to purchase the economically viable proven IMRT technology. The purchase of the compensator-IMRT system can also be fueled by Brazil’s new IMRT billing. Brazil has recognized the value of IMRT and will begin reimbursing in January 2014 for the treatment of head and neck tumors. Reimbursement for IMRT in Brazil will yield about three times the revenues of conventional therapy, which is adequate to cover the cost for compensator-IMRT (but not MLC-IMRT).
B. PRELIMINARY DATA

B1. PLUNC IMRT Treatment planning system

The brain of an IMRT technology is in its treatment planning system (TPS). PLUNC is the in-house TPS we have used for clinical service, teaching, and research for more than two decades[23]. Figure 6 shows a typical screen shot of PLUNC in head and neck planning. PLUNC will be used as the compensator-IMRT TPS by the LMIC test site in this project. Radiation therapy treatment planning is the computer simulation process to design and evaluate radiation dosimetry using a virtual but realistic reality. The patient is represented by a 3D CT image set, the treatment delivery machine by a machine model, and radiation dose deposition in patient’s body by dose computation algorithm. Typically, in a treatment planning process the planner defines the anatomical structures on a CT image of the patient in the treatment position, designs the treatment beams, computes the resulting radiation dosimetry, and evaluates the treatment dosimetry in terms of its clinical relevance. The last three steps are often repeated several times until a satisfactory dosimetry is obtained. In this conventional treatment planning process the planner manually varies several parameters (such as beam portal shape, beam weight, beam orientation) to create a satisfactory plan. For IMRT treatment planning, however, the number of the variable parameters is increased 100s times. Each of the radiation beams is divided into an array of small pencil beams and the weights of the pencil beams are the new variables in IMRT planning. The variables are used by a dose optimization engine in the TPS as fitting parameters in the attempt to reach the treatment goal of tumor control and normal tissue sparing. The dose optimization engine in PLUNC is index-dose gradient minimization algorithm[22].

Figure 7 illustrates the radiation intensity distributions (or intensity maps) from a compensator-IMRT and MLC-IMRT. PLUNC converts the intensity maps directly to compensator files for Par Scientific milling machine compensator fabrication. We use a dose computation algorithm that empirically models the photon beam quality change as it passes through the compensator. The changes include beam hardening, attenuation through high-Z compensator material and the compensator scatter[16] and they can be challenging to handle in commercial treatment planning systems [30-33]. To create a step & shoot MLC-IMRT treatment PLUNC converts each intensity map into MLC segment fields through an iterative optimization process to minimize the impact of the limited spatial resolution of the intensity maps generated by MLC segments and maximize the delivery efficiency.

B2. Comparison of compensator-IMRT and MLC-IMRT

It is important to understand what are the major differences between the mainstream and costly MLC-IMRT technology and the low-cost compensator-IMRT and if they are indeed comparable technologies. We have compared the IMRT plan quality and treatment delivery efficiency and published extensively on the topic [16, 18, 21, 34]. There are mainly three considerations in the comparison: 1) spatial resolution of the intensity modulation, 2) the treatment delivery time, and 3) MLC leaf related issues. We were in a good position to evaluate the impact of intensity modulation resolution as we implemented the compensator IMRT, 4-benk micro-MLC IMRT, and the standard 5mm and 10mm MLC IMRT all in our treatment planning system PLUNC. In early publications we have stated that the fine spatial resolution is important for high dosimetric quality. To improve MLC-IMRT spatial resolution Chang (PI) in 2004 developed a patented MLC-IMRT segmentation algorithm[35] that was used to generate the 4-benk micro-MLC IMRT in an early collaboration with Hemingway (subcontractor PI). Our work [16] has shown that among 3D treatment plan, compensator-IMRT, 10mm-leaf MLC-IMRT the compensator-IMRT is superior for a head and neck case. However, the impact of limited spatial
resolution of MLC-IMRT technology can be largely eliminated using a different approach (sliding window IMRT)[36] or by the use of direct aperture optimization technique[37, 38]. Although there other considerations such as leakage between MLC leaves and finite range of MLC motion it is well accepted that the compensator-based and MLC-based IMRT delivery technologies produce similar plan quality.

Treatment delivery time is a very important and practical consideration especially for treatment centers in LMICs. The treatment delivery time per patient determines how many patients can be treated per day. A common but unproven hypothesis is that the compensator-IMRT takes much longer to deliver than the automated MLC-IMRT. However, our own experience proofed otherwise. We then conducted a multi-institutional study on treatment monitor units (MUs) and treatment delivery time (defined as the time elapsed between the first beam-on time and the last beam-off time of patient treatment). The 6 institutions are UNC, University of East Carolina, Rex Regional Hospital, Moses Cone Community Cancer center, Moses Cone Regional Cancer Center, University of Wisconsin, Christiana Care Hospital. The accelerators used were from all vendors (Siemens, Elekta, Varian, and TomoTherapy). We used actual daily patient treatment timing data recorded in MOSAIQ record and verify system and 421 patients were analyzed. Conventional treatment (non-IMRT) data was used as a control. The result is shown in Figure 8. Our study showed that manual compensator-IMRT actually take less time to deliver than the automated MLC-IMRT. This is finding can be explained by the fact that compensator-IMRT treats the entire field at the same time while MLC-IMRT treats only one small segment at a time and therefore requires sequential treatment of many segments to deliver an intensity modulated field as shown in Figure 2 (Note: newer MLC-IMRT delivery technology may take less time to deliver than what’s shown in Figure 8.)

B3. Compensator fabrication and quality

There are mainly two types of IMRT-compensators in clinical use[16] although more have been investigated[39-43]. The most common used compensator type in US is solid-compensator and is manufactured and sold by vendors (DotDecimal, Inc, US). Solid compensator is milled from a solid piece of metal block by industrial strength milling machine (as shown in Figure 2). The other type is granule-compensator that is made of metal granules (Figure 9 right) in a Styrofoam mold as shown in Figure 9 middle. The mold can be fabricated in-house using a less powerful milling machine and therefore is well suited for in-house fabrication although it is also provided commercially (Axellis Holdings, Inc, US). We have published our proven system for compensator fabrication, assembly, and multi-step quality control for this crucial aspect of granule compensator-IMRT technology. We will made modifications to suit LMIC settings in this project.

Figure 8 Clinical treatment delivery time record of 421 patients as a function of number of fields per treatment in 6 institutions. Manual compensator-IMRT (data with solid line) treatment is generally faster than MLC-IMRT and similar to conventional non-IMRT treatment (data with dash line).

Figure 9 milling machine (left), and compensator mold (middle), and metal granules.
C. Investigators Team

We have assembled an ideal team of experts for the compensator-IRT technology transfer. The investigators team consists of medical physicists in the host and test site, radiation oncologists, software engineers, as well as seasoned professionals in product marketing and distribution in LMICs. The project Principal investigator Dr. Chang is the world recognized authority on compensator-IMRT technology development and clinical implementation. Dr. Chang developed the specific recyclable compensator-IMRT technology to be transferred to the LMIC in this project. Dr. Chang has led the technical development of both the hardware and software of the compensator-IMRT and the clinical implementation at UNC. Dr. Chang’s expertise include IMRT optimization, IMRT quality assurance, and comparison of MLC-based and compensator-based IMRT.[18, 19, 34] Dr. Chang is experienced in leading research and development projects and in working with vendors and multi-institution collaborations. Delano Batista, M.Sc. (co-investigator), is the Head of Medical Physics Department in Instituto Nacional de Câncer (INCA) the test site in the UH2 phase of the project. Batista is an experienced clinical medical physicist and leads the clinical physics clinical and research operation at the test site that this project heavily depends on. His participation and knowledge in radiation therapy technology and practice in LMICs settings (in and outside INCA) are instrumental in this project. He will work under the supervision the PI (Chang) and lead the test site personnel for compensator-IMRT transfer, testing, and clinical implementation in this project (note: because Batista will be paid by the grant UNC grant office asked not to put him on the budget justification). Timothy Cullip, MS (research staff) is an extremely talented clinical software engineer who has been the chief software engineer of PLUNC for the past two decades and wrote the computer code for compensator-IMRT. He will be responsible for any necessary PLUNC software modifications in the project. Randy Hemingway (subcontractor PI) has decade long marketing and sale experience of radiation therapy devices in LMICs. Hemingway has also a diverse experience in the field of radiation oncology from patient treatment to clinic management and to technology development in additional to product marketing and sales. Hemingway is crucial for identifying potential market in LMICs and establishing collaboration between host and test sites, and build business plan.

Physicians’ support and participation is instrumental for the success of this clinical technology transfer. Dr. Bhisham Chera (co-investigator) is the leading head and neck attending physician at the host institution UNC. He has extensive IMRT planning experience using PlanUNC and commercial TPS’ as well as using TomoTherapy (a more advanced IMRT technology). Dr. Chera will provide medical guidance for the technology modification, transfer, and training of the test site physicians. Although not officially on the investigator team Our Department Chair Dr. Larry Marks, a leading authority on radiotherapy-induced normal tissue toxicity clinical research [44, 45], has promised to provide guidance on how to best use IMRT technology to meaningfully reduce treatment toxicity. Drs. Marks, Chera and Chang have close collaboration on patient safety and process improvement [46] which will also benefit the safety and efficiency of the technology transfer in this project.
D. Approach (for UH2 and UH3)

D1. Approach for UH2 phase

**AIM1: Preparation of compensator-IMRT technology for LMIC application**

The goal of this specific aim is to prepare the compensator-IMRT technology and procedures that are developed and implemented at the UNC setting for the transportation, implementation, and testing of the technology in the LMIC test site setting by the test site personnel. Initial modifications of the technology and procedure will be performed in this aim although further modifications are expected throughout the HU2 and UH3 phases of the project as we gain more understanding of the LMIC settings and the practices.

**AIM 1.1: Modeling Co-60 unit radiation in treatment planning system PLUNC**

We will model the test site Co-60 unit in PLUNC treatment planning system. Accurate modeling of radiation delivery machine is crucial for the quality of IMRT treatment dosimetry it produces. Other than beam energy difference a Co-60 unit has also a quite different radiation source model and beam shaping devices compared to linear accelerators. For instance, Co-60 units are known to have a much larger radiation source size (~cm) comparing to that of the typical accelerator (~mm). We will use the Co-60 machine commissioning data from the test site and commission PLUNC in a similar manner as we commission accelerators for non-IMRT treatment including tuning the 3-source model currently used in PLUNC. We may require more data to be taken by the test site. Once the non-IMRT treatment of the Co-60 unit is commissioned we will pause the commissioning process and resume the compensator-IMRT commissioning in AIM 3 when the test site can collect compensator-IMRT data on their own treatment machine.

We will also model the older generation accelerator(s) at the LMIC test site for non-IMRT treatment. We expect this task is straightforward as the accelerator should be similar to the accelerators we have modeled in PLUNC already.

**AIM 1.2: Modification/simplification of PLUNC for LMIC application**

We realize that our inhouse treatment planning system PLUNC is designed to be used in academic institution settings in developed countries. In this aim we will define the needed simplifications and modifications for LMICs settings with the help of test site team and the vendor team and create a dedicated compensator-IMRT PLUNC software version that is safe, simple, and efficient in compensator-IMRT treatment planning. The simplification process includes disabling features that are not suited for LMIC settings and features are only used for research. Data input and output should be targeted to the test site settings. We realize that the software modification is an ongoing process in the project as the host institution gains more understanding of the test site and as the test site team gains more understanding of PLUNC and IMRT.

**AIM 1.3: Modification/verification of the compensator fabrication process**

The compensator fabrication process preparation starts from compensator file data transfer from PLUNC to the milling machine, milling machine configuration, Styrofoam mold milling process, compensator mold QA progress, compensator mold assembly, granule compensator material filling, and final assembly of the compensator box (shown in Figure 10) that is inserted into the head of treatment machine used (Figure 2). Different than the solid compensator that is machined from a solid piece of metal the manually assembled granule compensator needs special care to ensure the consistency and integrity of the compensator through the course of patient treatment. Detailed fabrication procedures must be followed to ensure the compensator quality. We have established such a procedure for our clinical use years ago[16]. We will use Figure 10 Compensator box with a tin granule-filled compensator enclosed (left) and a Styrofoam compensator mold (right). The three reference holes on the mold and the matching set on the box for easy verification of the compensator orientation in the box. The compensator box is designed to fit the specific therapy machine.
the experience gained in our own clinical practice to modify and then verify the important compensator fabrication process and QA process before the training of LMIC staff and the technology transfer. The verification and modification (if needed) process will be repeated again at the test site for the specific Styrofoam mold material and the metal granule material used.

**AIM1.4: End-to end test on the compensator-IMRT program**

We will conduct an end-to-end test for the modified compensator-IMRT program using the older generation accelerator at UNC. A typical head and neck cancer patient case as shown in Figure 1 will be used to create a compensator-IMRT plan. A corresponding MLC-IMRT plan will also be created for reference. The MRT-compensators will be fabricated and used for IMRT QA measurement using MapCheck (Sun Nuclear, FL USA) a standard IMRT QA dosimetry device. Figure 11 shows an example of the compensator-IMRT QA we achieved before. We used the identical IMRT QA device and process for MLC-IMRT treatment in our clinic. We will use the commonly used QA metrics and pass/fail criteria. Note that our own study and others have shown the 2D IMRT QA pass/fail criteria have poor correlation with clinical impacts of the lesser errors (caused by known uncertainties) found in the IMRT QA [47, 48]. We will consider modifying the IMRT QA metrics and criteria if they become available in the future. Once the compensator-IMRT system is installed and tested at the LMIC test site the end-to-end test will be performed again to ensure the quality of the compensator-IMRT program there.

**Risk and Remedies:** Although we have never modeled Co-60 treatment machine in PLUNC we are confident that the 3-source model (Figure 12) is powerful and flexible enough for Co-60 beams. We have gained extensive experience in the compensator fabrication process and do not expect significant risks in carrying out this aim.

**Aim 2: Training of LMIC test site (Brazil) personnel on compensator-IMRT technology**

Two core team members (a medical physicist and a head and neck cancer radiation oncologist) will come to the host institution UNC to learn all aspects of the compensator-IMRT for clinical application.

**Aim 2.1 Training of PLUNC and IMRT treatment planning**

We will provide a hand-on training of the PLUNC treatment planning system to the test site radiation oncologist and the clinical physicist. We have trained a large number of residents (medical residents, medical physics residents, as well as dosimetry students) for PLUNC usage and will follow the existing training material (test cases, checklist, and quiz) for the training of the test site team. For the test site physician we take the specific needs of the test site into consideration and tailor the training accordingly. For instance, if the physician already has experience in IMRT we will focus on the IMRT features specific for PLUNC and specific for compensator-IMRT. We will focus on the training on head and neck IMRT planning. For the test site clinical physicist we will add IMRT dosimetry verification, planning, and data input/output. PLUNC commissioning of compensator-IMRT will also be the training topic for the physicist.
Aim 2.2 Training of compensator fabrication process and IMRT QA

We will train the test site physicist on all aspects of the compensator fabrication and quality assurance process. The same equipment and procedures (or modified ones) will be used at the test site. The training includes compensator file transfer from PLUNC to the milling machine, milling machine configuration, machine operation, compensator mold preparation, compensator mold, QA, metal granule filling technique development and QA, assembly of the compensator system, and final compensator QA.

We will pay special attention to the commissioning of the IMRT compensator fabrication process. The tungsten granule packing density in the compensator mold is crucial for the quality and consistency of the IMRT treatment. We have developed an easy to follow instruction to achieve a consistent packing density in our clinical practice at UNC for 14 years. This is proven by the result from our routine IMRT QA, which we do for both compensator- and MLC- IMRT clinical treatments. We saw no more QA errors for compensator-IMRT than MLC-IMRT. In fact, we saw more errors in MLC-IMRT QA cases because of the known uncertainty in LMC leaf position (mm). We will train the test site physicist on the commissioning of the compensator granule packing procedure that includes training of the packing technique, measurement of the packing density variation, and measurement of the dosimetric impact. Figure 11 shows an example of the comparison between the calculated dose and measured dose of a test compensator, which demonstrates the quality of the compensator-IMRT technology at UNC.

Risk and Remedies: We do not anticipate major risks in this aim.

AIM 3: Installation and testing the compensator-IMRT technology at the LMIC test site (Brazil)

We will transport the entire compensator-IMRT system hardware and software at UNC to the test site for the feasibility demonstration. UNC will donate the milling machine, tungsten granule material, and all other compensator devices and materials to the project to speed up the LMIC setting feasibility demonstration and to save cost. The compensator-IMRT treatment planning software PLUNC will also be given to the test site free of charge. Although other hardware and software will be considered in UH3 phase for future commercialization in LMIC settings using these available systems will not diminish the value of testing the portability of the technology.

AIM 3.1: Installation and testing the compensator fabrication device and fabrication process

We will ship the entire compensator-IMRT system to the test site (INCA of Brazil). Ventana will facilitate the import tax related issue of the shipping. We will assist the local personnel from Medintec, the Brazil partner of Venenta LCC) and INCA physicists to install the system. We will follow the same procedures as we used in the training at UNC (AIM 2) and make modifications to the system as needed. We will perform detailed dosimetric verification and quality assurance on IMRT phantoms as we did in USA at UNC. That QA/QC in phantoms will be done according to IAEA guidelines.

AIM 3.3: Evaluation of the compensator-IMRT program and identifying modifications for sustainability at the test site

An end-to-end phantom test of the compensator-IMRT program will be conducted at the test site by the test site clinical physicists with the assistance from the host institution physicists. We will follow a similar procedure as we used in the end-to-end test described in AIM 1 and 2. When the phantom test is successful we generate a compensator-IMRT program commissioning report stating the technology is ready for clinical use. The report will be submitted to the Head of Medical Physics and the Chair of Radiation Oncology at INCA for permission for limited clinical use. We anticipate that the experience gained so far in the compensator-IMRT technology transfer will identify a number of modifications that must be addressed for LMIC application. We will make necessary modifications accordingly either on the current system (if possible) or on the future system to be used in UH3 phase of the proposal.

Risk and remedy: We anticipate minor potential issues that can arise from the difference in Styrofoam material. We use a high density Styrofoam material in the US and the high density Styrofoam material might be different at the test site. The solution is to be very diligent in compensator fabrication test and QA procedure and modify it if needed to achieve similar quality.

AIM 4. Initiation of compensator-IMRT clinical trial at the test site (Brazil)
In this last aim of UH2 phase proposal we will start clinical use of the compensator-IMRT at the test site and finalize the feasibility demonstration. Although commercial product for clinical use requires Brazil regulatory approval the test site Instituto Nacional de Câncer (INCA), the reference institution in oncology for the Ministry of Health of Brazil, has the privilege to evaluate the compensator-IMRT technology in clinical use under careful control and monitoring of the institution.

**AIM 4.1 Pilot clinical use of compensator-IMRT (Brazil)**

Five head and neck patients will be treated in the pilot study. All patients will be selected palliative cases that can benefit from IMRT treatment as determined by test site physicians. The IMRT treatment plans will be individually reviewed by the host institution (UNC) team (radiation oncologist and clinical physicists) and the test site team (INCA). Figure 13 (used in UNC for every head and neck patient for plan evaluation) will be used as a reference to evaluate the quality of the IMRT treatment. The compensator-IMRT program commissioning report will be reviewed and approved by the test site clinical leadership (Head of Physics and Department Chair) before the first clinical use. Dr. Chera from UNC will review the pilot head and neck IMRT plans before clinical use.

We will start with the pilot clinical use on one patient first and add more patients after the first 5 treatments of the first patient have been successfully completed. In vivo dosimetry will be used to validate the IMRT delivered dose. Any issues discovered will be directly reported to the INCA clinical service team. We will terminate the pilot clinical use if there is any indication that the compensator-IMRT patient treatment has errors that negatively affect the patient. In this case, we will identify the source of errors, make corrections, and repeat the steps in the previous aims depending the nature of the error.

**Figure 13** The automatically generated summary sheet in PLUNC that shows the IMRT treatment planning goals for treatment target volumes, the critical organs. Green indicates the goal has been met and red means the goal has not been met.

**AIM 4.2 Clinical trial design**

Once we successfully applied the compensator-IMRT technology in the pilot clinical use we will carefully design an appropriate clinical trial to answer specific questions on the efficacy of compensator-IMRT for head...
and neck cancers. Currently, there are few published compensator-IMRT clinical trials. The only study is by Nangia et al from Batra Hospital and Medical Research Centre, New Delhi, India on 18 head and neck patients using MLC capable modern accelerator [49]. They reported that compensator-based IMRT is feasible with regard to target coverage and parotid volume sparing. And parotid volume dose has significant clinical implications on the grade of xerostomia. It is quite interesting that they used a compensator approach while their accelerator (with MLC) is capable of automatic IMRT delivery using MLC collimator. We plan to use a similar approach to design our clinical trial. We aim for a study of 40+ patients with median follow-up time of 12 months. We will collect clinical endpoints of complete response rate, locoregional relapse-free rate, and disease-free survival rates, as well grade I and II xerostoma. The treatment target and organs at risk dosimetric parameters collected will be the parameters used on the goal sheet as shown in Figure 13. LMIC cancer centers like INCA are treating significantly more patients than in the US. It is likely that clinical trials can be faster than in developed countries where strict regulations often hinder the process. Once completed we plan to publish the clinical study to improve and promote compensator-IMRT application. We plan to carry out the clinical trial throughout the UH3 phase of the project.

**Risk and Remedies:** We do not anticipate major issues in pilot clinical application at the test site. The clinical trial design may be simplified to better suit the LMIC setting, as data collection for cancer patients traveling from rural areas for treatment can be challenging to follow up. INCA is a major cancer research and treatment institution in Brazil and their physicians should be familiar in clinical trial design. In case help is needed, our hosting institution physicians (Drs. Chera and Marks) can help to design and review the protocol. We aim to report on the initial data analysis of the clinical trial by the end of the UH3 phase.

**AIM 5: Regulatory approval for compensator-IMRT commercialization in Brazil**

A critical part of making a medical advancement available for clinical use is to meet the requirement of a nations’ regulatory clearance. In the test site country Brazil there are 2 processes required to equivalence of Good manufacturing Practice and Good Distribution Practice (GMP/GDP) and Product registration (ANVISA). We will directly file for both processes in Brazil since we have Medintec (a company resides in Brazil) to process or manufacture the compensator-IMRT products. Although we may ultimately file for the FDA 510 (k) equivalence latter for general LMIC application, the fastest and easiest path is to file in Brazil. There are also incentives if we manufacture in Brazil. Taxes for Import/Export are much favorable to make the product economical viable. Neighboring countries have free trade agreements with Brazil and this will make the expansion of the compensator-IMRT regionally very feasible once we have established it in Brazil.

Our approach is to utilize a local host for our GMP/GDP application under an agreement Ventana (a US small business) has with Medintec (Brazil) for our product registration (ANVISA). Medintec is a partner with Ventana in this project. Medintec has GDP/GMP and has the rights to offer their manufacturing plant as a partner under the Health Ministry guidelines. Utilizing a Host, we will save no less than 2 years and significant costs in establishing GMP in Brazil. Ventana will create the documentation including but not limited to manuals, test data, brochures, and submission documents. These documents are quite similar to the FDA process and will most likely be utilized at a later date for the FDA. We will utilize Raquel Benedetto, MS as our consultant to assist in the process and submission of the registration. We will prepare documents in both English and Portuguese, and prepare some documents for a Certified Translation Process. After payment of fees and submission to the Health Ministry, we anticipate a 6- month or less clearance process. We also feel that this process will be expedited as it benefits the Health Ministry in their clinics. We plan the submission in Year 2 of UH2 phase, with the anticipation of Clearance within early Year 3, the first year of the UH3 phase. Compilation of the needed documents will take place during the first Phase of this project. Once completed with Brazil, we will begin work on regulatory clearance in the United States. FDA 510(k) Clearance will allow us to market in many other countries including India.

**Risk and Remedies:** We do not anticipate major issues in this aim.
D2. Milestones (timelines) for UH2

Year 1:
- AIM 1.1: Modeling Co-60 therapy machine in PLUNC (Q2)
- AIM 1.2: PLUNC user interface ready for LMIC setting (Q1)
- AIM 1.3: Compensator fabrication process modified and verified (Q2)
- AIM 1.4: Compensator-IMRT technology is ready for the LMIC test site staff training (Q3)
- AIM 2: Initial training of test site staff at UNC (Q3)
- AIM 3: Transfer the compensator fabrication system to the test site (Q4)

Year 2:
- AIM 3.1: Installation the compensator fabrication system to the test site (Q1)
- AIM 3.2: Complete testing of the compensator fabrication system to the test site (Q2)
- AIM 3.3: Compensator-IMRT ready for pilot clinical use (Q3)
- AIM 5: Submit applications to Brazil GMP/GDP for compensator-IMRT product commercialization (Q4)
- AIM 4.1: Clinical use of compensator-IMRT (Q4)
- Journal publications and national and international meeting presentations (Q4)

Risk and Remedies: We understand that the milestones and timelines seem to be tight. But we are confident that we can reach the milestone if the transportation of the equipment from the US to Brazil is on time. This is because we have total control of the inhouse developed compensator-IMRT technology, especially the control of the software and electronic interconnectivities, and we use the same equipment and procedures as we have successfully used at the host institution (except for the modifications) for the feasibility demonstration at the test site. In case the equipment shipping is delayed extensively we will consider to purchase a new milling machine using the available fund originally allocated for compensator material and other items of less impact.
D3. Approach for UH3 phase

In this second phase of the project we will modify the compensator-IMRT technology based on the experience gained from the feasibility demonstration at one LMIC test site (UH2 phase) and enhance and expend the platform for wide clinical use of compensator-IMRT in Brazil, India, and other LMICs.

AIM1: Sustainability enhancement of the compensator-IMRT technology in LMIC settings

<table>
<thead>
<tr>
<th>Material</th>
<th>Pro</th>
<th>Con</th>
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<tbody>
<tr>
<td>Cerrobend (with and without mold)</td>
<td>• readily available</td>
<td>• need an industrial strength milling machine (without mold) or a to be developed fabrication method (with mold)</td>
</tr>
<tr>
<td></td>
<td>• inexpensive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• recyclable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• high density</td>
<td></td>
</tr>
<tr>
<td>brass/steel/lead (cube or sheet)</td>
<td>• no milling required</td>
<td>• poor IM resolution due to discreteness</td>
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<tr>
<td></td>
<td>• recyclable</td>
<td>• can be labor-intensive for assembly.</td>
</tr>
<tr>
<td></td>
<td>• inexpensive</td>
<td>• can be hazardous (lead)</td>
</tr>
<tr>
<td>Lucite (solid)</td>
<td>• easy to machine</td>
<td>• low density thus low IM magnitude</td>
</tr>
<tr>
<td></td>
<td>• nonhazardous</td>
<td>• need a milling machine</td>
</tr>
<tr>
<td></td>
<td>• nonhazardous</td>
<td>• not recyclable thus can be expensive</td>
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<tr>
<td></td>
<td>• recyclable</td>
<td></td>
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<tr>
<td></td>
<td>• can produce smooth IM</td>
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</tr>
<tr>
<td></td>
<td>• high mechanical integrity</td>
<td></td>
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<tr>
<td>tin/steel (granule in mold)</td>
<td>• high IM resolution</td>
<td>• medium density</td>
</tr>
<tr>
<td></td>
<td>• nonhazardous</td>
<td>• need a milling machine</td>
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<tr>
<td></td>
<td>• recyclable</td>
<td>• manual control packing density</td>
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<td>• consistent packing</td>
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<td>• high density</td>
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<td></td>
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Table 2. Pros and cons of selected materials for the IMRT compensator

we need to find reliable and economical source of compensator material. In this aim we will investigate the availability of several high density granule materials (tungsten, tungsten alloys) in LMICs countries, their cost, and their packing performance for the compensator application. We will also investigate the use of Cerrobend as a compensator material. Cerrobend is an extremely attractive compensator material as it is already been used in practical every LMIC radiation therapy clinics in LMICs to define the radiation field on older generation therapy machines including Co-60 units. It would add no additional cost to use the same Cerrobend for compensator-IMRT. Cerrobend is a low melting temperature lead alloy containing Bismuth, Lead, Tin, and Cadmium. When it is poured into a mold it forms the given shape in solid form in minutes. Cerrobend has not been used for compensator purposes because currently we have no fine control on the smoothness of the surface (very important for the quality of compensator) when liquid Cerrobend solidifies. However, there are several known but less investigated approaches we will explore in this aim as a remedy to the uneven surface problem including new designs of the temperature-controlled Cerrobend cooling station and the new reservoir of liquid Cerrobend.

AIM 1.2 Milling machines

We will use ACD-3 milling machine from Par Scientific (Odense S Denmark) in the test phase of UH2 for compensator fabrication as we have gained tremendous experience with the system at UNC. For broad application in LMICS settings we will investigate other equipment that are 1) low cost (ideally $5000 or less instead of 20,000), 2) easy to use, 3) good connectivity with TPS, and 4) capable of large compensator depth and size. The latter is very important for the quality of IMRT for cases require large amplitude of intensity modulation[16]. The potential compensator mold fabrication systems we will investigate are other commercially available milling machines and modern 3D printers. 3D printer for compensator-IMRT application has already been investigated in a Master thesis work of the University of Brazil cancer center, which has great enthusiasm for this proposal (see Letter of Support). Their preliminary study has shown potentials of such application and we will take advantage of their work and investigate further this modern and portable approach for compensator
fabrication in LMIC setting. The key for the 3D printer approach is economic viability – the cost of the printer and the printing (mold) material need to go down in cost to a few thousands of dollars and under $50 (per compensator material) to be considered as a strong competitor to the compensator milling machine. We think a 3D printer is a promising potential as they are increasingly popular tools for increasingly broad applications large and small. In this aim we will focus on compensator mold fabrication systems that can be used clinically in the next few years.

**Aim 1.3 Compensator-IMRT QA**

We will investigate compensator-IMRT QA devices and systems that are lower cost, easier to use, and produce the same quality as the currently used device ($15,000). There are several alternative approaches available now or in the near future that will be studied and tested in the aim. The systems include the GAFchromic film and scanner approach (currently used in the US) and a low-cost experimental nanocrystal optical detector system [50] for dosimetry of photon and electron radiation from accelerators as demonstrated by the inventor and the PI (Chang). We aim to reduce the cost of IMRT QA device to $5000 or below. Note that the QA include the radiation detection system, data transfer, and data analysis systems.

**Aim 1.4 Compensator-IMRT treatment planning system and interface**

A treatment planning system is the brain of IMRT technology and we must find a viable treatment planning solution for the wide compensator-IMRT application in LMICs. There are many sites that have acquired commercially available Treatment Planning Systems that do not include IMRT Optimization. Some of the units include Eclipse (Varian), XIO and Monaco (Elekta), Pinnacle (Philips) and Prowess. We will evaluate the possibility of interfacing with these commercial treatment planning systems with the compensator mold fabrication device. We will develop a “Black Box” interface solution to allow these commercially viable systems to seamlessly communicate to our compensator-IMRT solution. We will need to assess our solutions requirements to each TPS individually and create a compliant interface, test and validate the solutions. The quality of the commercial treatment planning system will be commissioned for compensator-IMRT application using test compensators to validate the dose computation accuracy as shown in **Figure 11** previously.

The biggest hurdle of the commercial treatment planning system solution is the high cost. We hope the low cost solution we provide in this project for wide application of compensator-IMRT in LMICs will lead to a significant reduction in the commercial treatment planning system to a LMIC affordable price. In this aim we will also investigate the path to commercialize PLUNC for compensator-IMRT application - negotiate the license agreement with the University of North Carolina, obtain regulatory clearance in using the system commercially in the countries of interests, and develop a business plan to support the commercial effort.

**Risk and Remedies:** We do not anticipate treatment planning and interface issue in this project for feasibility demonstration of compensator-IMRT clinical use in LMICs. We do anticipate potential issues in establishing connectivity between the “black box” and the commercial treatment planning systems. The TPS vendors might need to modify their treatment planning systems for the task and it may take longer time than we expect. Our other option of commercializing the PLUNC software for compensator-IMRT treatment planning will bypass this issue as we have total control of the software.

**Aim 2: Feasibility demonstration of LMIC compensator-IMRT technology local hub (Brazil)**

Safe and reliable clinical application of the compensator-IMRT in LMIC settings has different requirements than that of the modern IMRT delivery systems in the US. Treatment delivery from the modern system relies largely on automation that can be set up one time and recalled from computer for daily treatment. Compensator-IMRT technology is largely manual and need to be performed every time when compensator is fabricated and used for patient treatment. Our years of experience in clinical use of our compensator-IMRT in a US academic setting taught us that periodic training/education is very important for the consistency in the quality of the compensator-IMRT program after its initiation. In LMICs settings technical and medical resource and experience in compensator-IMRT (or IMRT in general) are very limited. We will remedy the situation by establish a local hub as the first line of support for regional compensator-IMRT application. The local hub is instrumental for the success of the widespread compensator-IMRT application. The local hub is instrumental for the success of the widespread compensator-IMRT application. The local hub is instrumental for the success of the widespread compensator-IMRT application. Both the Brazil test site INCA and the University of Brazil have shown the strong interest to be the local hub in region of Brazil. They are well suited for the task as they have the resource and influence as well as connection to small centers to provide the
first line help to implement the compensator-IMRT in their centers. In this aim we will establish a test local hub for Brazil with the collaboration of INCA (HUB as an alternative). We will establish 1) a regular format of communication with UNC with the local hub, 2) a system for the local hub to communicate with small cancer centers interested in or have the compensator-IMRT system already, 3) definition of the service/help to be provided by the local hub, 4) the assistance needed from the host institution UNC, and 5) the business plan to sustain the local hub.

**Risk and Remedies:** We anticipate practical and solvable issues in establishment of the local hub. We expect to be able to find remedies needed. The smaller radiotherapy clinics we intend to expend the compensator-IMRT technology to in Brazil already have close connection with the test site. The host institution has extensive experience in organizing regional and national workshops.

**AIM 3: Business plan development and execution for compensator-IMRT technology in the test site country (Brazil)**

Ventana will partner with Medintec to commercialize the compensator-IMRT technology in Brazil. Ventana (the US industry partner of the project) will commercialize the compensator-IMRT technology and service through the partnership with Medintec in Sao Paulo, the largest third party service company in Brazil, if the project is successful. Ventana will license any specific compensator-IMRT technology that is developed by UNC for commercialization through UNC Office of Technology Development. Medintec has the local sales force and regulatory clearance that will simplify Ventana's entry into the marketplace.

**We plan to open up the compensator-IMRT market in Brazil though the influential test site INCA.**

The National Cancer Institute (INCA) plays a multiple role in all areas of cancer prevention and control in Brazil - prevention, epidemiological surveillance, treatment, information, education and research. As a technical branch of the Federal Government, under the direct administration of the Ministry of Health, INCA delivers cancer care within the Integrated Public Health System (SUS) and formulates and coordinates public policies, develops research activities and disseminates practices and knowledge on medical oncology. Due to its patterns of excellence, which are comparable to the world’s major cancer care centers, INCA has become a national and international model in cancer control. INCA delivers complete cancer care at no cost to its patients with an average of 8,500 new admissions, more than 240,000 consultations and approximately 13,000 inpatients. INCA’s outcomes are comparable to the best oncology centers in the world due to sophisticated systems, which provide online data to all its units and help monitoring our patients. The analysis of information leads to continuous and effective improvement in all practices providing the population with quality in cancer care. INCA is now on track for accreditation by the Joint Commission on Accreditation of Healthcare Organizations. That means that we submit to evaluations of our compliance with international hospital standards on a continuing basis. Therefore, if we successfully competed the specific aims of this proposal including the feasibility demonstration at the test site INCA, we have opened up great business opportunities for compensator-IMRT in Brazil and in other LMICs.

**We aim Brazil SUS cancer treatment facilities at the first customers.** There are over 270 SUS (Public Health System) facilities in Brazil (government funded) that are most interested in providing cost-effective advancement cancer treatment like compensator-IMRT. The INCA has direct influence and connection with the SUS hospitals through staff training and establishing standardization of treatment throughout the SUS facilities. The training and local hub proposed in the project will lay down the infrastructure needed for safe and successful clinical application and for the success of the business. We will look at best paths to move outside Brazil into neighboring nations to penetrate all viable neighboring countries. Although Brazil hosts half of the Latin American population, neighboring nations have greater needs in enhanced radiation therapy delivery. We will look closely at the manpower, tools and marketing to enter local-regional markets.

**Risk and Remedies:** We anticipate challenges in the development and execution of a strong business plan. The success of the business plan depends on the success of the feasibility demonstration of compensator-IMRT in LMIC test sites and of the local hub to support the expansion of the technology as well as the IMRT reimbursement in LMICs. From the strong support we received already from the two national cancer institutions in Brazil and India and from our international colleagues we know compensator-IMRT is the right solution for MLICs. The recent established IMRT reimbursement in Brazil will be a great help for the success of the business plan.
AIM 4: Transferring compensator-IMRT technology to a new test site (India)

We have selected the Tata Memorial Centre as the second test site in LMIC India. TATA Memorial Centre is a renowned center for clinical service and research institution in LMICs. TATA is a classic example of private philanthropy augmented by Government support with a mandate for Service, Education & Research in Cancer. TATA has two sites: Memorial Hospital (TMH) and Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), each has a 50/50 mixture of older generation systems (Co-60 units and accelerators without MLC) and state-of-the-art equipment (Truebeam accelerator and TomoTherapy). We are very happy that Department of Radiation Oncology of Tata Memorial Hospital (Dr. S. K. Shrivastava MD DNBR, Head of the department) has agreed to be the test site for this project.

We will test the modified compensator-IMRT technology initially tested in INCA Brazil in TATA India in this second phase of the project. We expect to encounter new issues in TATA that we have not seen in INCA because the potential difference in treatment approach, patient population, and operation style between the two cancer institutions. Perhaps more so than INCA TATA has a strong research and educational resource that will be used to evaluate, improve, and implement the compensator-IMRT to a new standard that is best suited for the LMIC setting and has the best quality and efficiency in clinical use. For the India and south Asian market we also need to re-evaluate the compensator fabrication technology and material. In this region of the world and this time (2-3 years later than INCA) there may be a better (more cost-effective) fabrication process for TATA. TATA has similar influence to the smaller cancer treatment facilities in India as INCA in Brazil. We will follow a similar path as in the UH2 phase to education and training and for broader application of compensator-IMRT in India and nearby LMICs such as Thailand. We expect that once this two test sites, INCA and TATA, have successfully completed the feasibility demonstration of compensator-IMRT technology for head and neck cancer treatment we will have largely proven the feasibility and benefit of compensator-IMRT and opened up its market potential in LMICs.

Risk and Remedies: We do not anticipate major issues in this aim.

AIM 5: Development training/Education and Support infrastructure in LMICs for compensator-IMRT

We propose to develop the infrastructure for sustained compensator-IMRT clinical use in LMICs at the end of the project. Conceptually, most people believe in the low cost compensator-IMRT for developing counties. The reality is, however, that few cancer centers, large or small, in developed or developing countries, have used this proven technology clinically other than UNC where we have used the compensator-IMRT system clinically for 14 years and treated 1500 patients. There are several reasons for the lack of wide application in LMICs. The most important reason is a commercial solution that is well suited for LMIC settings where technical resource is extremely limited. The business plan has addressed the commercialization solution. Another reason is the lack of education/training and support. The local hub concept and feasibility demonstration (AIM 2) is the first step of the much needed infrastructure building.

In this aim we will develop training materials (manuals), educational materials (sample compensator-IMRT plans and QA results, clinical procedures), online presentations from the host institution (UNC), LMIC test sites, and small radiotherapy clinics that have adapted the compensator-IMRT, and workshops in LMICs. Brazilian Society of Radiation Oncology and Physics will be targeted for presentations, demonstrations and workshops. The neighboring nations of India, such as Vietnam, Cambodia, Thailand, Malaysia and Indonesia, are the LMICs we will target for education of compensator-IMRT technology. We will use the online tools to facilitate timely communication in the LMIC compensator-IMRT group. Ventana and the academic institutions (INCA and TATA) will jointly develop a plan to support this effort. We will establish “centers of excellence”, such as INCA and TATA, to train the technology adaptors. We will establish a team of applications and clinical experts to perform training and ensure that manuals and training materials are consistent with language and knowledge base. We will solicit partnerships with academic institutions in University setting that train Physicists and Physicians in Radiation Oncology. While seeking the best partners for marketing, we will also solicit collection of clinical outcome data to substantiate the value of our technology to the improved outcomes.

Risks and Remedies: We do not anticipate major risks in this aim.
AIM 6: Data analysis of the compensator-IMRT clinical trial at Brazil test site

We will analyze the data we collected so far on the clinical trial designed at the end of UH2 phase and started at the beginning of the UH3 phase. We understand that clinical trial can be slow but we expect to perform initial correlation analysis and dosimetric comparison between conventional treatment and IMRT, and between compensator-IMRT and MLC-IMRT for head and neck cancer treatment. We expect to produce joint publications on the clinical application of compensator-IMRT technology in LMICs in this aim.

Risks and Remedies: It is possibly that clinical trial and/or data collection process are much slower than we aimed in the LMIC setting. In this case, we will carry out and publish in terms of case studies and dosimetric studies to share the compensator-IMRT experience in the test site to LMIC radiation therapy community.

D4. Milestones (timelines) for UH3 phase

Year 1:
- AIM 4: Transferring compensator-IMRT technology to a new test site in India (Q2)
- AIM 3: Brazil regulatory approval for commercialization of compensator-IMRT product (Q4)

Year 2:
- AIM 2: Establish the demonstration of Brazil local hub (Q2)
- AIM 3: Completion of testing of the compensator fabrication system at India test site (Q1)
- AIM 4: Compensator-IMRT ready for pilot clinical use in India test site (Q2)
- AIM 4: Clinical use of compensator-IMRT in India test site (Q4)

Year 3:
- AIM 1.1-2: Selection of suitable compensator fabrication material and device for LMIC (Q1)
- AIM 1.3: Complete compensator-IMRT treatment planning solution (Q1)
- AIM 5: Demonstration of training/education and support infrastructure in LMIC (Q4)
- AIM 4 (UH2): Initial publication on the compensator-IMRT clinical trial (Q4)

Risk and remedies: Commercial solution of compensator-IMRT can be complicated/delayed by connectivity issue if current commercial treatment planning systems are used, and by license agreement process with UNC if PLUNC is modified as the treatment planning solution. These commercialization processes, however, should not have major effects on the feasibility demonstration of this cost-effective IMRT treatment technology in LMICs for head and neck cancer treatment.
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