



Review article

Clinical trials in low and middle-income countries – Successes and challenges



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ABSTRACT

Gynecologic malignancies affect women in low and middle-income countries (LMICs) at equal or higher rates compared to high income countries (HICs), yet practice guidelines based on clinical trials performed in HICs do not routinely account for resource disparities between these regions. There is a need and growing interest for executing clinical trials in LMICs. This has led to the creation of multinational cooperative groups and the initiation of several ongoing clinical trials in Mexico, China, and Korea. In this article we describe the challenges involved in initiating clinical trials in LMICs, review current efforts within surgical, medical, and radiation oncology, and introduce high priority topics for future research.

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1. Introduction

Gynecologic malignancies such as breast, cervical, and uterine cancers represent the first, third, and fifth most common cancers in women globally (Ferlay et al., 2015). Together, these malignancies account for 24% of all cancer deaths in women (Ferlay et al., 2015). Gynecologic cancers also disproportionately affect women in low and

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middle-income countries (LMICs). Less developed regions of the world carry 84% of the burden of cervical cancer diagnoses and 87% of cervical cancer mortality yet frequently lack the necessary resources to optimize diagnosis and treatment (Ferlay et al., 2015). Acknowledging these disparities, professional societies and cooperative groups have sought to stratify treatment guidelines by resource availability (e.g. National Comprehensive Cancer Network (NCCN) Framework Guidelines and American Society of Clinical Oncology (ASCO) Resource-Stratified Clinical Practice Guidelines) (Carlson et al., 2016; Chuang et al., 2016). However, best practices within LMICs should ideally be established through clinical trial evidence.

In resource-limited populations, numerous barriers exist to prevent clinical trial design and execution. Commonly cited examples are lack of infrastructure, heterogeneity of resource availability among countries, unfamiliarity with clinical trial regulations, cultural/ethical issues, and other legal constraints around data-sharing. The few examples of large-scale clinical trials conducted in LMICs for HIV/AIDS and cervical cancer screening serve as valuable models for clinical trial design for gynecologic malignancies (Sankaranarayanan et al., 2009; Campbell et al., 2012; Adefuye et al., 2013). Unfortunately, oncologic treatment requires the expertise of multidisciplinary physicians and ancillary staff as well as the accompanying operating room equipment, chemotherapeutics, imaging machines and/or radiation therapy (RT) machines that can add an additional, and potentially prohibitive, layer of expense.

Herein we describe the unique obstacles for clinical trial execution in gynecologic oncology in LMICs, review current efforts for trial design in surgical, medical, and radiation oncology, and introduce high priority topics for future research.

2. Existing obstacles for clinical trials in LMICs

Clinical trials in oncology have increased in parallel to increasing cancer prevalence in LMICs. In the recent past, conducting clinical trials in LMICs drastically curtailed costs and resulted in a transient increase in clinical trials. Many of these trials were unfortunately enabled by exploitation of ignorance, poverty, and poor awareness of the human subject rights and safety issues. For instance, in India, there was an initial surge in pharmaceutical clinical trials until 2010 and a sharp fall with decreasing trend subsequently (Chawan et al., 2015). Major concerns included poor quality of informed consent, poor quality of scientific and ethical review processes, sub-optimal regulatory processes for new drugs and clinical trials, inadequate protection of the patient's rights and compensation for trial-related injury and, more importantly, lack of post-trial population access to prohibitively expensive cancer drugs which were proven effective in LMIC settings (Shapiro and Meslin, 2001). Subsequent rapid amendments in regulations at frequent intervals related to patient rights, compensation, and timelines in India have resulted in loss of enthusiasm for both the investigator-initiated and industry-sponsored trials (Sirohi et al., 2014). Similarly, many other LMICs have their own laws, regulatory requirements, policies and guidelines for the conduct of clinical research, especially in regard to international multi-center collaborative trials. This not only complicates the conduct of collaborative trials, but also prevents the ability to address cancers with higher prevalence in LMICs.

Other obstacles include logistics, research relevancy and implementation issues (Saini et al., 2013; Dandekar et al., 2016; Seruga et al., 2014). Logistically, there are a paucity of facilities, trained human resources, expertise, capacity building and motivation for the conduct of research. Clinical trial execution in these settings would therefore need to identify a payer, whether governmental, non-governmental, sponsor, or other, who would be able to fund for these deficiencies. Clinical trials in LMICs may also be subject to completing research priorities. Funding for clinical trials may not prioritize conditions that are seen most frequently in LMICs due to decreased prevalence (and decreased estimated revenue) in HICs. Even if clinical trials could successfully demonstrate efficacy in LMICs, the ability to provide a plan for long

term implementation of these interventions pose major challenges to global funding and ethics committees.

While not specific to conducting clinical trials, disparities in healthcare systems, social and cultural differences, reimbursement policies, and healthcare professional staffing are additional obstacles. Most patients have to assume the cost of their health care, including initial treatment and possible subsequent management of complications associated with treatment (White, 2015). In addition, competing local traditional treatment and the lack of patient education and support present as other major barriers for conducting clinical trials in LMICs (White, 2015). High-quality pathology and cancer registries are limited in LMICs. In sub-Saharan Africa, there is less than one pathologist per 500,000 persons (Adesina et al., 2013). Similar to the lack of pathologists, there are limited trained cancer surgeons. The number of surgeons is fewer than two per 100,000 persons (Lavy et al., 2011; Meara et al., 2016). These numbers are substantially lower than one pathologist per 15,000 and 35 surgeons per 100,000 persons in the United States. The ability to conduct clinical trials are hampered by the limited ability to provide cancer care in setting of limited human resources.

3. Current status of gynecological cancer clinical trials

The Gynecological Cancer InterGroup (GCIG) orchestrates many of the current trials in gynecological malignancies. The GCIG is an organization of international cooperative groups that perform gynecological cancer research. It is a nonprofit corporation that has structured governance, bylaws and standard operating procedures. GCIG aims to promote and facilitate high quality clinical trials in order to improve outcomes for women with gynecological cancer. GCIG was conceived in 1993 and formalized in 1997 and has 29 member groups including representation from North America, Europe, Asia and Australia. The GCIG has a number of standing committees including cervix, endometrial, ovarian, rare tumors and a dedicated committee to accomplish phase 2 trials. The group has been very effective and has a history of successful collaboration and completion of randomized phase III trials, consensus conferences, brainstorming (state-of-the-art) initiatives, publications and reviews. International participation in trials has enabled achievement of rapid recruitment and international credibility for the results. Current GCIG trials are looking at all aspects of gynecological cancer treatment including systemic, radiation and surgical questions. The group strongly supports the mission of providing access to relevant, high quality clinical trials in LMICs.

Table 1

Examples of clinical trials for gynecologic malignancies in low- and middle-income countries. RT = radiation therapy.

Trial	Design	Investigators
ConCerv	Cone biopsy or simple hysterectomy with or without pelvic node dissection in low-risk, early cervical cancer	Global Gynecologic Oncology Consortium
Interlace	Induction chemotherapy plus chemoradiation vs. chemoradiation in advanced cervical cancer	National Cancer Research Institute (NCRI), United Kingdom
Outback	Weekly cisplatin/RT vs. weekly cisplatin/RT followed by outback chemotherapy in advanced cervical cancer	Australia/New Zealand Gynecologic Oncology Group (ANZGOG) and the NRG Oncology Group, USA
Shape	Radical hysterectomy and pelvic node dissection vs. simple hysterectomy and pelvic node dissection in low-risk, early cervical cancer	National Cancer Institute of Canada (NCIC) Clinical Trials Group
TACO	Weekly cisplatin/RT vs. tri-weekly cisplatin/RT in advanced cervical cancer	Korean Gynecologic Oncology Group (KGOG) and Thai Cooperative Group

Unfortunately, there is underrepresentation of LMIC member groups in GCIG. In particular, the cervix committee, which is highly relevant to LMICs as cervical cancer the leading cause of morbidity and mortality among women in these countries. The cervix committee has designed trials with emphasis on benefit to LMICs, including trials looking at delivering cisplatin less often during definitive combined modality treatment of cervical cancer (TACO trial) and less aggressive surgery for early stage cervical cancer (SHAPE trial). GCIG has also attempted to have LMICs participate in clinical trials through the Cervical Cancer Research Network (CCRN) (Table 1).

4. Initiatives in conducting trials in LMICs

The GCIG developed the CCRN to help promote cervical cancer clinical trials in countries where the disease is endemic (Suneja et al., 2015; Gaffney et al., 2015). To date, there have been over 80 accruals to CCRN clinical trials. In 2016, an international conference was held with 63 representatives from 16 different countries in Bangkok, Thailand. The progress of the clinical trials was discussed as well as the challenges of new and ongoing trials. Through the inaugural international meeting, it became clear that education, especially in radiation oncology and brachytherapy, and quality assurance in cervical cancer treatment were critical aspects in many LMICs. Adherence to implementation science priorities is necessary to follow and incorporate appropriate guidelines such as chemotherapy administration and use of brachytherapy in advanced cervical cancer (Gaffney et al., 2015).

There are also many other examples of efforts to help support clinical cancer centers in LMICs. Academic institutions have partnered with countries and healthcare systems to help promote the oncologic treatment of women (Efstathiou et al., 2016). Radiating Hope is a nonprofit organization that was founded to provide radiation equipment to LMIC (Fisher et al., 2014). Ideally, partnership with organization in HICs will help translate important research findings to promote the known survival benefits of cervix cancer treatment.

5. Surgery and clinical trials in LMICs

Globally, more than 80% of the 15.2 million new cancer cases estimated in 2016 will require surgical management (Sullivan et al., 2015). Less than one-fourth of these cases will receive appropriate and safe surgery. Though many women present with advanced cervical cancer requiring chemoradiation therapy in LMICs, many resource-limited areas in Southeast Asia, Western Pacific Asia, Africa, and Latin America lack adequate radiotherapy and chemotherapy capabilities and therefore surgery may continue to play an important role in cervical cancer management (Abdel-Wahab et al., 2013; Grover et al., 2015). In particular, surgical management may play a key role in patients with early cervical cancer or locally advanced cervical cancer after neoadjuvant chemotherapy (Chuang et al., 2016). Clinical trials conducted in LMICs are important to address which surgeries are appropriate. The SHAPE trial is a randomized study comparing radical hysterectomy and pelvic node dissection with simple hysterectomy and pelvic node dissection in patients with low-risk, early cervical cancer. Another international study is the ConCerv trial, which assesses the outcomes of conservative surgery (i.e. cone biopsy or simple hysterectomy with or without pelvic node dissection) for patients who have completed child-bearing (Ramirez et al., 2014). The outcomes of these trials have potential to change practice.

Despite the obstacles to effective clinical trial execution, there are successful examples of surgical trials conducted in LMICs. Pareja et al. reported their experience on quality of laparoscopic radical hysterectomy in Colombia (Pareja et al., 2012). Through collaborations between MD Anderson Cancer Center Global Academic Programs in the United States and Instituto de Cancerologia in Medellin, Colombia, the surgical and oncological outcomes of management of patients with early cervical cancers were found to not be different between the two institutions.

Involvement of multiple organizations is needed to help improve patient care, research, and training of pathologists, oncology nurses, and oncologists specializing in gynecologic cancers in LMICs (Adefuye et al., 2013; Schmeler et al., 2013; Chuang et al., 2014; Chuang et al., 2015; Sagae et al., 2016). These organizations include CCRN, International Gynecologic Cancer Society, Society of Gynecologic Oncology, ASCO, and World Health Organization.

6. Chemoradiation and clinical trials in LMICs

Cost-effective trials for the developing world need to be easy to conduct in resource-challenged settings and relevant in addressing the needs of their population. Endpoints need to be simplified and, because of cost, advanced imaging may not be feasible. The CCRN has four clinical trials open for patients with cervical cancer including the TACO trial (weekly cisplatin/RT vs. tri-weekly cisplatin/RT), OUTBACK trial (weekly cisplatin/RT vs. weekly cisplatin/RT followed by outback chemotherapy), INTERLACE trial (induction chemotherapy plus chemoradiation vs. chemoradiation) and SHAPE (Simple Hysterectomy And Pelvic node dissection in Early cervix cancer). Of these trials, the TACO trial has been successfully opened in LMICs countries with good enrollment. INTERLACE has most recently been opened in Mexico and SHAPE is opening in China and Korea.

Many challenges have been confronted when trying to open these trials in LMICs including lack of research infrastructure, compliance with Good Clinical Practice (GCP), cost of the treatment and the need of administrative approval, which can be quite onerous. In India, the government required that the sponsored country pay the cost of treatment, which was not feasible. Even though the institutions had infrastructure and compliance with GCP, OUTBACK could not be opened in India. In Mexico, it took at least 2 years to open up INTERLACE due to the need to get the necessary approvals. An additional burden is restrictions on the international transfer of biomaterials, which can hinder the ability to conduct centralized translational research. The main reason why the TACO trial has been so successful is that it is designed and owned by local investigators (Korean Gynecologic Oncology Group and Thai Cooperative Group) and is low cost and easy to run.

Despite all of these challenges, there is general consensus that overcoming these issues is critical not only in enabling cervical cancer clinical trials to be performed globally, but also to improving current inadequate care standards which is substandard in many of these countries with the highest burden of disease and the highest death rates.

7. High priority topics for LMICs

7.1. Hypo-fractionation

In countries where cervical cancer is the most prevalent, RT machines are few or rare. Hypo-fractionation is an attractive option because it can reduce the amount of days a patient is on treatment machines therefore hopefully reducing wait times and thus potentially improving access to care for all patients. Shortening treatment time can also reduce the inconvenience and cost to patients that is associated with protracted treatment schedules. It is important to have a study that will improve care without increasing complications. Randomized studies in breast cancer have shown that delivery can be given in a shorter period of time without effect on overall survival, local control or toxicities compared to standard fractionation (Haviland et al., 2013; Whelan et al., 2010; Owen et al., 2006). Similar findings are being reported in prostate cancer (Kupelian et al., 2007; Hoffman et al., 2014; Pollack et al., 2013).

A study from Nigeria, one of the few studies using hypo-fractionation in cervix cancer, randomized 500 patients with cervix cancer, to standard fractions (50 Gy in 25 fractions) vs. hypo-fractionation (50 Gy in 15 fractions) followed by one brachytherapy in both arms and found similar response and survival (Campbell et al., 2000). However

late-toxicity was higher in the hypo-fractionation arm. The problem with this study was that the hypo-fractionated arm had biological equivalent dose (BED) that was much higher than the standard arm leading to a higher rate of late toxicity in the hypo-fractionation arm. An alternate option that may be safer would be to have the hypo-fractionation arm have a BED that is equivalent to the standard arm such as 37.5 Gy in 15 fractions. The BED for 37.5 Gy in 15 fractions is 68.8 Gy to the tumor and 46.9 to the normal tissues compared to 45 Gy in 25 fractions that has a BED of 72 Gy to the tumor and 53.1 Gy to the normal tissues. A possible study would be to randomize patients between 45 Gy in 25 fractions versus 37.5 Gy in 15 fractions followed by brachytherapy or surgery in countries where brachytherapy is not available.

In summary, a hypo-fractionated trial in cervix cancer is very attractive but it needs to be instituted in a safe and sensible manner.

7.2. Palliative care, palliative radiation, and palliative surgery

Every year, over 19 million adults are in need of palliative care at the end of life, 34% of which have cancer, and nearly 80% of which live in LMICs ([Global atlas of palliative care at the end of life](#)). Important strides have been made to increase palliative care services, including distribution of educational materials by the Worldwide Palliative Care Alliance (WPCA)/World Health Organization (WHO) and increased availability of opioid analgesics since it was placed on the WHO Essential Medicines list in 1977 ([Global atlas of palliative care at the end of life](#); [Cleary, 2014](#)). However, education and training for healthcare professionals is still lacking and opioid analgesics are still inadequately utilized in many countries in Africa, Asia, Central and South America, and Eastern Europe ([Berterame et al., 2016](#); [Hu & Feng, 2016](#); [Hannon et al., 2016](#)). Furthermore, widespread adoption of palliative care is hindered by political, psychological, social, and cultural barriers ([Hu & Feng, 2016](#); [Hannon et al., 2016](#)).

Limited literature describes the use of non-pharmaceutical modalities for palliative treatment, such as surgery or radiation. This is unfortunate, as palliative RT constitutes 30–50% of the workload in Radiation Oncology Departments in HICs and would likely represent an even higher percentage of RT use in LMICs due to increased proportion of patients presenting at advanced stages of disease ([Rodin et al., 2016](#); [Lutz & Chow, 2014](#)). Palliative surgery may also have a role in LMICs to relieve suffering resulting from intestinal perforations, tumor blockages, or bleeding ([Riesel et al., 2015](#); [Folkert & Roses, 2016](#)). More clinical research is therefore needed to describe palliative RT and surgery in resource-limited settings, especially as it pertains to access, durable palliation, and cost effectiveness.

Given the strong and growing need for palliative care in LMICs, capacity building, research, and advocacy for palliation is a high priority.

7.3. Neoadjuvant chemotherapy and less invasive surgery: alternative treatments where no RT is available

Approximately 85% and 87% of the 528,000 and 266,000 new cervical cancers and deaths develop in low-resource settings, respectively ([Ferlay et al., 2015](#)). Most of these patients present with advanced stage disease due to the lack of screening programs and effective treatment modalities, including radiation machines and chemotherapy. In the 2016 ASCO Resource-Stratified Clinical Practice Guideline, recommendations were made on alternative best treatment options for clinicians practicing in these settings ([Chuang et al., 2016](#)). The Guideline was developed based on review of existing guidelines or expert consensus opinions when evidence was not available ([Colombo et al., 2012](#); [Ebina et al., 2015](#); [Hirte et al., 2015](#); [Koh et al., 2015](#)). A four-tier approach (basic, limited, enhanced, and maximal) was developed based on recommendations by the Breast Health Global Initiative ([Anderson & Distelhorst, 2008](#)).

In LMIC settings there is limited access to RT. The availability of chemotherapeutic drugs is unpredictable and the surgeries provided are limited to simple (extrafascial) hysterectomy. The Guideline recommends less radical surgery, such as extrafascial hysterectomy or its modification for patients with stage IA2, IB1, or IIA1 diseases if the surgical capacity is present and the disease can be removed with negative margin. For the patients with stage IA2 or IB1 and tumor <2 cm in size and <1 cm in depth, the SHAPE and ConCerv trials are exploring if cone biopsy or extrafascial hysterectomy and pelvic lymphadenectomy are adequate. For more advanced stage disease, neoadjuvant chemotherapy (NACT) followed by extrafascial hysterectomy with modification has been recommended when feasible. Two randomized phase III trials (European Organization for Research and Treatment of Cancer 55994 and ClinicalTrials.gov identifier NCT00193739) are comparing NACT followed by surgery with primary chemoradiation therapy for patients with stage IB2 to IIIA disease. Results of these trials may elucidate or support the roles of NACT in the management of cervical cancer.

In the limited setting where external radiation is available but not brachytherapy, extrafascial hysterectomy is recommended if there is residual tumor after RT or chemoradiation with a boost of 68 Gy or if initial tumor size is >6 cm. Radical hysterectomy may be considered after RT or chemoradiation to a dose of 50 Gy. This recommendation was based on the result of a randomized clinical trial conducted in Mexico ([Cetina et al., 2013](#)). The survival and progression-free survival of patients with stage IB2 to IIB disease were equivalent between traditional chemoradiation therapy and chemoradiation to 50 Gy followed by radical hysterectomy. As many as 72% (62 out of 86 patients) who underwent radical hysterectomy were found to have no residual disease. Although there was no difference in complication rates between the two treatment modalities, concern remains with performing radical hysterectomy after chemoradiation in LMICs. Additional trials are needed to assess the effectiveness and safety of an additional boost to 68 Gy followed by surgery for patients with residual disease at 6 weeks of follow-up.

8. Conclusion

Gynecological malignancies are highly prevalent and therefore the subject of new and ongoing clinical research in LMICs. The obstacles to conducting clinical trials are numerous and fraught with ethical, political, and logistical considerations. Yet, multinational groups such as the GCIG and others have started to make significant inroads to conducting large-scale cooperative trials. These trials will answer important clinical questions while simultaneously serving as models for future cooperative endeavors. In the interim, surgical, medical, and radiation oncologists working in LMICs continue to strive to tailor treatment paradigms to each region's unique resource profile. Hypofractionation, palliative care, and alternative treatment combinations are currently being targeted as high priority initiatives for capacity building.

Impressive foundational work has been laid to initiate oncologic clinical trials in LMICs and we look forward to increasingly comprehensive multinational and cooperative efforts in the future.

Conflicts of interest

The authors have no conflicts of interest to report.

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