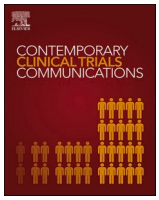
Contemporary Clinical Trials Communications 36 (2023) 101224

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc



Affordable cancer technologies: Lessons learned from the design and implementation of two randomized clinical trials to develop innovative treatments for cervical precancer

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1. Introduction

In 2020, there were 23.6 million new cases of cancer and 10 million deaths globally, a 26% rise from the previous decade [1]. Increases in incidence and mortality were most notable in low-and- middle income countries (LMICs), where cancer mortality rates are already higher independent of incidence [2]. Strategies for cancer control that have been successful in high-income countries (HICs) are not translatable to settings that lack the necessary infrastructure and face different socioeconomic challenges [3]. A notable example is cervical cancer, a leading cause of cancer death in LMICs [1]. Cervical cancer results from persistent infection of oncogenic types of the human papillomavirus (HPV) [4] which induces precancerous changes that lead to invasive cancer over several years. However, even high-grade precancer (cervical intraepithelial neoplasia grade 2 or more severe, or CIN2+) can be successfully treated with minimally invasive procedures. Despite this extended window of opportunity, prevention programs in LMICs have failed to decrease incidence and mortality. In 2018 the World Health Organization (WHO) issued a call to action [5] to achieve the global elimination of cervical cancer through widespread HPV vaccination, screening, and treatment. To meet these ambitious goals, effective and scalable technologies are needed.

In 2013, the United States National Cancer Institute (NCI) launched the Affordable Cancer Technologies (ACT) program and called for proposals targeting cancer control in LMICs. The objective was to support the development of low-cost screening, diagnostic, and treatment tools for low-resource settings [6]. The initiative focused on cancers that were both prevalent in LMICs and amenable to early detection and treatment. Seven out of 14 funded projects, including those carried out by our two research teams (Johns Hopkins/Jhpiego and Cleveland Clinic Foundation/Basic Health International [CCF/BHI]), focused on cervical cancer. Here, we describe our experiences designing and implementing clinical trials to develop effective, affordable, and market-ready CIN2+ treatments. The lessons learned may prove helpful to stakeholders working on the development of innovative cancer prevention tools for LMICs.

2. Preliminary considerations

2.1. Defining the problem

Since 2011, the WHO has endorsed both excisional and ablation treatments for CIN2+ [7]. The former require anesthesia and highly trained providers and are therefore not feasible for low-resource settings. Gas-based cryotherapy, a form of ablation, remains the most common treatment for CIN2+ in LMICs. This method utilizes cryogenic gas to cool a probe to sub-freezing temperatures which is then applied to the cervix. Gas-based cryotherapy is effective, results in minimal side-effects, and can be applied by providers at all levels [8,9]. However, the ongoing need for medical-grade gas (CO_2 or N_2O) presents significant implementation challenges (Fig. 1) [10].

The difficulties associated with gas-based cryotherapy have spurred interest in alternative treatments, including thermal ablation (aka cold coagulation, thermocoagulation, thermoablation) [10–12]. This treatment relies on heat rather than cold and has been used to treat cervical precancer in the United Kingdom since the 1970s [13]. In 2019, the WHO included thermal ablation in its CIN2+ treatment guidelines [14]. The conventional device consists of a desktop unit powered by electricity (Fig. 2). Although it shares ease-of-use features with cryotherapy,

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https://doi.org/10.1016/j.conctc.2023.101224
Received 12 June 2023; Received in revised form 24 September 2023; Accepted 23 October 2023
Available online 30 October 2023

Fig. 1. Gas cylinders for cryotherapy at a rural clinic in El Salvador (the cryotherapy unit can be seen in the box on the right). The costs and logistical challenges of refilling and transporting heavy gas cylinders is a major implementation barrier of gas-based cryotherapy.

Fig. 2. The conventional thermal ablation device (WiSAP Medical Technologies GmbH, Brunnthal, Germany), consists of a desktop unit with attached probes of different shapes and sizes that apply heat to the cervix. It is a delicate instrument that requires electricity; thus, it is not suitable for use in remote or low-resource settings.

this desktop device is not feasible for widespread use in LMICs.

2.2. Finding testable solutions

Our teams focused on development of portable and durable CIN2+ treatment alternatives for LMICs. The Johns Hopkins/Jhpiego team developed the CryoPop®, a device that utilizes CO_2 much more efficiently. The CCF/BHI team began working with CryoPen®, a non-gas cryotherapy machine, and expanded the project to include the development of a battery-powered handheld thermal ablation unit. For both teams, an important endpoint was ensuring the feasibility of a single-visit approach where women can receive screening followed by CIN2+ treatment. Such "screen-and-treat" strategies are recommended by the WHO when routine biopsies are not feasible [7]. This requires a combination of point-of-care screening and CIN2+ treatment that is portable and simple to use. The trials described below were designed with these features in mind (Table 1).

3. Early device development

3.1. CryoPop®

Development of the CryoPop® started in 2011 as a collaboration between Jhpiego, a Johns Hopkins University global health affiliate, and the Johns Hopkins Center for Bioengineering Innovation and Design. The impetus was a challenge initiative launched by Dr Harshad Sanghvi, Medical Director at Jhpiego, to address drawbacks of gas-based cryotherapy. Team members undertook a 3-week field visit to India and Nepal to gain a deeper understanding of the local context. Interviews and shadowing of local physicians, nurses, and midwives revealed that the primary constraint of the community-based cervical cancer prevention program was lack of access to treatment methods. With this insight, the design team developed a mechanical treatment device to collect and deliver dry ice as the freezing element. The concept was validated in two ways: 1) using a prototype to bench test for temperature of at least −60 °C and "fill performance" (i.e., achieving enough dry ice to sustain temperature), and (2) assessing probe tip temperature and necrosis (cell death) in goat cervical tissue. [personal communication] Subsequently, the first human clinical study using the functional prototype (see Fig. 3) took place between 2015 and 2017. Women were randomized to standard cryotherapy or CryoPop® 24–48 h prior to elective hysterectomy for benign disease. The primary outcome was post-treatment depth of necrosis (DON) of the cervix as a surrogate for treatment efficacy. DON was assessed on pathology and found to be non-inferior on CryoPop®-treated tissue than tissue treated with standard cryotherapy. Continued NCI funding allowed the team to move forward with a randomized efficacy trial (NCT04154644).

3.2. CryoPen®

The CryoPen® Cryosurgical System (CryoPen®, Inc., Southlake, TX) obtained pre-market FDA approval for CIN2+ treatment in 2011. The CCF/BHI team members proposed a partnership with the company to adapt the technology into a portable machine. Device development began with input from a series of facilitated meetings with global cervical cancer experts. The prototype consisted of Stirling cooler housed in a toolbox case refitted with off-the-shelf parts and powered through the electrical grid or a car battery (Fig. 4) [15]. After bench testing on animal tissue, preliminary clinical studies assessed cervical DON in patients scheduled for hysterectomy. The CryoPen® did not achieve non-inferiority to gas-based cryotherapy, but DON did meet an *a priori* threshold of a 3.5 mm [16], which was based on the depth of CIN2+ involvement in 90% of cases in a previous study [17]. The clinical significance of these findings was unclear. Further funding from NCI allowed the team to move forward with a clinical trial (NCT03084081).

Table 1
Newly developed ablation devices for treatment of high-grade cervical precancer in LMICs.

Device	Functioning	Features	Maintenance	Accessibility	Retail price (USD)
CryoPop®	Uses one tenth of CO_2 than conventional cryotherapy	Small, lightweight, fully portable	Mechanical parts, easy to maintain, durable	Manufactured and sold by Pregna, Inc.	~$730 per device plus cost of CO_2
CryoPen®	Runs on small quantity of ethanol; electricity or car battery	Medium size, portable, sturdy	Requires manufacturer services or replacement	Currently not in production	N/A[a]
WiSAP C3 portable thermal ablation device[b]	Runs on electricity or rechargeable battery	Very small, lightweight, portable, handheld	Requires manufacturer services or replacement, durable	Manufactured and sold by WiSAP Medical Technologies	~$2800 per device, no consumable goods needed

[a] The device is currently not commercially available.
[b] There are currently two additional portable thermal ablation devices in the market produced by other manufacturers.

Fig. 3. The current CryoPop® device is portable, durable, and has few moving parts that allow for on-site, easily fixable mechanical problems. It does not require a tether to a CO_2 tank and uses only a tenth of the CO_2 per procedure compared to standard cryotherapy equipment.

3.3. Portable thermal ablation device

The CCF/BHI team approached WiSAP Medical Technologies GmbH (Brunnthal, Germany) in 2014 to develop a portable thermal ablation device. Funding was secured from a private foundation to build a prototype and add an arm to the planned CryoPen® trial. Team members visited a Scottish clinic where conventional thermal ablation has been used for decades, and collaborated with the company's engineers on the design of a battery-operated unit. Unlike the conventional desktop device, which is cumbersome to transport and requires electricity, the new units are lightweight, sturdy, and portable. These features allow use as a point-of-care treatment in remote and resource-poor locations. WiSAP obtained regulatory clearance for commercial distribution (i.e., CE Mark) in 2015. The model is currently marketed as the C3 cold coagulator (Fig. 5). The team has another trial underway to further optimize the device and to compare a single vs. two-probe treatment protocol (NCT 03429582). The conventional two-probe technique has high long-term efficacy [18], but this will be the first direct comparison between a single and a two-probe approach.

Fig. 4. The CryoPen® uses compression cooling technology instead of gas and consists of a sturdy and portable toolbox. The treatment application metal probe, held on the left hand, is detachable from the cooling unit.

4. Implementation of clinical trials

4.1. Definition of outcomes

In preliminary projects, DON was used as the endpoint of device performance because it was the benchmark in previous studies [19,20]. This raised unforeseen questions, including the differential effects of ablation with cold vs. heat, the effect of immune activation and/or inflammatory reactions induced by ablation on necrosis, the lack of pathologic consensus on precise criteria for DON, and the interpretation of DON in healthy vs. diseased cervices. The relevance of DON as a surrogate for clinical efficacy was uncertain, and it became evident that pathology confirmation of diagnosis and disease clearance was essential. However, as described below, this resulted in numerous research design challenges, and ultimately, a more prolonged recruitment process.

Fig. 5. The C3 WiSAP portable thermal ablation device is lightweight and easy to handle. It can run on electricity or connected to a small rechargeable battery.

4.2. Study design and setting

Both teams designed non-inferiority randomized trials that used pathology to assess enrollment eligibility and cure rates as the main endpoint. The CryoPop® trial (NCT04154644) by the Johns Hopkins/Jhpiego team was carried out in Karnataka, India. Visual inspection with acetic acid (a screening test consisting of unaided visual examination of the cervix after application of dilute acetic acid; [ref] [VIA]) [21] was used to screen the 10,000 women necessary to find 100 histologically defined CIN2+ cases in order to confirm non-inferiority at 0.05 level of significance accounting for 12% loss to follow-up. This estimate was based on recommendations of India-based investigators and their success in prior studies with similar procedures. Screening with either HPV testing or cytology was not feasible due to cost. The post-treatment schedule included visits at 6 weeks to assess side-effects, at 3 months for cytology, and at 6 months for repeat cytology, HPV testing, and colposcopy with biopsy.

The CryoPen® and thermal ablation trial (NCT03084081) by the CCF/BHI team took place in El Salvador, Colombia, and China. Women with histologically confirmed CIN2+ were randomly assigned to three arms: CO_2-based cryotherapy (referent), CryoPen®, or portable thermal ablation. The sample size of 1154 women was calculated to detect non-inferiority at a clinically acceptable 10% margin difference between the cure rates of the referent and the experimental treatments at 0.05 level of significance [22]. We anticipated a 20% loss to follow-up based on the estimates of local partners. Women were followed-up at 6 weeks to assess treatment side-effects, and at 12-months to ascertain cure rates through cytology, HPV genotyping, and colposcopy and biopsy.

4.3. Recruitment challenges

4.3.1. CryoPop® trial

Enrollment began in July 2021 in the cities of Belagavi, Hubli and Vijayapura. Since cervical cancer screening is not routine at these locations, the first step involved developing and implementing community-level screening strategies. Cervical cancer awareness sessions were employed to promote screening in primary health centers. Providers were trained in VIA and a community health worker cadre, the ASHAs (Accredited Social Health Activists), received cervical cancer education. ASHAs accompanied women to screening and, for those screening positive, to medical centers for colposcopy and biopsy to confirm pathology diagnosis prior to enrollment. However, the COVID-19 pandemic resulted in hospital lockdowns and reassignment of staff to pandemic-related care; women were also reluctant to present for screening or colposcopy for fear of contagion.

Moreover, the projected sample proved to be a surprising underestimate, possibly due to low-risk characteristics in this population. Although 5.5% of 9137 women were VIA positive, only 16 CIN2+ cases were confirmed, not sufficient to power non-inferiority calculations. Trial findings, including treatment efficacy, safety, and acceptability, are forthcoming.

4.3.2. CryoPen® and thermal ablation trial

Site selection was contingent on a trade-off between high disease burden and adequate pathology capacity. Enrollment began in July 2017 in San Salvador, El Salvador. A site in Bogotá, Colombia was added some months later and another one in Shanxi Province, China in June 2018. Recruitment presented different challenges at each site. El Salvador introduced an HPV screen-and-treat program in 2018, but this was not a recruitment source since HPV positive women are treated without biopsy confirmation. Referrals from colposcopy clinics were lower than expected. In Colombia, the national insurance scheme changed during the initial stages of the project and potential subjects were referred to other facilities. In China, an opportunity to increase enrollment occurred through a screening campaign in Hunan Province. However, this required transportation of trained physicians from the original site to deliver treatment, which was costly and logistically complicated. Finally, the COVID-19 pandemic suspended all non-essential procedures across sites for long periods during 2020. Despite these drawbacks, study enrollment was completed in July 2022. Follow-up visits are expected to end in December 2023, when treatment efficacy results will be ready for publication Preliminary data on safety and acceptability is now available [23].

5. International clinical research considerations

Cervical cancer disproportionally impacts LMICs, yet the technologies being tested, the research designs and methods, and most funding tend to originate in HICs. These disparities raise logistical challenges, regulatory hurdles, and ethical questions [24]. A full discussion is out of the scope of this paper, but we will highlight some important considerations.

5.1. Infrastructure

Many LMICs do not have the infrastructure to implement a large-scale clinical trial. Barriers include a lack of adequate facilities (from available examination rooms to a stable internet connection), clinicians with heavy workloads and limited time for research activities, low levels of health literacy, and stakeholders that lack research experience. In addition to trial implementation, the burden is on the study team to engage local authorities, train local personnel (i.e., research coordinators, healthcare providers, outreach staff), promote community awareness, and disseminate results to local actors.

5.2. Choice of study site

Existing infrastructure is closely tied to study site selection, but there are other considerations such as disease prevalence, institutions that facilitate recruitment (e.g., large-scale screening, a community health worker program), or the political will to prioritize the health issue of interest. In the case of cervical cancer, stigma and other sociocultural factors associated with sexually transmitted infections or gynecological care may be relevant.

5.3. The "double-standard" and other ethical concerns

A long-standing debate is whether clinical trials that take place in low-income settings are ethical because they may offer clinical care that is not the gold standard [25]. On the other hand, there are interventions not used in HICs that can significantly improve health in LMICs. In the case of cervical cancer, the gold standard confirmation of disease is

pathology diagnosis. Facilities that have access to pathology services often have the resources to offer the gold standard of treatment (i.e., excisional treatment), and are therefore unlikely to participate in a trial involving ablation. Mitigation strategies include conducting a non-inferiority instead of a superiority trial and incorporating extensive efficacy and safety checks to reassure stakeholders. It is also important to keep in mind that there are historical antecedents in LMICs that engender distrust toward clinical research, particularly if funding comes from abroad [26–29]. Researchers housed in Western institutions should be mindful of these dynamics and strive to maintain cultural competence in research design and conduct. Actively including local collaborators in the scientific process, from research design to publication, is an important step to design effective international trials and promote greater equity in clinical research.

5.4. Regulatory issues

Compliance with researchers' home institution and local site regulations is a particularly challenging aspect of international clinical research. At least four interrelated areas require extensive, and often difficult to obtain, documentation:

- *Human subjects:* Agencies that oversee human subjects research may involve multiple levels (i.e., local, state, national). The priorities of the researchers' institution may differ from those of the local site, or there may be a mismatch between the procedures and documentation required by each. Other challenges include the need to find certified trainings for protection of human research subjects that can be completed by the local team or translating notions of privacy and confidentiality that vary cross-culturally. In some cases, it may be difficult to find an appropriate local internal review board (IRB) or ethics committee to review the project.
- *Customs and medical instruments:* Introducing new treatment devices to a country for research purposes requires either domestic or internationally recognized regulatory approval (e.g., FDA or CE Mark), special permits from the local agency governing medical instruments, and several layers of custom and tariffs duties. It is critical to have a thorough understanding of the regulatory environment from both the originating and the target country to successfully navigate these hurdles. These costs and time frames should be included in the project timeline at the outset.
- *Legal restrictions (data sharing, material transfer agreements, payment and fees, conflicts of interest, etc.):* Academic institutions in HICs have dedicated legal departments that oversee compliance with state and federal law, but equivalent agencies may not exist at the proposed research sites. There can also be a lack of concordance in laws and regulations governing everything from data sharing to stipends for subjects. For example, some countries legally require a health insurance policy for subjects participating in research trials, while others do not. Ensuring compliance at all participating sites is complex and requires a significant amount of effort.
- *Administrative/fiscal issues:* Closely related to legal issues are the administration and disbursement of research grants. At the local site, it is imperative that personnel are trained in accounting and record-keeping practices that are aligned with the research institution and funding agency's reporting obligations. Understanding regulations to comply with budgetary and fiscal obligations adds another layer of complexity to international collaborations.

To facilitate these processes, it may be necessary to include a designated point person in the research budget for the duration of the trial (ideally, someone who speaks the necessary language and is culturally competent to communicate directly with local institutions) to manage regulatory issues. Another potential strategy is employing a Contract Research Organization (CRO) with experience in the research setting. Finally, it is incumbent on investigators to establish a good working relationship with their institution's IRB and grants administrators to ensure any requirements or mismatched expectations can be explained and resolved in a timely manner.

6. Post-research: from idea to commercialization

6.1. CryoPop®

The initial CryoPop® study used a limited number of devices manufactured by hired contractors, which added cost and time. Negotiations with a commercial partner, Pregna, Inc., an India-based industry leader in reproductive health products and devices, began in 2016. Pregna has had a long association with Jhpiego and is interested in ensuring broader access to high-quality reproductive health products. However, cervical cancer prevention is a relatively new area for the company. To help jumpstart their entry into this field, Jhpiego collaborated in the early retooling process of the CryoPop® for commercial production start-up. Concurrently, Jhpiego also undertook a market assessment focusing on the Indian and African markets to develop a set of forecasts and recommendations for commercial entities (internal, unpublished report - CryoPop® Implementation and Scale-Up Strategy Report to Jhpiego, 2017). From Pregna's perspective, key considerations in the decision to take on the commercialization of CryoPop® included: the manufacturing readiness for a simply designed device, familiarity with the regulatory environment, an existing marketing platform, a network of women's health-related facilities to deploy the technology, and the de-risking investment Jhpiego had already undertaken to create a manufacture-ready device. The agreement was signed in 2017, and in April 2020, an initial batch of the devices was rolled out. Pregna received CE mark approval for the CryoPop® in March 2021, and currently sells the device for approximately one-half of the cost of standard cryotherapy devices.

6.2. CryoPen®

The CCF/BHI collaboration with CryoPen Inc. began after the company had obtained pre-market FDA approval to utilize their original device for CIN2+ treatment. After development of the LMIC-adapted version, manufacturing occurred locally. As a small medical device company with few employees, sales and marketing relied on independent contractors and distributors. Difficulties arose in scaling up production without expanding the enterprise, and in 2018 the CryoPen Inc. founder made the decision to forgo further growth. Currently, the company services existing devices but has discontinued production of any new machines. If the current trial demonstrates efficacy of the CryoPen®, other business ventures may continue to develop this technology.

6.3. Thermal ablation

WiSAP is a well-established company focused on minimally invasive gynecological devices. As the manufacturer of the sole commercially available desktop thermal ablation machine, the company had extensive familiarity with the technology and potential marketing channels prior to collaboration with the CCF/BHI team. With in-house engineering and manufacturing capacities, WiSAP had the ability to efficiently design and produce prototypes of a handheld device that could be used in a trial, in addition to experience meeting safety compliance requirements. WiSAP obtained CE certification for the portable C3 model in 2019 which is currently sold through their existing networks.

7. Lessons learned

Although we worked in diverse settings and with different commercial partners, our teams encountered common hurdles and solutions during development, efficacy testing, and commercialization of three

CIN2+ treatment devices. As our respective projects come to completion, we have an opportunity to disseminate important lessons learned that may facilitate similar multi-partner collaborations:

1. **Start with the end in mind.** The ultimate objective of these projects was the large-scale implementation of affordable and accessible technologies. It is essential to conduct a needs assessment or situational analysis prior to study design, avoiding assumptions about conditions on the ground and taking into account post-research end goals. In the case of the CryoPop® project, the initial analysis focused on feasibility (i.e., developing an effective, less expensive, and simpler alternative to standard cryotherapy), rather than commercialization or wide dissemination. We would have benefitted from mounting a concurrent market analysis to better inform the process and outcome, reduce costs, and shorten the timeline to marketing of the device.
2. **Establish site feasibility.** The importance of choosing a site and local partners that are compatible with the project's goals cannot be overestimated. Although our teams conducted preliminary inquiries to select study locations, our initial focus on potential research collaborators over other considerations was too narrow. In hindsight, there were areas where further assessments were needed. For example, the decision to use pathology to confirm initial diagnosis and treatment outcomes introduced difficulties since sites with high cervical cancer incidence have limited screening and pathology services. This delayed start-up, slowed recruitment, and introduced additional costs.
3. **Accept failure and sunk costs.** Research projects have limited budgets and timelines, and it is important to work efficiently and know "when to quit", particularly when ongoing costs are high. Such a situation occurred in one of the CCF/BHI team's potential sites. After two years of attempting to find acceptable documentation requested by researchers' and local institutions, the decision was made to abandon the effort. Moving on to better suited locations earlier would have saved time, effort, and costs.
4. **Choose an appropriate partnership**: An implementing organization such as Jhpiego is not set up for device manufacturing. In similar cases, partners with production and commercialization abilities are critical to transform an idea into a marketable product. It is also crucial to take advantage of the partners' existing research and development experience with regulatory issues when bringing a product to market. In the CryoPop® project, an early partnership with a device-manufacturing commercial entity would have resulted in a shorter and more cost-effective development process ("de-risk" investment). The CCF/BHI team experienced both sides of this situation: WiSAP was able to develop and commercialize a new thermal ablation device rapidly and efficiently, but CryoPen® was linked to a small operation that could not sustain production.
5. **Consider balance of evidence generation and regulatory requirements**: It is important to carefully weigh the rigor of a clinical trial with the evidence needed to meet regulatory requirements associated with a novel device, instrument, or test. This may be particularly important for an established form of treatment that uses a new delivery approach, since in such cases regulatory processes are likely to focus on the device itself, rather than the efficacy of the treatment. Cognizance of the requirements that govern research and those that regulate commercialization of medical technologies is essential to efficiently allocate time and resources to both enterprises.
6. **Strengthen local and academic partnerships**: These projects were only possible through years of efforts by multiple parties, including research team members, in-country collaborators, industry partners, and funding agencies. Identifying the strengths and gaps of each party is essential to optimize efforts and resources. In LMICs, collaborators may have extensive programmatic experience but be unfamiliar with the administrative and regulatory requirements of clinical trials. On the other hand, members of institutions in HICs may be familiar with domestic requirements but have little international research experience. The research team can work to increase capacity on both ends. For example, the CCF/BHI team organized a field visit by grants specialists from the Cleveland Clinic to El Salvador, which served to facilitate administrative negotiations between sites. Seeking collaborations with local experts and like-minded colleagues, even those in different fields (e.g., tuberculosis or HIV research as blueprints for cancer), can facilitate problem-solving.

The considerations above are targeted primarily at researchers considering international collaborations. However, it is important to point out that these projects were made possible through award mechanisms focused on research-commercial partnerships and cancer control in LMICs. Funding agencies have an essential role to play in spurring the development of innovative technologies that can be transformative in global cancer control, and researchers have a role to play in pushing for such initiatives.

8. Conclusion

These are exciting times in cervical cancer research. The WHO call for action has created momentum to develop new technologies that allow for the possibility of eliminating a cancer during our lifetime. CryoPop®, now marketed globally, offers a more efficient method of cryotherapy treatment in regions where demand is very high. In addition to the WiSAP C3 thermal ablation device, there are two additional handheld devices on the market, one of which also emerged from the ACT program. Interest in these portable machines has spurred guideline changes that are critical for widespread use. El Salvador recently updated its guidelines to include the use of thermal ablation for CIN2+ treatment, and we anticipate similar changes in other countries. While there are challenges to conducting international cancer research, there is critical work to be done in order to reduce global gaps in cancer detection, diagnosis, and treatment. It is our hope that lessons described here provide a preliminary roadmap for those considering involvement in this field.

Funding

National Institutes of Health Grant numbers: UH2/UH3 CA189923 and UH2/UH3 CA189883, Rising Tide Foundation CCR 17-800

Declaration of competing interest

Miriam Cremer is on the speaker bureau for CooperSurgical.

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