CANCER PREVENTION AND CONTROL

Oncology Clinical Trials in Africa: Partnering for Quality

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abstract

Oncology clinical trials are requisite for testing the safety and effectiveness of promising treatments and deciphering new knowledge into concrete benefits for patients. They present opportunities to innovate promising, novel cancer remedies. A dearth of local evidence to guide cancer treatment in Africans is creating an increased interest in oncology clinical trials to improve patient care. This is primarily because of limitations in pathology, surgery, medical oncology, radiation, and palliation that are leading to worse cancer outcomes on the continent.

Investment in oversight of Human Research Ethics committees and Medicines Regulatory Authorities in Africa has improved the potential for many countries to host clinical trials. However, the distribution of cancer trials remains poor across the continent, resulting in inadequate treatment options for patients with cancer.

There are some initiatives aimed at developing research capacity to host trials in Africa. However, there is now a need to establish strategic partnerships whose aim should be to achieve harmonized, accredited Clinical Trials Units capable of running trials to meet Good Clinical Practice standards. This article discusses what has been achieved and proposes a model for quality oversight of Clinical Trials Units in Africa.

JCO Global Oncol 7:572-576. © 2021 by American Society of Clinical Oncology

INTRODUCTION

Oncology clinical trials are indispensable for testing the safety and effectiveness of promising treatments, translating new knowledge into tangible benefits for patients, and presenting opportunities to innovate novel cancer therapies. A dearth of local evidence to guide cancer treatment in Africans has led to a heightened interest in oncology clinical trials to improve patient care. This is primarily because of limitations in pathology, surgery, medical oncology, radiation, and palliation that are leading to worse cancer outcomes on the continent.[1]

The emerging cancer burden in Africa can be attributed to many factors, including growth and increased lifespan of the population, as well as behavioral factors such as smoking and obesity.[2] Despite this growing public health crisis, cancer is still considered a low priority compared with other pressing diseases such as malaria and HIV/AIDS. However, the number of estimated cancer deaths in 2015 was 60% higher than the number of malaria deaths in Africa.[3] In 2014, health expenditures per capita in sub-Saharan Africa amounted to only US $98—100 times less than the United States.[3] In addition, only 5% of global funding for cancer prevention and control is spent in Africa and other low- and middle-income regions.[3] Yet these regions are home to 65% of cancer deaths and 75% of premature deaths as a result of cancer.[3] Furthermore, nearly one-third of cancers in sub-Saharan Africa are related to infectious diseases such as hepatitis B, HIV, and human papilloma virus, mostly affecting the young as opposed to the elderly cancer population of high-income countries.[4] The developing burden of cancer in Africa needs to be addressed, and progress can be achieved by developing sustainable platforms for oncology clinical research and clinical trials in Africa.

CURRENT PARTNERSHIPS AND INITIATIVES

Innovative approaches are being applied to stimulate an interest to conduct high-quality research in some countries, which can have an impact on policy and stimulate government commitment to support clinical trials.[5] Countries such as South Africa and Egypt host significantly higher volumes of clinical trials than in other African countries.[6] More than half of all trials in Egypt were cancer trials in 2017, and Egypt is second only to South Africa on the African continent in terms of the number of pharmaceutical company–sponsored clinical trials it hosts.[6] This landscape is set to change

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on September 21, 2020 and published at ascopubs.org/journal/go on April 22, 2021: DOI https://doi.org/10.1200/JGO.19.00315

and will need innovative, culturally sensitive guidelines and structures to ensure efficiency of operations and sustainability of the ongoing effort to structure the growing clinical trial enterprise in Africa. A proven approach in managing infectious diseases was to develop alliances and other partnerships between various entities (such as government, academic institutions, and health care facilities) to improve research infrastructure and capacity in Africa.

The Mapping African Research Ethics Capacity (MARC) project is a timely initiative aimed at identifying existing capacity.[7] The aim of MARC is to provide the first comprehensive interactive database of Research Ethics Committees (RECs) in Africa. The database is hosted by the Council on Health Research for Development's Health Research Web site (HRWeb) and can be used by RECs and key stakeholders in health research to identify capacity, constraints, and development needs.[7] RECs report on physical infrastructure, finances, processing of research proposals such as meeting frequency, membership and staff information, and training requirements. As of 2013, the top five countries by the number of RECS listed in HRWeb were South Africa (30), Nigeria (25), Egypt (23), Uganda (9), and Cameroon (8).[8] The potential of MARC lies in the mapping of current ethical review activity onto capacity needs. The MARC initiative is a project established by the Council on Health Research for Development in partnership with the South African Research Ethics Training Initiative program,[2] and it is funded by the European and Developing Countries Clinical Trials Partnership (EDCTP)[3] and an unconditional grant from Pfizer.[8]

The EDCTP was developed to confront issues in developing and progressing clinical trials, which require funds, experienced personnel, and other resources.[5] The joint program was set up to develop and support multidisciplinary and translational research among European and developing countries. It provides support from private and public sectors to network and create new partnerships, have a legal body to evaluate proposals and support ethical reviews, and provide logistics and training. The EDCTP has invested 255 million euros in African-led research capacity, development, and training; it has funded 141 projects that involve 126 institutions in 28 Sub-Saharan African countries and with 43 institutions in 17 European countries.[9]

The EDCTP has also created Networks of Excellence led by scientists at African institutions and centers to promote research and conduct clinical trials. Networks of Excellence's objectives were listed as follows: (1) sustainable multisite research coordination and grant management capabilities, (2) generating capacity for upscaling the number of qualified African scientists and health practitioners, and (3) securing infrastructure, partnerships, and funds capable of responding efficiently to regional diseases and threats through synergy and multidisciplinary collaboration.[10] This initiative has resulted in the formation of new networks within the program, resulting in increased number of participating institutions, increased funds spent on projects, increased number of clinical trials, and capacity building activities such as regulatory and ethics training and fellowships.[9] These partnerships also provide an opportunity to share good practices and resources and take advantage of the various expertise present at different centers or institutions.

This rise of investment in regulatory and research ethics capacity development and strengthening buttresses the need to map progress to date, as well as to verify how realistically these learned ethical frameworks are being applied practically. This is being addressed by an ongoing effort to create a virtual platform (a Carnegie-funded African Diaspora Fellowship project titled "Development of a Virtual Platform for Oncology Clinical Trials Infrastructure, Resources and Registry for Africa), which will provide comprehensive information on oncology clinical trials infrastructure, resources, and registries for Africa. Collaborating with the African Organization For Research & Training In Cancer (AORTIC), the virtual platform will be publicly accessible. Its aims will be to conduct an environmental scan of the infrastructure and resources for cancer clinical trials in Africa and assess the capacity and readiness of African institutions and investigators for oncology clinical trials research, using the Global Health Network assessment survey. The project also intends to consult with both private and public funding agencies to identify public and private registries for oncology clinical trials in Africa, as well as conduct an exhaustive review of the Internet for clinical trial registries.[11]

Additional lessons can be learned from the Malaria Clinical Trials Alliance (MCTA), which was established to facilitate and support a network of centers in Africa with the capacity to conduct clinical trials, enabling its progression into a sustainable network of clinical research centers. The MCTA's activities included organized, frequent Good Clinical Practice (GCP) and Good Clinical Lab Practice (GCLP) training programs; managed acquisition and updates of equipment and other resources accompanied with technical support; and provision of support for processes involving ethics review boards and regulatory authorities.[12] With support of the MCTA, in partnership with the Malaria Vaccine Initiative, the Medicines for Malaria Venture, and the Swiss Tropical and Public Health Institute, the Ifakara Health Institute in Bagamoyo, Tanzania, has been able to conduct malaria vaccine trials through a well-equipped laboratory, renovated pediatric ward, enhanced telecommunications, and a quality assurance team to ensure compliance to protocol and GCP requirements.[13] The site has also received personnel training, equipment and infrastructure upgrades, and financial and managerial systems including human resources management.[13] These organizations provide ample evidence that joint programs can strengthen the infrastructure and capacity in Africa to develop clinical trials. With improved systems in place,

centers can attract capital (funds, as well as modern and reliable equipment) and accomplished investigators, which supports sustainability. Several innovative models have been initiated, focusing mostly on fostering the strength of Pan-African Networks and leveraging support of global partners.

Weak regulatory standards have fostered an inefficient system of medicine registration processes that leads to delays, a major obstacle that deters establishment and success of clinical trials. But there has been continued improvement in regulatory capacity, especially in quality control, postmarketing surveillance, and clinical trials oversight. In 2018, in Geneva, the African Ministers of Health adopted the Treaty for the establishment of the African Medicines Agency (AMA), which seeks to ensure the coordination and strengthening of continental initiatives to harmonize medical products regulation; and provide guidance and technical support to improve access to quality, safe, and efficacious medical products and health technologies on the continent. The AMA will work within the existing continental architecture of Regional Economic Communities and Regional Health Organizations to support African Union Member States.[14] Clinical trials in Africa require an independent and effective regulatory and ethical oversight of clinical trials to ensure safety of participants and integrity of clinical data. The AMA is expected to work collaboratively with the various National Medicines Regulatory Authorities to provide coordination of regional harmonization efforts, provide guidance and support, and reduce duplication in Africa's resource-scarce countries.[15] Under the aegis of the Clinical Trial Site Standards Harmonization Action Collaborative—the Collaborative of the Forum on Drug Discovery, Development, and Translation of the National Academies of Sciences, Engineering, and Medicine—clinical research stakeholders discussed opportunities to improve clinical trial site functioning, with the goal of increasing productivity in medicinal product development. The Collaborative concluded that harmonization of standards for clinical trial sites has significant promise in improving clinical trials. The template of this "Harmonization of Standards" could be leveraged to accommodate formation of a global site-accreditation system. A clinical trial infrastructure that reduces redundancies and increases efficiencies would, in turn, accelerate the pace and productivity of new product development to the benefit of patients and society.

These efforts are supported by the WHO, which has a mandate to assist and support nations in the development of effective cancer treatment strategies within the context of their national cancer programs and encourages formal and substantive links between academic centers and their equivalents in the developing world.[16] We recommend that this WHO mandate to work collaboratively and establish institutional linkages be strengthened along with using African regional collaborative networks/structures (such as the African Clinical Trials Consortium [ACTC], Prostate Cancer Transatlantic Consortium, AORTIC, Weill Cornell Medicine-International Center for the Study of Breast Cancer Subtypes, Institute of Human Virology in African Countries and H3Africa [which is supported by the National Institutes of Health], and the Wellcome Trust) as part of their continuing research portfolio in Africa to close the gap (detected in 2009) of most African countries being left behind in the genomic revolution.[17] These structures have fostered links with global institutions that include clinical research, research ethics training, as well as teaching and technology transfer (such as image-guided biopsies and immunohistochemistry technology). Through these collaborative engagements, genomic studies are gathering momentum in Africa. Intra-African mentorship programs have resulted in the establishment of Clinical Trial Centers, such as the University of Nigeria Centre for Clinical Trials, whose mentor is the Clinical Research Centre at The University of Cape Town. Evidence of open clinical trials in cancer in Africa in 2019 is provided by Odedina et al[18] in *JCO Global Oncology*. It remains unknown whether these are GCP-diligent sites. However, many countries lack the presence of cancer trials and, together with the well-known phenomena of barriers to running trials, there is a clear mandate for strategic development of clinical trial sites in Africa.[18]

BUILDING STAKEHOLDER CONFIDENCE AND SITE SUSTAINABILITY

As institutional review board and master reliance agreement oversight in Africa continues to improve through efforts from organizations such as the EDCTP, it is now time to establish harmonized trial units/sites capable of running trials to meet GCP standards. To circumvent the problem of Clinical Trials Units (CTUs) with variable standards, Europe created criteria for accreditation of sites and, more recently, the United States produced a document detailing the harmonization and accreditation of all research units, including trial sites (Association for the Accreditation of Human Research Protection Programs, Inc.). Accreditation processes are designed to ensure optimal performance at all levels of trial implementation. Despite the growth in the requirement for clinical trials to be run in populations other than those of high-income countries, site governance of trials and the necessary infrastructure in Africa are lacking in general and, where they exist, the standard is variable. The next step is to establish governance structures at the CTU level to meet a minimum set of standards.

The ACTC would therefore like to propose a model for the initial development, certification, and oversight of quality standards of CTUs in Africa. The model proposes a system for the establishment of accredited CTUs in each country. Building confidence in industry and funding agents is critical to the growth of trials in Africa. Furthermore, commitment to the proposed model at the Department of Health and industry levels is essential.

CTUs were established in Europe and the United States to standardize practice according to GCP. The general rule now is that all trials are required to be supported by a CTU. This was not an easy transition, but it has instilled confidence in industry and funding agents alike. This is the leap of faith that African countries need to take. We need to instill confidence quickly and efficiently, with minimal cost and sustainability for the future.

Innovative Model and Consortium Benefits

We propose that the ACTC, with partners such as the Prostate Cancer Transatlantic Consortium, EDCTP, AORTIC, and Africa Vaccine Regulatory Forum, establish a gateway and coordinating center to trial sites in Africa. The coordinating center would support the development of sites and investigators and maintain a database of GCP-ready sites. All sponsors of trials would have access to these data. In the case of pharmaceutical trials, the coordinating center could distribute feasibility notifications to countries with CTUs that have met a minimum requirement (staff, training, facilities, and so on). Each country would assign individuals responsible for updating the coordinating center's list of potential investigators and their therapeutic areas.

Voluntary accreditation of CTUs would include the following benefits:

1. Training for core competencies
2. Share all standard operating procedures, templates for clinical trial agreement or medicines transfer agreement
3. Benefit from budget development for sites
4. Access to cross-country training/mentoring
5. Access to reciprocal monitoring of sites/studies
6. Access to advice and guidance with respect to master reliance agreement and institutional review board submissions
7. Access to online training
8. Database sharing opportunities
9. Database of trials in Africa
10. Marketing of sites by therapeutic area by the coordinating center
11. Confidence in industry is achieved by demonstrating a commitment, no matter how hard, to upholding standards with a bottom-line expectation of delivering competitive quality services.

Training and Development of Sites: Setting Standards

Capacity development through training of investigators and site staff will form a criterion for certification as a GCP-ready site. In support of this, the Global Health Research Network has developed competencies for research site staff that could inform the certification of the CTU team.[19] Increasing consistency of operational processes at all points of a trial could reduce costs and timelines, increase data quality, and provide a better experience for participants. Those countries with barriers to becoming a consortium partner would be supported by the coordinating center and other CTUs to try to overcome them.

Accreditation of Sites

Several organizations have produced site qualification and training tools (TransCelerate; Society for Clinical Research Sites; Association for the Accreditation of Human Research Protection Programs, Inc.; Alliance for Clinical Research Excellence and Safety). In addition, Johnston et al[20] provide an excellent summary of the key components for setting and measuring standards. The first step toward accreditation would be to harmonize standards to ensure that feasibility and acceptability lies within the real-world setting. Following this, accredited sites would be subject to ongoing audits performed by members of the coordinating center.

Sustainability of Sites

The next leap of faith is to view the CTU as a clinical trials (business) center. All CTUs need to be self-sustaining. This means they must think and run like a business, which is a strategic imperative for success. Business training would be provided centrally for each unit representative. Site visits would follow with business advisors from the Graduate School of Business at University of Cape Town or a regional partner business school.

Coordinating Center Governance

It is envisaged that the coordinating center would be subject to external financial audits according to the business plan. Furthermore, a board of directors (public and private representatives) would ensure that strategic direction of the business model is regularly reviewed. The role of the board would include sourcing funding to manage the ongoing work of the coordinating center.

We have briefly described an outline of an ambitious model, which was the subject of a Clinical Trials Consortium Summit meeting in August 2019 at University of Cape Town. The aim of this summit was to provide opportunities for various partners to consider the above model as a solution to the ongoing dearth of clinical trials on a continent where they should be a public health priority.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or https://ascopubs.org/go/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.

REFERENCES

1. Gopal S: Cancer trials in sub-Saharan Africa: Aligning research and care. PLoS Med 14:e1002351, 2017
2. Thun MJ, DeLancey JO, Center MM, et al: The global burden of cancer: Priorities for prevention. Carcinogenesis 31:100-110, 2010
3. Dent J, Manner CK, Milner D, et al: Africa's emerging cancer crisis: A call to action. https://bvgh.org/wp-content/uploads/2017/07/Africas-Emerging-Cancer-Crisis-A-Call-to-Action.pdf#:~:text=Care%20Underlie%20Africa%E2%80%99s%20Emerging%20Cancer%20Crisis%20The%20growing,of%20access%20to%20definitive%20diagnosis%20and%20life-saving%20medications
4. Okuku F, Omoding A, Walusansa V, et al: Infection-related cancers in sub-Saharan Africa: A paradigm for cancer prevention and control. Oncology 84:75-80, 2013
5. Fekadu A, Hailu A, Makonnen E, et al: Short-term impact of celebrating the international clinical trial day: Experience from Ethiopia. Trials 18:332, 2017
6. WEMOS: https://www.wemos.nl/wp-content/uploads/2017/07/JH_Wemos_Clinical- Trials_v5_def.pdf
7. IJsselmuiden C, Marais D, Wassenaar D, et al: Mapping African ethical review committee activity onto capacity needs: The MARC initiative and HRWeb's interactive database of RECs in Africa. Developing World Bioeth 12:74-86, 2012
8. Mokgatla B, IJsselmuiden C, Wassenaar D, et al: Mapping research ethics committees in Africa: Evidence of the growth of ethics review of health research in Africa. Developing World Bioeth 18:341-348, 2018
9. Matee MI, Manyando C, Ndumbe PM, et al: European and Developing Countries Clinical Trials Partnership (EDCTP): The path towards a true partnership. BMC Public Health 9:249, 2009
10. Miiro GM, Oukem-Boyer OO, Sarr O, et al: EDCTP regional networks of excellence: Initial merits for planned clinical trials in Africa. BMC Public Health 13:258, 2013
11. ecancer: Oncology clinical trials platform development for Africa. https://ecancer.org/en/news/14195-oncology-clinical-trials-platform-in-development-for-africa
12. Ogutu BR, Baiden R, Diallo D, et al: Sustainable development of a GCP-compliant clinical trials platform in Africa: The Malaria Clinical Trials Alliance perspective. Malar J 9:103, 2010
13. Mwangoka G, Ogutu B, Msambichaka B, et al: Experience and challenges from clinical trials with malaria vaccines in Africa. Malar J 12:86, 2013
14. Chisango T: African Union Ministers of Health adopt treaty for the establishment of the African Medicines Agency Treaty to be submitted to the Specialised Technical Committee on Justice and Legal Affairs later on this year. https://au.int/en/pressreleases/20180520/african-union-ministers-health-adopt-treaty-establishment-african-medicines
15. Ndomondo-Sigonda M, Miot J, Naidoo S, et al: Medicines regulation in Africa: Current state and opportunities. Pharmaceut Med 31:383-397, 2017
16. World Health Organisation: https://www.who.int/publications/en/
17. H3Africa: https://h3africa.org/index.php/about/
18. Odedina FT, Ginsburg O: Oncology clinical trials in Africa: Emerging and operational issues. JCO Global Oncology: 6:929-931, 2020
19. TDR Global Competency Framework for Clinical Research: https://globalhealthtrainingcentre.tghn.org/pds/core-competency-framework/
20. Johnston C, Lewis-Hall F, Bajpai A, et al: It's time to harmonise clinical trials site standards. National Academy of Medicine, Discussion paper. https://nam.edu/its-time-to-harmonize-clinical-trial-site-standards/

