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ABSTRACT

Less than 1% of all clinical trials are conducted in Africa. In 2019, only six of 26 oncology clinical trials conducted in Africa were conducted in countries with subjects of African ancestry. There are multiple barriers that hinder the conduct of cancer clinical trials in Africa. Time to trial activation (TTA) is the administrative and regulatory process required before a study can be activated—an important metric and often a major barrier for site selection. In Kenya, TTA involves review by Institutional Review Board (IRB), Pharmacy and Poisons Board, National Commission for Science, Technology and Innovation and Ministry of Health, all in a sequential fashion. We performed a prospective review of TTA for all clinical trials initiated and began enrolment at the Aga Khan University-Clinical Research Unit between June 2020 and November 2022. TTA was defined as total time from submission of study documents (to regulatory bodies) to site activation by the sponsor. A total of 12 studies were submitted for regulatory review. Eleven (nine industry sponsored and two investigator initiated) were approved for activation. Three were COVID-19-related studies and eight were non-COVID-19-related studies. Mean TTA for COVID-related studies was 80 days (range 40–120). Mean TTA for non-COVID-related studies was 259 days (range 190–399). This TTA difference was statistically significant (p=0.02). TTA remains a significant barrier to the efficient regulatory approval of and subsequent conduct of clinical trials in Africa. COVID-19 pandemic revealed that parallel processing and expedited review of clinical trials allows efficient TTA without compromising human subject safety or data integrity. These lessons need to be applied to all clinical trials in order for African sites to become competitive and contribute data from African patients to global knowledge.

SUMMARY BOX

- ⇒ Time to trial activation (TTA) is the time from receipt of a clinical trial protocol and the activation of the clinical trial site to enrol research subjects and includes the entirety of approval processes (clinical, scientific, regulatory and administrative) before a study can be activated and is an important metric for site selection.
- ⇒ It is a critical measure of the efficiency of clinical trial activation process within an academic institution and the country in which the study is activated.
- ⇒ TTA represents an important metric and a major hurdle in positioning clinical research sites in sub-Saharan Africa to become part of the multicentre international clinical trials network.
- ⇒ There are multiple barriers facing the conduct of clinical trials in sub-Saharan Africa and TTA represents one such major hurdle.
- ⇒ Our data provide, for the first time, a true reflection of the on-the-ground reality for the activation of clinical trials at a well-established academic clinical research unit in sub-Saharan Africa, and compare the TTA for COVID versus non-COVID studies (80 vs 259 days) conducted over a 2-year period.
- ⇒ Our study reveals institutional as well as regulatory hurdles that disadvantage low and middle-income country (LMIC) sites from being selected for international multicentre clinical trials.
- ⇒ These objective data provide the basis for a dialogue between the respective stakeholders (academic institutions, pharmaceutical sponsors, governmental regulatory authorities) towards the restructuring of the clinical trial approval process in LMICs, home to a population under-represented in the international clinical trials arena.

INTRODUCTION

Clinical research is a universal driver for quality healthcare. While the African continent has been the site for major trials in the prevention and treatment of infectious diseases, this has, however, not translated into comparable strides in non-communicable diseases (NCD), which today represents a major health threat for the African population.[1] Despite carrying nearly 20% of the world's burden of illness, Africa is only marginally represented in the conduct of NCD clinical trials.[2] Less than 1% of the world enrolment on clinical trials comes from the African continent. In 2019, less than 5% of all cancer clinical trials were conducted in the African continent, and of those a majority were conducted either in South Africa or Egypt where a minority of accrued patients were African.[3 4] It may seem understandable that little attention is being given to NCD clinical investigation and clinical trials in the African continent given

the dire need for clinical practitioners to provide basic clinical care. In sub-Saharan Africa (SSA), there is one doctor serving a population of 10 000[5] and two specialists per 100 000 population.[6] However, clinical trials represent best practice and provide opportunity for low and middle-income countries (LMICs) to overcome the lack of diversity, equity and inclusivity observed in global clinical trials. Not to mention the dire need to contribute to global knowledge given that ethnicity determines genomic characteristics which in turn has a significant influence on pharmacogenetic and pharmacokinetics and how the therapeutic agents may affect individuals of different genetic make-up.

BARRIERS TO CONDUCT OF CLINICAL TRIALS IN SUB-SAHARAN AFRICA

Pharmaceutical companies have previously been slow in embracing SSA for the conduct of clinical trials,[7] with most NCD clinical trials from the African continent being conducted in South Africa or Egypt.[4] The lack of established clinical trial units with trained investigators and staff has also hampered the inclusion of sites from LMICs, Africa included, onto the clinical trial space.[8] The uptake of clinical trials in LMICs is also affected by the pressure on clinicians to see more patients and the drive towards revenue generation in a fee-for-service model, the lack of role models and mentors and the lack of institutional commitment to focus on clinical investigation as part and parcel of best clinical practice.[9] This, however, is gradually changing as many Western trained African clinicians and clinical investigators return to the continent, and thanks to a growing North–South collaboration in capacity building and research partnerships. The growing imperative for diversity and equity in clinical trials, and calls for providing access to minority patients in order to translate clinical trial finding to the global population, is also gaining traction across the academic and pharmaceutical industry.[10 11] This is in part due to the appreciation of the impact of pharmacogenetics and pharmacogenomics on the toxicity and efficacy of a new generation of targeted molecules, whereby the findings in the Caucasian population may not be directly translatable to people of different ethnicity and genomic characteristics, particularly the African host.[12]

A key, frequently discussed yet hitherto unsolved hurdle facing clinical trials in SSA is the prolonged, arduous and often replicative administrative and regulatory processes associated with activation of a clinical trial.[13] This regulatory burden hampers sites in Africa from getting a foothold in the competitive global clinical trials landscape.[14] The regulatory infrastructure remains siloed, coupled with an acute lack of adequately trained and experienced reviewers to deal with a new generation of novel clinical trial designs and investigational products and an understaffed regulatory system.[15 16] These issues are not dissimilar to those faced in the West,[17] yet are much more acute given the lack of prior experience with clinical trials in the African continent. Compounding these issues is the absence of real data that can inform dialogue and a reformation of the clinical trial regulatory approval process.

REGULATORY PROCESS IN KENYA

The existing regulatory review process for the activation of clinical trials in Kenya is similar to that operational in most sub-Saharan countries (figure 1).

The process follows a sequential pathway whereby each entity must approve the protocol before submission to the next regulatory body. All clinical trials must receive approval from the institutional ethics review board before moving towards review and approval by governmental regulatory authorities (Pharmacy and Poisons Board (PPB), National Commission for Science, Technology and Innovation (NACOSTI), Ministry of Health (MoH)). However, any changes required by one regulatory entity have to invariably be reviewed and approved by the previous entity. In addition, for studies involving tumour testing or central validation of biomarkers, the material transfer agreement (MTA) to ship patient samples requires a separate and additional review both at the PPB and MoH level. This sequential, often siloed, review process contributes to significant duplication of effort and prolongs the time to trial activation (TTA), a critical metric used by pharmaceutical sponsor in selecting clinical trial sites. The TTA of >12 months has often been quoted as a major hindrance to the inclusion of African sites on international clinical trials.[4] Reliable TTA data from African clinical trial sites, however, have been lacking.

The COVID pandemic and the dire urgency to conduct clinical trials across the globe in order to identify effective ways to initially treat and subsequently prevent COVID-19 infections provided African sites with the opportunity to be included in the wave of global COVID-19-related clinical trials.[18] On 30 January 2020, following the recommendations of the Emergency Committee, the WHO Director General declared that the COVID-19 outbreak constitutes a Public Health Emergency of International Concern (PHEIC).[19] This imperative accelerated the approval process for COVID-19-related clinical trials, both in the Western world as well as LMICs. As a result of this declaration,[11] the WHO and African Vaccines Regulatory Forum (AVAREF), one of the Continental Technical Committees of the African Medicines Regulatory Harmonization Initiative, reached an accord to permit joint review pathways.[20] National regulatory and ethics committees from across Africa agreed to combine their expertise to expedite clinical trial review and approvals for multinational prevention, diagnostic and therapeutic interventions aimed at combating the COVID-19 pandemic.[21] The WHO/AVAREF Joint Review Pathways aimed to achieve regulatory approval times of 60 days for regular trials, 30 days for expedited trials and 15 days for emergency trials.[20] However, non-COVID-19 studies were not covered by this mandate at the country level.

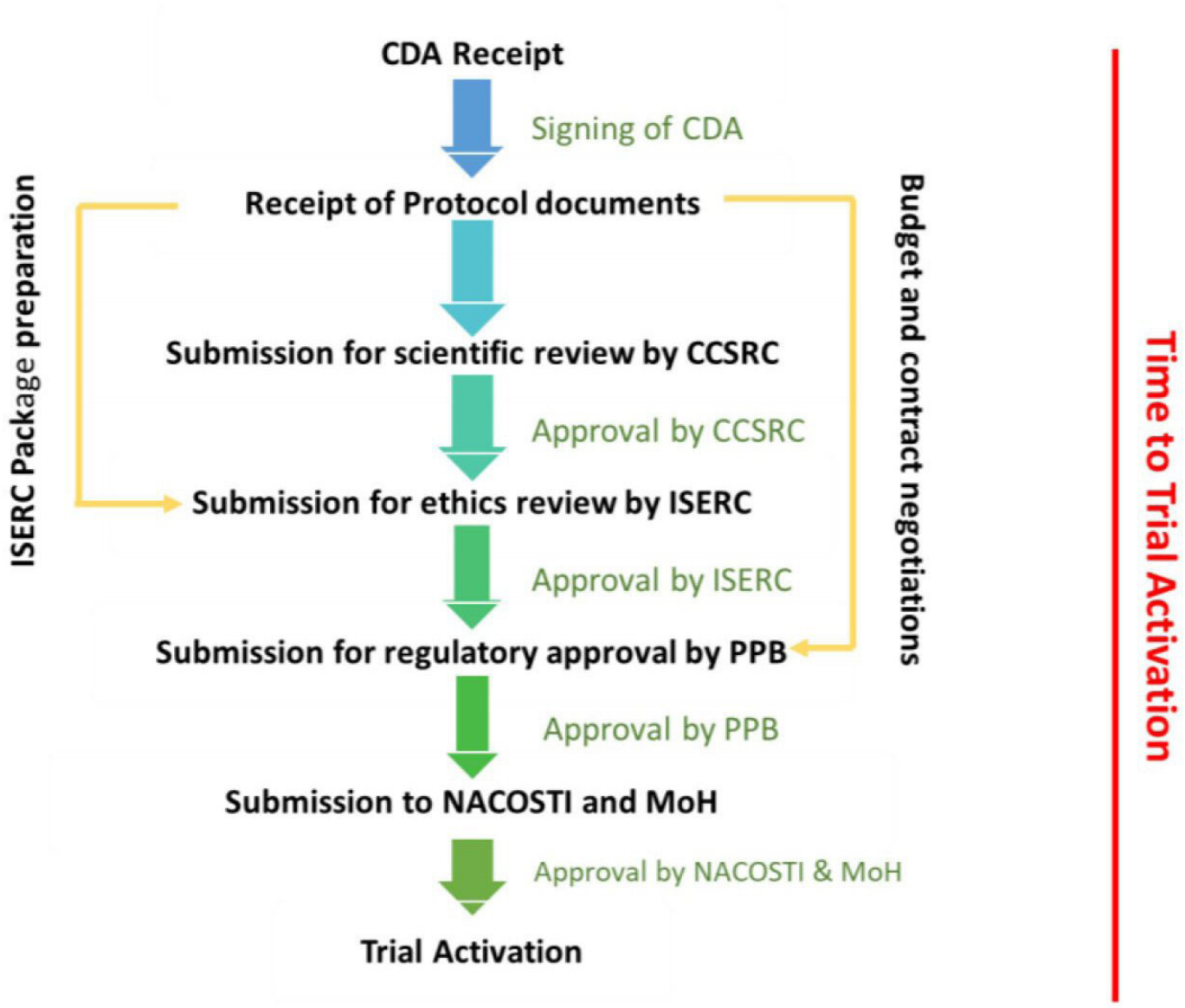

Figure 1 Time to trial activation review process. CCSRC, Cancer Centre Scientific Review Committee; CDA, confidentiality disclosure agreement; ISERC, Institutional Scientific and Ethics Review Committee; MoH, Ministry of Health; NACOSTI, National Commission for Science, Technology and Innovation; PPB, Pharmacy and Poisons Board.

TIME TO TRIAL ACTIVATION: EXPERIENCE FROM THE CLINICAL RESEARCH UNIT AT THE AGA KHAN UNIVERSITY HOSPITAL, NAIROBI

In 2020, the Aga Khan University (AKU) in Nairobi, Kenya, established a first of its kind Clinical Research Unit (CRU) to serve as a core facility for the conduct of clinical trials and to specifically address the gap in NCD clinical trials in SSA. Led by an experienced North American trained investigator and staff, the CRU opened during the peak of the COVID-19 pandemic in East Africa. Given the timing of its establishment, the CRU very quickly became involved in the conduct of COVID-19-related clinical trials in the first year before embarking on NCD studies. This serendipitous circumstance enabled the CRU to compile data on the TTA process for COVID-19 as well as non-COVID-19-related clinical trials that went through regulatory approval during this period.

We compiled TTA data for all clinical trials submitted for administrative and regulatory review from June 2020 until the cut-off date of November 2022. A total of 12 studies were submitted for review during this time period. One investigator-initiated trial (IIT) was disapproved by the Institutional Scientific and Ethics Review Committee (ISERC), did not proceed to implementation and thus was not included in our data set. Of the 11 studies conducted by the CRU during this period, nine were industry sponsored and two were IITs. Of the 11 trials implemented, one was a mixed-methods health service improvement study (Breast Cancer Stigma Study) and one was a surveillance study to validate the use of an artificial intelligence-assisted point-of-care test (Retinal Imaging Study). The remaining nine were therapeutic studies (1 COVID-19 vaccine study, 2 therapeutic

Table 1 Comparison of time to trial activation for COVID and non-COVID studies

	COVID studies (n=3)		Non-COVID studies (n=7)	
Regulatory body	Days to approval (median)	Range	Days to approval (median)	Range
ISERC	63	(28–119)	57.5	(18–197)
PPB	63	(29–72)	94	(70–250)
NACOSTI	12	(11–14)	20	(6–24)
MoH	21	(21)	20	(8–39)
TTA	80	(40–120)	259	(190–399)

COVID trials underwent parallel and expedited processing. Median TTA for COVID studies <sum of individual steps listed. Non-COVID trials underwent routine sequential processing including intervening approval steps to reconcile revisions by the various independent review bodies. Additional separate review was required if study involved a material transfer agreement (MTA) (data not shown). Total TTA for non-COVID studies >sum of individual steps listed.
ISERC, Institutional Scientific and Ethics Review Committee; MoH, Ministry of Health; NACOSTI, National Commission for Science, Technology and Innovation; PPB, Pharmacy and Poisons Board; TTA, time to trial activation.

COVID-19 studies, 5 oncology trials, 1 neurology trial) (see online supplemental table 1).

Online supplemental table 1 depicts the TTA (defined as the elapsed time in days between submission of clinical trial documents for approval by the principal investigator (PI) and activation of the site for patient enrolment). Data are provided for COVID-19-related trials (n=3) as well as the non-COVID-19-related trials (n=8) submitted for regulatory review by the same research team and reviewed by the same regulatory bodies during this time frame.

TTA for COVID-related studies was a median of 80 days with a range of 40 days (Evaluating Minority Patients with Actemra [EMPACTA]) to 120 days (Low Dose Radiation Therapy [LDRT]). The respective median approval times for ISERC, PPB, NACOSTI and MoH were 63, 63, 12 and 21 days, respectively (table 1 and online supplemental table 2). Conversely, the median TTA for non-COVID-related studies conducted during the same time frame and reviewed by the same regulatory entities was 259 days with a range of 190 days (Retina Imaging Study) to 399 days (A phase III adjuvant study of Girdestrant vs physicians choice of Endocrine therapy in patients with Estrogen Receptor positive HER2 negative early breast cancer [LIDERA]). The respective median approval times for ISERC, PPB, NACOSTI and MoH were 57, 94, 20 and 20 days, respectively. Included in the TTA but not listed separately were time for review reconciliation and MTA approval. There was a statistically significant difference between the overall TTA for COVID-19 and non-COVID-19 studies (p=0.02). The three COVID-19 studies required an average of one round each of back-and-forth responses between the PI and the ISERC and the PPB, while non-COVID-19 studies required an average of two rounds of responses each to the ISERC and PPB.

Our data reflect the capability of the clinical trial administrative and regulatory system to efficiently approve COVID-19-related clinical trials using a process whereby various administrative/regulatory entities could review the trial in parallel, communicate effectively and minimise the to and fro that results in delayed study approval. The dire urgency of the COVID-19 pandemic also reduced unnecessary bureaucratic hurdles, for example, permitted centralised reviews of international trials including use of external reviewers (as recommended by the WHO/AVAREF), increased regulatory staff dedicated to administrate COVID-19-related protocols, accorded priority to COVID-19-related studies and expedited communication with investigators and sponsors. This effectively resulted in substantially reduced wait times. The mean TTA of 80 days at the AKU-CRU reflects an efficient and effective clinical trial approval process designed to respond to a life-threatening pandemic. Conversely, the mean TTA of 259 days for all non-COVID-19 trials that underwent review during the same period is a reflection of the historical sequential and siloed process that was applied to all non-COVID trials conducted by the same investigator team and submitted for regulatory review during the same period. The key facilitating factor for COVID-19 trials was the expedited centralised parallel review process agreed on by AVAREF and African clinical trial sites in response to PHEIC.[22] The COVID pandemic and the PHEIC accord demonstrated that clinical trial processes both in the West as well as in Africa could be expedited, resulting in timely activation and completion of clinical trials, without evidence of compromising human subject protection or data integrity.[23]

Our data affirm what has been previously noted that sequential clinical trial review often results in duplication of effort, discrepancies and often contradictory reviewer comments that result in major delays in TTA.[24–26] Our data clearly demonstrate that when administrative and regulatory authorities come together to address a life-threatening clinical condition, for example, COVID-19 pandemic, the review process can be streamlined and made efficient without compromising Good Clinical Practice (GCP) requirements.

Our TTA findings during this period and the comparison between COVID-19 and non-COVID-19 clinical trials

provide a unique, objective insight in the historical clinical trial approval processes operational in a majority of LMICs. These data provide the opportunity to address barriers that delay clinical trials and consequently significantly impede expansion of clinical research to SSA and the inclusion of African patients on global international studies. Review of the literature stemming specifically from African countries indicates that factors influencing TTA include lack of experienced reviewers within the IRB,[12 23 25 26] duplication of effort by institutional review bodies and governmental regulatory reviewers[26] and overcautious approach to review of human subject research often based on historical experience.[27–29] While individual publications as well as scoping reviews have identified such barriers, objective TTA data have thus far being lacking.

In follow-up to the data collected by the CRU, several stakeholder meetings have been held to bring attention to this issue. Conversations between regulatory bodies and governmental agencies to improve TTA are being discussed. Institutionalising efforts that worked well for COVID-19 studies are being revisited. The solutions proposed to improve TTA in SSA have the potential to promote diversity, inclusivity, and allow patients in LMICs to have access to novel therapeutic molecules. This, in turn, allows African sites and African patients to contribute to new knowledge and the transcontinental generalisability of data from international multicentre clinical trials. We acknowledge that our data and experience have several limitations: (1) The fact that the CRU is a specialised core facility dedicated to providing a one-stop support for clinical trial execution, something not available in most SSA sites. In which case TTA would be expected to be much longer. (2) Being an academic centre, the institutional ISERC is often overly cautious.[3] Our study lumps TTA steps into four key regulatory buckets (ISERC, PPB, NACOSTI, MoH) based on the system in Kenya. This may not reflect the modus operandi at other SSA sites. In addition, we did not tease out some of the adjunct processes, for example, review reconciliation/MTA approval, which were ascribed to either of the major buckets. Overall, our data do, however, provide an objective picture of the clinical trial approval process in Kenya and many of the sites in SSA.

CONCLUSION

TTA remains a significant barrier to the conduct of clinical trials in Africa. African countries will need to work on re-envisioning of the infrastructure, workforce and regulatory procedures in order to promote the efficient and timely approval of clinical trials in their respective countries.[22 30] Unless we 'reinvent the wheel', clinical trial data from African sites and the African population will remain absent in published literature.[7 31]

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