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Patient Benefit of Clinical Research in Diversely Advanced African Developing Countries

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ABSTRACT

Background: The globalization of clinical research should also benefit the population in developing markets. In this context, the approval of tested medicines and the associated expansion of medical care beyond clinical studies would be desirable as a possible long-term benefit.
Objectives: This study was designed to compare the development of the number of clinical trials with the number of marketing authorizations of medicines on the African continent. To contrast these 2 parameters, the data were analyzed using the model of an ecological study.
Methods: To reflect the broad spectrum of African developing countries with diverse levels of development, the data collection was based on 2 geographically selected sample countries each from Central, North, East, West, and Southern Africa. Based on the ClinicalTrials.gov registry, the first step was to collect trends data on the development of the clinical trials in the 10 selected countries of the country list of the African Region published by the World Health Organization for the period 2015 to 2018. Subsequently, data on the current number of marketing authorizations of medicines in the selected sample countries were identified using the online registries of the national authorities. The data were utilized in comparative analyses.
Results: Eight out of 10 model countries showed an increase in the number of clinical trials, with the exceptions of Cameroon and Libya, which showed an overall decline in research activity over the entire time. In direct comparison with drug registrations, the numbers indicate a similar development. The only exception here is Nigeria, a country with a solid performance in clinical research and yet a decrease in medicine registrations since 2015.
Conclusions: The expected increase in the development of clinical research as result of the globalization trend can basically be observed in most of the model countries. However, this increase does not guarantee an improvement in the number of medicine registrations. Although this is evident in some of the selected model countries, it cannot be projected to the entire African region. This may be linked to the diverse development of the individual countries due to the different political situations and the varying degrees of clinical research infrastructure. (*Curr Ther Res Clin Exp.* 2022; 82:XXX–XXX)

Introduction

Along with the worldwide trend toward globalization, the globalization of clinical research is growing more dynamic,[1] and is leading to a shift of clinical research from Western countries, such as those in North America and Western Europe, to developing markets, such as Asia and Africa.[2] Ideally, this shift should also result in various long-term benefits for the population of the developing markets because, according to Leisinger et al,[3] "improving the health of poor people is a central issue in development." Especially for people from poorer countries, health is a "crucially important economic asset" because "their livelihoods depend on it."[3] If people from poor countries fall ill, there exists the risk that "their en-

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tire household can become trapped in a downward spiral of lost income and high healthcare costs."[3]

The African continent, with its multitude of differently advanced developing countries, appears to be a growing destination for clinical trials that attracts major international sponsors due to disproportionately high burden of disease, thus increasing growth in clinical research particularly for the development of new vaccines and treatments.[4] On the African continent, advancements in the field of information technology has also increased its importance for conducting cost-effective clinical trials.[4] Several African countries, such as Kenya, Nigeria, Tanzania, Uganda, and Zambia, offer a diverse patient pool for conducting clinical trials.[5] Over the past few years, guidelines related to clinical trials have been evolving in the African countries to provide a good foundation to international sponsors for conducting clinical trials while keeping the interest of patients as a priority.[5] In the context of "improvements in the state of health in the developing world," access to a wide range of medicines would be a significant benefit for the population because "medicines are an essential component of our health systems" and they are "key elements in disease control."[3,6,7] However, before medicines are registered with the responsible national authorities and made available to the public, their safety, efficacy, and quality must be proven in preclinical and clinical trials.[7] It is therefore reasonable to assume that an increase in the number of clinical trials carried out could also lead to an increase in the number of medicine registrations.

Consequently, the aim of this study was to compare the development of the number of clinical trials carried out in diversely developed emerging markets with the development of the number of medicines registered there over the past few years. An ecological study was performed to compare the frequencies of the 2 parameters to see if a possible association between them can be identified.[8] Because the development process of new medicines usually takes several years to reach market authorization, the most recent clinical trials carried out cannot yet be included in the registration statistics. In addition, we also aimed to explore whether people will have access to the medicines after registration. Because the African continent is hosting many diversely advanced emerging markets, member states of the World Health Organization belonging to the African region were selected for the analysis, and the respective national regulatory authorities for medicines were consulted to answer the research question.[9] The developing markets were defined according to the Development Assistance Committee list of the Official Development Assistance recipients of the Organisation for Economic Co-operation and Development, effective for reporting on 2011 flows in countries with a lower-middle income (in US dollars) of $1006 to $3975 gross national income per capita in 2010 or an upper-middle income (in US dollars) of $3976 to $12,275.[10]

To reflect the broad spectrum of development levels in the selected developing markets, both politically stable and unstable countries were considered in addressing the research question. Consequently, the model countries do not have a uniform level of development in the area of clinical research infrastructure. This should enable potential conclusions to be drawn regarding the globalization trend on the African continent, irrespective of the political situation or the development level of the clinical research infrastructure.

Methods

To identify whether or not the globalization trend in the African region is also reflected in the registration of medicines, the total number of clinical trials were compared with the number of medicine registrations between 2015 and 2018. For this purpose, both parameters were first considered separately before they were compared with each other.

Table 1
Selected countries from the different African regions

Region	Country model 1	Country model 2
Central Africa	Cameroon	Gabon
North Africa	Libya	Algeria
East Africa	Tanzania	Uganda
West Africa	Gambia	Nigeria
Southern Africa	Botswana	Zimbabwe

Selection of the African countries

To obtain a comprehensive overview of developing countries of the entire African region, 2 model developing countries each from Central, North, East, West, and Southern Africa were randomly selected according to their geographical location (Table 1 and Figure 1). Both politically stable and unstable countries were selected. The stable category includes Uganda, Tanzania, Botswana, Gabon, Gambia, and Nigeria, whereas Zimbabwe, Cameroon, Algeria, and Libya are considered politically unstable countries. Because only developing markets were considered to answer the research question, industrialized countries such as Egypt or Morocco were excluded from the analysis.

Identification of the clinical trials

A corresponding database query was done in the ClinicalTrials.gov registry of the US National Library of Medicine at the National Institutes of Health, to identify all Phase I through Phase III clinical trials carried out in the selected African countries between 2015 and 2018 for providing an overview of the temporal development in the clinical research business on the African continent.[11] For each country, the total number of the clinical trials was determined annually for the time period.

Identification of medicine registrations

The total annual number of medicine registrations was identified from the online database accessible via the websites of the respective national regulatory authorities of the model countries (Table 2). Where necessary, filters were applied in relation to the registration date.

The collected data were then processed with the statistical software R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) to graphically represent the temporal development in the business of clinical research as well as in the registration of medicines between 2015 and 2018. Because the magnitude of clinical trials and the number of drug registrations vary widely, a natural logarithm transformation for the actual values was performed in addition to the descriptive graphical representation. This was used to generate scatter plots followed by Spearman rank correlation for the variables number of clinical trials and medical registrations. The axes of the scatter plots were also logarithmized by replacing the value 0 with 1 and increasing each additional number on the scale by 1. The Spearman rank correlation of the individual countries was supplemented by an overall correlation for all selected model countries in order to obtain an overview of the general trend of both variables in the selected model countries of the African region. Considering the individual parameters included, the following results can be observed.

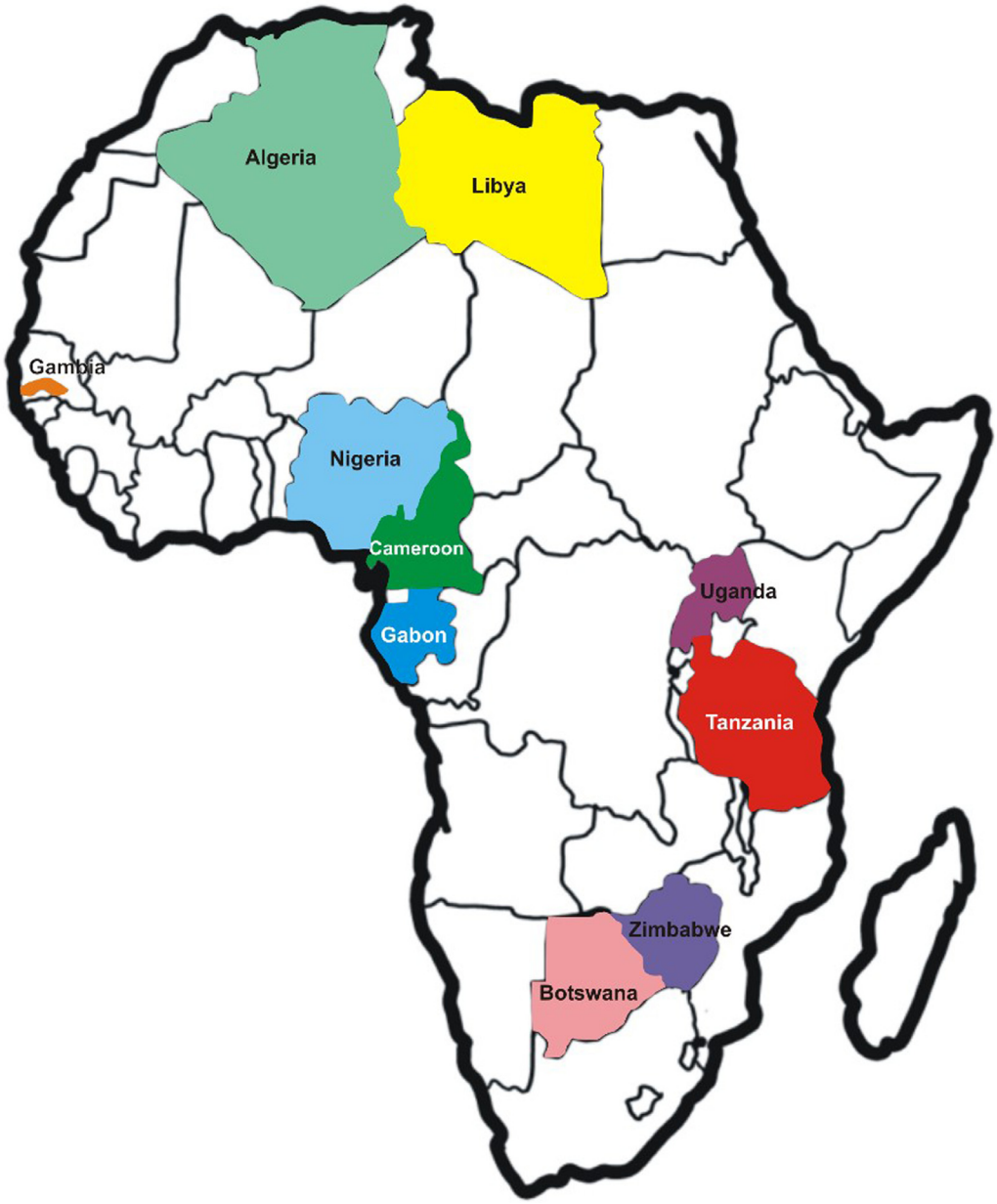

Figure 1. Overview of the selected countries within the African region.

Results

Total number of clinical trials

Figure 2 depicts an apparent increase in the total number of clinical trials conducted in majority of the model countries. The only exceptions are Cameroon and Libya because these countries show a rather varying development in the number of clinical trials conducted.

Total number of medicine registrations

Comparing the total number of medicine registrations shows a similar development as the comparison of clinical trial numbers. Again, there is an increase in numbers in many model countries except Nigeria (Figure 3).

Exclusion criteria for some model countries

Due to the lack of data on medicine registrations and the resulting noncomparability, the model countries from Central and North Africa were excluded from further analysis. In the course of data collection, it was found that all model countries with a politically unstable situation and limited clinical research infrastructure also lacked meaningful registers for medicine registrations on the websites of the respective national regulatory authorities.

Through direct comparison of the number of clinical trials conducted with medicine registrations (Figure 4) it is clearly illustrated that, apart from Nigeria, all countries show an upward trend in both areas. This indicates a possible association between both parameters and reflects also an expansion and development of the health care systems in these countries. This suggests that local people gained better access to medicines over the years.

In contrast, the generation of the scatter plots (Figure 5) performed after the natural logarithm transformation of the actual

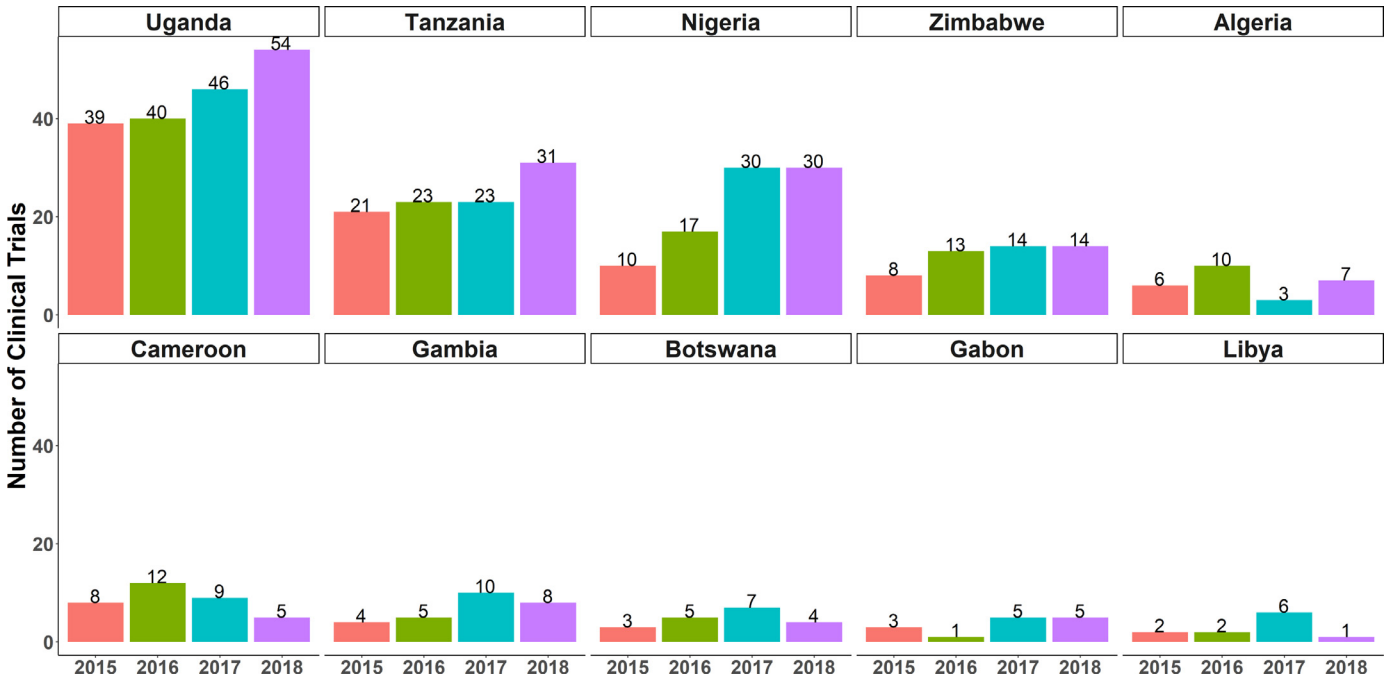

Figure 2. Development of the numbers of clinical trials per country between 2015 and 2018.

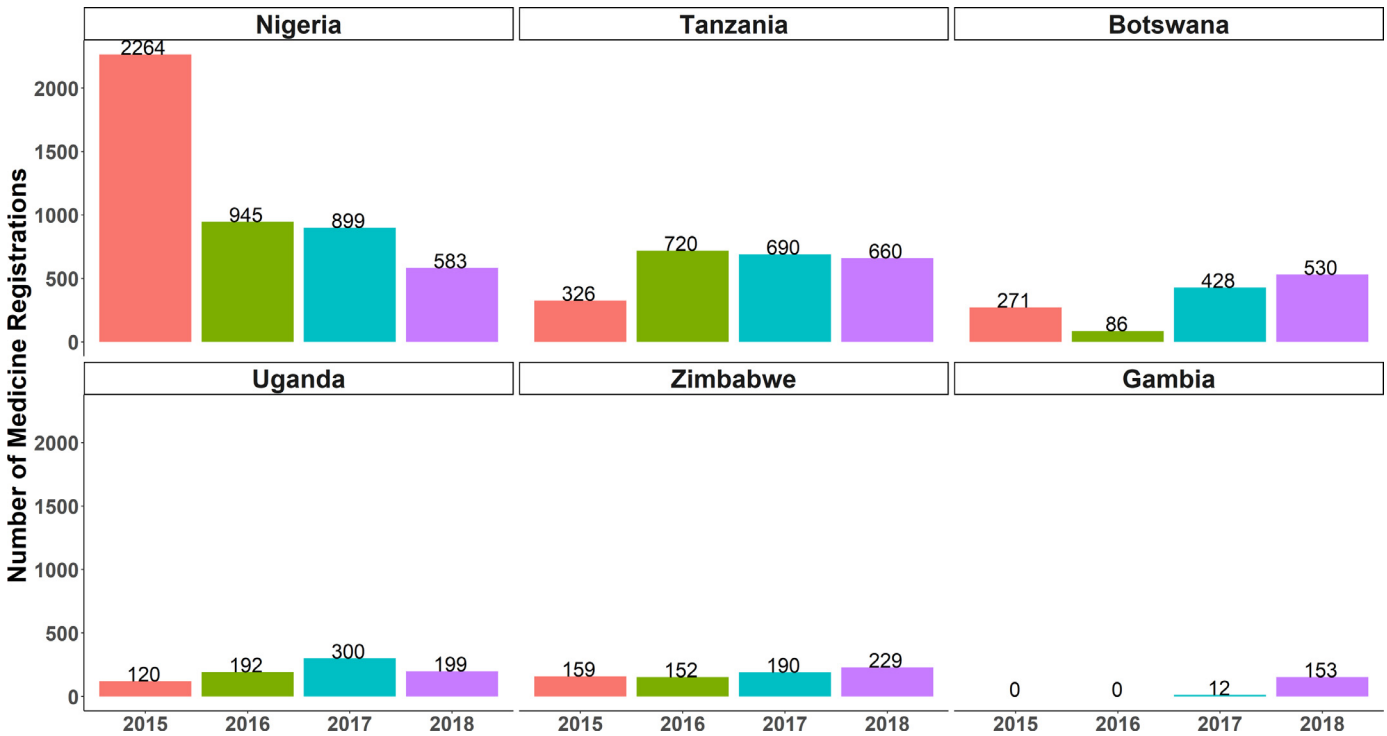

Figure 3. Development of the numbers of medicine registrations per country between 2015 and 2018.

values shows a mixed trend in the selected countries. Although in Botswana no association between the selected variables could be found, Gambia and Nigeria even show a negative association. Only for Tanzania, Uganda, and Zimbabwe is the positive association between clinical trials and drug registrations shown graphically also confirmed by means of the scatter plots.

These trends are also supported by the Spearman rank correlation for the selected variables (Table 3). The values show that Tanzania, Uganda, and Zimbabwe seem to have a positive correlation, whereas Botswana shows no correlation between the variables. Gambia and Nigeria show the same negative correlation between the selected variables as previously in the scatter plot.

In contrast, considering the overall correlation for all selected model countries (Figure 6), it becomes obvious that there is indeed a weak positive correlation between the 2 variables. Consequently, the 2 variables develop in the same direction. It can therefore be assumed that an increase in the number of clinical trials also leads to an increase in medical registrations.

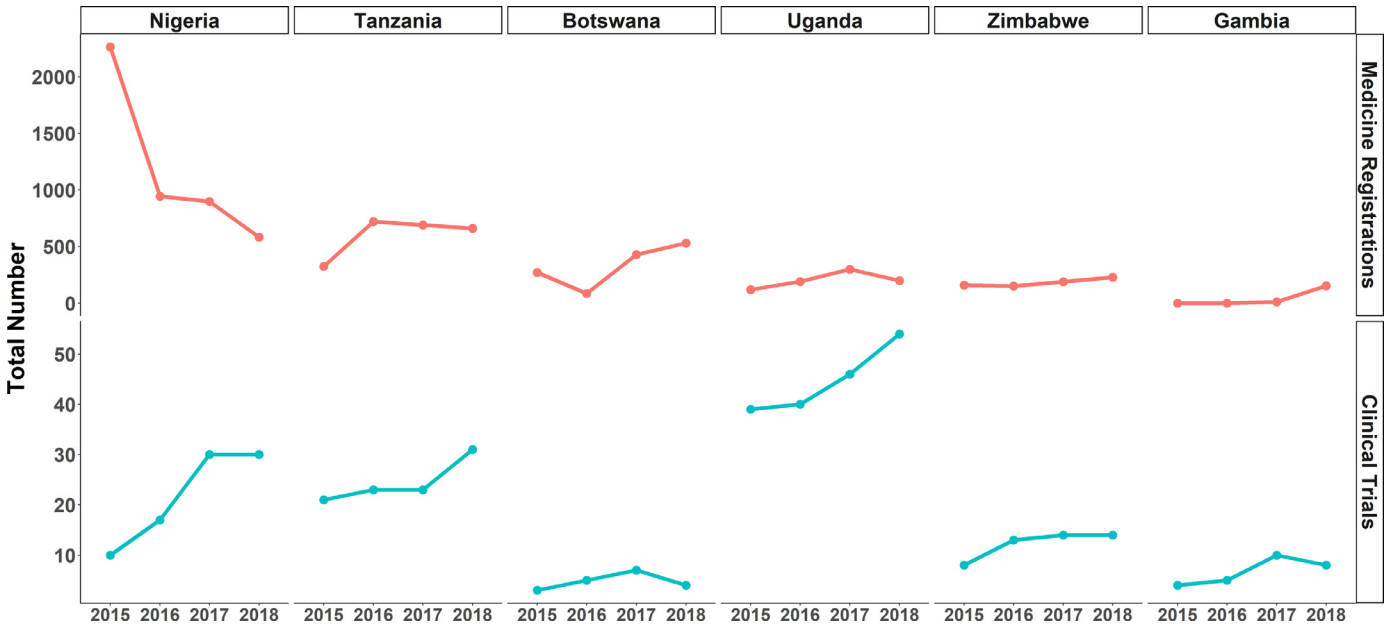

Figure 4. Comparison of the number of clinical trials conducted with medicine registrations.

Table 2
List of the data sets used by the national regulatory authorities of the model countries.

Country	National regulatory authority	Data set
Cameroon	Ministry of Public Health	Directory of appproved drugs (currently not useable)
Gabon	Ministry of Health and Public Hygiene	No register available
Libya	Ministry of Health	No register available
Algeria	Ministry of Health, Population and Hospital Reform	No register available
Tanzania	Tanzania Medicines & Medical Devices Authority	List of Registered Medicines
Uganda	National Drug Authority	Drug Register
Gambia	Medicines Control Agency	Register of Medicines & Related Products
Nigeria	National Agency for Food and Drug Administration and Control	National Agency for Food and Drug Administration and Control Product Table
Botswana	Botswana Medicines Regulatory Authority	List of Registered Human Medicines Database
Zimbabwe	Medicines Control Authority	Human Medicines Register

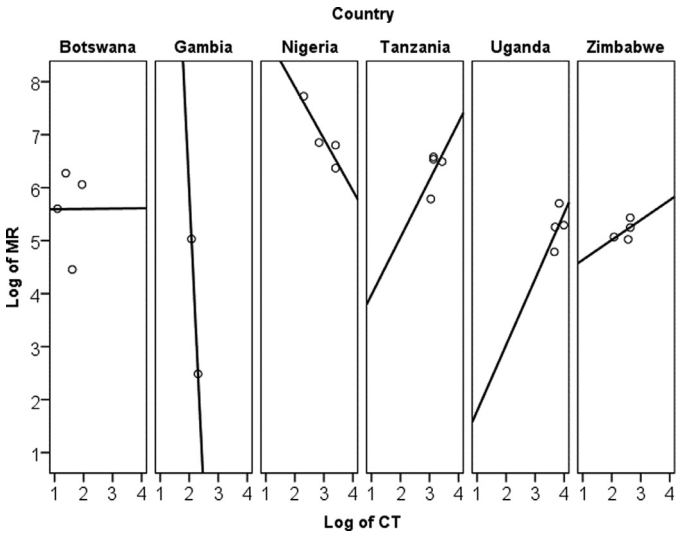

Figure 5. Scatter plots with trend lines for the association between the number of clinical trials (LogCT) and medicine registrations (LogMR) after natural logarithm transformation for each individual model country.

Table 3
Spearman rank correlation coefficient for the number of clinical trials and medicine registrations after natural logarithm transformation.

Country	Spearman's rho	*P* value
Botswana	0.00	1.00
Gambia	−1.00	NA
Nigeria	−0.95	0.05
Tanzania	0.32	0.68
Uganda	0.80	0.20
Zimbabwe	0.74	0.26

Discussion

The current literature shows that there has been a clear shift in clinical research from developed to developing countries during the past few years.[2,12,13] Likewise, this upward trend is also confirmed by our study findings based on model countries selected from the African continent. Eight out of 10 selected countries in the African region show a noticeable increase in the total number of clinical trials, except Libya and Cameroon, which reported a slightly declining trend over the entire period. However, when looking at the annual number of clinical trials in these 2 countries individually, there are years that show a clear increase in research activity. This fluctuating pattern suggests that the development of clinical research in Libya and Cameroon depends on a variety of

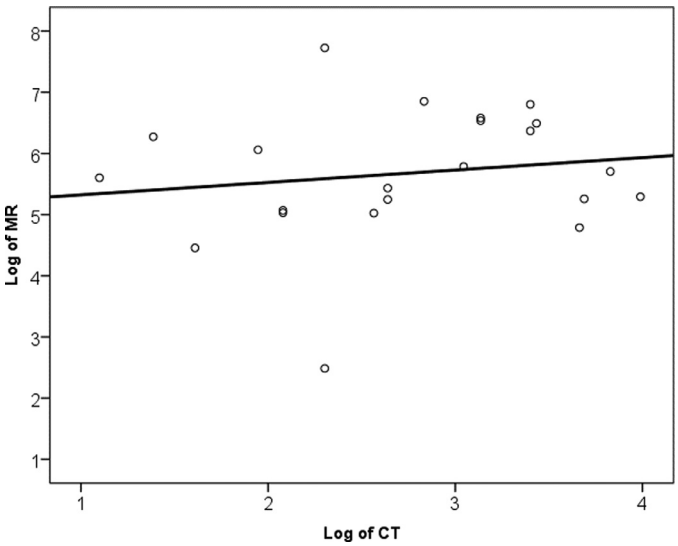

Figure 6. Scatter plot with trend line for the association between the number of clinical trials (LogCT) and medicine registrations (LogMR) after natural logarithm transformation for all selected model countries.

factors that make them unique, thus resulting in a limited number of clinical trials. According to Alemayehu et al,[14] these factors include ethical and regulatory issues, administrative issues, lack of finance, lack of infrastructure, poor data quality, and a lack of training. It may be assumed that the political situation certainly does affect the development of the clinical research infrastructure.

Although developing countries have relatively the highest burden of disease versus developed economies, some of them lack the capacity to carry out substantial research and development activities due to aforementioned factors. However, research-led solutions may reduce the higher mortality rates particularly in the developing countries lacking basic infrastructure.[14]

This results in the requirement for long-term benefits for the participants of clinical trials. In fact, according to the National Bioethics Advisory Commission "the governments of and most people who live in the developing countries where new medical interventions have been tested cannot afford them."[15] Similarly, the National Bioethics Advisory Commission describes this phenomenon as "justice as reciprocity."[15] "In the context of clinical trials, justice as reciprocity could mean that something is owed to research participants even after their participation in a trial has ended, because it is only through their acceptance of risk and inconvenience that researchers are able to generate findings necessary to advance knowledge and develop new medical interventions."[15] Danzon[16] also supports the requirement for long-term benefits, stating that "for the general population in developing nations to have appropriate access to medicines, existing drugs must be affordable, and new innovation is needed to develop new medicines." However, potential long-term benefits include affordability of existing medicines, and the development of new medicines.[17] According to Thiers et al,[17] a diffusion of medical knowledge and effective medical practice are also the potential long-term benefits of using approved medicines properly. According to the National Bioethics Advisory Commission, variety of sponsors such as government agencies, foundations, or private companies in developed countries are of the opinion that "the ethics of research address what happens when a study ends."[15] "For example, South African guidelines refer directly to the availability of treatment to research participants after a trial is completed," whereas the Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda obliges investigators to make every effort to ensure the provision of treatment, without charge to participants in the trial following the conclusion of the trial.[15] Because this study has confirmed the overall increase in the number of clinical trials carried out in the model countries; however, it can be assumed that a similar development in the number of registered medicines can be observed as more testing leads to more successful approvals. This assumption is confirmed by this study. Out of the 6 remaining model countries in the African region, 5 countries, except for Nigeria, show a clear upward trend in the total number of medicine registrations. The increase in the number of registered medicines indicates the expansion of countries' health care systems and suggests that over time, the population will gain more access to medicines to improve what Banerjee et al[18] have described as the worst overall situation in developing countries. According to Edwards et al[19] and Hardwicke et al,[20] the price of medicines plays a major role in this process. Indeed, when medicines are paid for out of pocket, ensuring affordability is also critical.[19] If medicine prices are too high, "cheap drugs are needed, the infrastructure for their effective storage and distribution is needed, as well as the education to ensure their correct administration."[20]

From 2015 to 2018, the apparent decline in medicine registrations in Nigeria from the total of 2264 registrations to 583 reflects the economic crisis of the country, which has been depressing the sales of pharmaceutical products in the Nigerian market since 2015 and, according to experts, had its lowest point in 2018.[21] The situation is expected to ease in the coming years, so that significantly more medicines may be registered for sale in the country. This would be of great importance for the African region because Nigeria's pharmaceutical sales market does not play a major role in a global comparison but is among the most potential market in the Africa alongside those of South Africa and Kenya. This also explains the comparatively high registration figures of Nigeria, in contrast to those of Gambia, Uganda, or Zimbabwe. It is obvious that when the sales market collapses, inevitably less medicine registrations are extended or renewed.

Finally, it can be stated that the globalization has not only increased clinical research in developing countries, but also led to a further development of health care systems, particularly through the expansion of medicine availability. However, an increased availability of more registered medicines does not automatically mean a granted access to these medicines for patients because this still depends on factors such as the pricing policy of the country and possible health insurance schemes. Thus, the idea of the ideal health care situation will only be achieved when all populations have access to essential medicines, even in those countries that do not yet have a well-developed clinical research infrastructure.

Limitations

This study has certain limitations. Firstly, the inclusion of politically unstable countries such as Cameroon or Libya did not prove to be very effective in addressing the research question, as only 1 of the 2 parameters could be investigated due to the lack of data. In these countries, only data on the number of clinical trials conducted could be identified. Due to the lack of data on medicines registrations, these countries had to be excluded from further analysis. Thus, politically unstable countries are not very representative for the research question.

Secondly, we only selected ClinicalTrials.gov registry as an internationally recognized database for the registration of clinical trials to answer the research question on the development of clinical research activities. If available in the model countries, a further search of the total number of clinical trials conducted should be performed in the respective national study registries to check whether a similar development of clinical trial numbers can be observed there as well. If there are no independent national study

registries, it might be useful to search the Pan African Clinical Trials Registry, which is the continental African study registry.

Thirdly, registration figures from 2019 were publicly not available for some model countries, so that a uniform comparison could only be made with the data sets up to 2018 as the most accurate data. It was therefore not possible to conclude on the further development of registration figures during 2019 and 2020.

Fourthly, the medicine registers used by the national regulatory authorities do not differentiate between new drug approvals and extensions of existing medicine approvals. Some registers only allow for a classification of the medicine registrations into original preparations or generic medicines. This means that no conclusions can be made on the total number of new drug registrations, but only on the overall trend in the medicines registration. More detailed information on new drug registrations can only be obtained from the respective national regulatory authorities. This was attempted on a random basis during the processing of the research question on the development of medicine registrations but this effort was not successful.

Conclusions

Contrary to the previous theory that an increase in clinical research inevitably leads to an improvement in medicine registrations, this expectation is only fulfilled in some model countries, despite the correct implementation of the ecological study of 2 parameters. On the other hand, some of the selected countries do not even have a publicly accessible medicine register on the website of the respective national authority, which could provide information on developments in medicine availability. These countries are the country models, which basically show only limited research activity. These differences may be due to factors such as administrative issues, lack of finance, or lack of infrastructure. Differences in political environment among model countries may also be a factor. Thus, a generalization of the increase in research activity and medicine availability cannot be generalized to the entire African region. The individual African developing markets are differently developed in regard to their clinical research infrastructures. So, even if a fundamental increase in medicine availability for the entire population of the countries is urgently needed to contain the prevailing burden of disease and to narrow the bridge between developed and developing countries, and although worldwide development with its continual increase in research activities cannot be ignored, the results of the data collection cannot simply be projected to all other African developing countries. It would be quite challenging to analyze, in a further study based on the collected data, to what extent the tested medicines have led to a marketing authorization in the model countries.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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