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Review Article

Oncology Early-Phase Clinical Trials in the Middle East and North Africa: A Review of the Current Status, Challenges, Opportunities, and Future Directions

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ABSTRACT

Clinical trials, the empirical discipline of medical experimentation conducted on human subjects, have engendered a paradigm shift in medical research. The need for new clinical studies is paramount in the Middle East and North Africa (MENA) region, with its rising cancer incidence and demand for efficient oncology treatments. This paper comprehensively reviews the challenges, opportunities, and future directions of phase I oncology clinical trials in the MENA region. Early-phase trials are vital in determining drug dosage and assessing toxicity, bridging the gap between preclinical research and clinical practice. Considering the unique landscape of MENA, this review explores regulatory aspects, specific hurdles faced, potential advantages, and areas for improvement in conducting these trials. Various future directions can be pursued to maximize the potential of phase I oncology trials in MENA. While regulatory bodies like the Ministry of Health adhere to the International Conference on Harmonization–Good Clinical Practice guidelines, a unified system meeting high standards would yield better results. Strengthening research infrastructure, establishing research centers, incorporating clinical trial education into the curriculum, and improving access to medical facilities are crucial. Enhancing consumer understanding of research would facilitate increased participation and promote sustainability in trial recruitment. Navigating various funding sources would open the door for more funding opportunities. Collaborations between academia, industry, and regulatory bodies, both international and local, should be fostered to promote knowledge sharing, resource pooling, and harmonization of standards. Such collaborations would contribute to the sustainability of clinical trial activities by leveraging collective expertise, sharing research infrastructure, and distributing the burden of regulatory compliance. By adopting these strategies, the MENA region can advance its capacity to conduct early phases of oncology trials and contribute significantly to the global medical research landscape.

Keywords: oncology, early-phase clinical trials, Middle East and North Africa, MENA, practical application, sustainability

INTRODUCTION

Cancer, defined as the rampant growth of anomalous cells, is currently one of the most common groups of diseases affecting different parts of a body. It has a wide range of therapeutic history involving the start of chemotherapy usage in the 1930s for fightback using strong chemicals.[1] With the advent of technology, properly established gene-specific therapies and microtubule-targeting agents are modifying and replacing cytotoxic chemotherapy in developing cancer drugs as phase I clinical trials constantly change to keep up with this new paradigm.[2–4]

Overview of Phase I Oncology Clinical Trials in Drug Development

The accustomed oncologic drug development process includes the following three successive stages: phase I

trials cover the initial examination of novel therapies in humans focusing on toxicity assessment; phase II studies cover the initial formal assessment of treatment with a limited patient count; and phase III trials are arbitrary contrasting studies that assess the effectiveness of the novel therapy in comparison to that of commonplace therapy.[4]

Commonly known as "toxicity trials," phase I studies are employed by medical researchers to determine the recommended dose and timing of an experimental medicinal chemical because they are the foundation for converting the results from preclinical investigation into clinical application. The general consensus is that phase I trials have little to no therapeutic objective and are primarily focused on understanding investigational medicine's pharmacokinetic and adverse event characteristics.[5] Additionally, phase I studies regularly involve phase II additions as proof of their effectiveness, and the period of phase I trials on restricted, unaltered patient groups has started to fade since the turn of the millennium. As a result, throughout the past several years, the Food and Drug Administration (FDA) has granted approval for experimental medications based on the findings of phase I trials. For instance, in the 2014 paper by Chabner[6], ceritinib was authorized for use in patients with non–small cell lung cancer (NSCLC) with an anaplastic lymphoma kinase rearrangement based on an early-stage study's overall response rate (ORR) of 58%[5–7] Other examples include the usage of crizotinib in *ROS1*-altered NSCLC that started as phase I with ORR and later reduced to progression-free survival at endpoints,[8] and embrolizumab in NSCLC, which started as phase I then became seamless with multiple expansion cohorts until approval.[9] Phase I trials carried out in the 1970s and 1980s showed ORRs to range from 5% to 11% compared with 2019 of 20%, proven to increase to 42% by using genomic biomarkers for patient selection.[10,11]

Clinical Research in the MENA Region

According to studies conducted from 2010 to 2012, 31% of clinical trials worldwide are presently being done outside of the United States, and 24% of investigational new drug uses contain data from trials conducted at foreign research sites.[12,13] Many of these clinical trials are being carried out in low- and middle-income nations like India, China, and Egypt, as well as the developing economies of Central and Eastern Europe and the Commonwealth of Independent States.[14] In the last decade, because of the region's fast-growing economy, high population growth, longer life expectancies, decreased mortality rates, and rising rates of lifestyle-related disorders, the need for pharmaceuticals has grown in the Middle East and North Africa (MENA) region.[12]

There was a marginal increase in the number of oncology clinical trials (phases I–IV) in the MENA region, from 47 in 2015 to 53 in 2020.[15] Delving deeper, between 2003 and 2023, 277 clinical trial studies have been related to early phase I and phase I/II oncology based in the MENA region.

However, despite the optimism implied by pharmaceutical industry forecasts, the region is lagging compared with foreign markets in clinical research despite the numerous research-friendly variables such as a huge and diverse patient pool, potentially cheaper operational expenses for clinical trials, and conformity with the International Conference on Harmonization–Good Clinical Practice (ICH-GCP) guidelines. The research utilities, consumer knowledge, and understanding of research have been cited as key elements that create difficulties when conducting clinical trials.

Different MENA countries have different healthcare policies and different financial and context-related considerations.[16] For instance, per the systematic review from Almazrou et al[17] in 2021, the region has subpar access to efficient use of fundamental medical facilities. Additionally, some MENA nations, including Egypt and Morocco, experience a rising incidence of both types of diseases despite the global decline in transmissible illnesses and the rise in noncommunicable disease rates.[18] The lack of physicians per 1000 inhabitants in middle-income nations, such as Yemen, Morocco, Palestine, and Iraq, raises serious concerns for the region's workforce. Additionally, this factor is compounded by the absence of vocational education and instruction, particularly in remote locations.[17]

A Preview of Recent Clinical Trial Studies

Al-Hajri, Al-Khabori, and Rasool evaluated the productivity of clinical trials in the Gulf Cooperation Council (GCC) region for the past two decades, ranging from 2000 to 2020. There were 682 trials reclaimed from National Library of Medicine records, the majority though fixated on phase III and IV trials, with 49.1% thoroughly conducted and 22.1% ongoing in the enrolment process. Of 185,285 worldwide trial records during that period, the GCC nations contributed a relative minimum (0.37%), depicting a rising tendency by a mean of 4.1 trials per year (0.6%) despite the variations.[19] The highest number of contributions came from Saudi Arabia, with 66.6% of clinical trials claimed by the Kingdom, as Bahrain claimed the least with 2.5%.[20] According to Table 1, while clinical trials are ongoing, oncology-related trials in early phases stay at a minimum, apart from Turkey, when considered among the Middle East region. Among the extensive span of domains comprising the clinical trial study, oncology stood out as the most aimed at, weighing 15.5% of all trials conducted, again influenced by the results from the Kingdom of Saudi Arabia.[20] As reported in a study by Alghamdi et al,[21] the Kingdom has sought to have a strong oncologic setup with an increase in the number of cancer and consulting research center facilities and a

Table 1. MENA region countries with leading oncology clinical trials studies[12,15,20,21]

Country	Clinical Studies With Status by December 31, 2012, *N*	Completed Oncology Phase I Clinical Trials	Early Phase I/ Phase/II Oncology Clinical Trials (2003-2023), *N*	Percentage Government Health Spending From Health Expenditure (2019)
Egypt	395	23	43	27.80
Iran	424	10	17	49.50
Iraq	n/a	1	1	49.40
Lebanon	n/a	2	5	49.00
Saudi Arabia	235	2	7	69.20
Tunisia	133	1	2	57.10
Turkey	1091	11	198	78.00

substantial rise in publications in the 2013 to 2017 interval alongside a rise in worldwide collaborations.

Furthermore, as published by Nature News in 2019, the King Abdullah International Medical Research Centre led the Kingdom of Saudi Arabia to its first phase I clinical trial, having assessed a prospective vaccine against the Middle East respiratory syndrome coronavirus, the ChAdOX1. A full research study was established in 2015 after a Middle East Respiratory Syndrome outbreak at a hospital in Riyadh. This followed an association with Oxford, the National Command Center for Clinical Trials, and the Saudi Food and Drug Authority.[22] Meanwhile, the King Faisal Specialist Hospital and Research Centre has an ongoing phase I/II on the safety and effectiveness of investigational anti–PD-L1 monoclonal antibody Durvalumab in combination with paclitaxel for the fight against metastatic triple-negative PD-L1–positive breast cancer.[23]

The current review paper explores the challenges researchers face in conducting early drug development clinical trials in the MENA region, emphasizing oncology phase I trials. It provides a detailed introduction that highlights the latest studies and trends. This is followed by an overview of regulatory bodies and processes in the region, as well as the infrastructure and funding opportunities. Furthermore, challenges researchers face in the region have been discussed in-depth with effective reset strategies for trial control, future research and collaboration recommendations, and, finally, a conclusion.

REGULATORY LANDSCAPE

The MENA nations have different requirements for importing and implementing pharmaceuticals for novel experimental drugs. Regional differences exist in legitimate drug experimentation rights. The procedure for acquiring an investigational new drug is established by the Ministry of Health of each nation. It entails research ethics committee approval after the participating institutions have approved every proposal. Manufacturers of drugs must abide by national labeling, licensing, expiration, and shipping regulations.

Overview of Regulatory Bodies for Clinical Trials in the MENA Region and Comparison with Other Countries

Important regional health authority bodies include the Saudi Arabia Food and Drug Authority, the Republic of Yemen Ministry of Public Health and Population, and the Ministry of Health–Sultanate of Oman. These are congruent with ICH–GCP and GMP guidelines in the drug product registration while documenting the electronic common technical document dossier files as per requirement.[24] Procedure demands typically fluctuate depending on a nation's governing capability, priorities, and standardization. The most extensive, science-based processes align with international norms (ICH) generally appear in well-known organizations such as the US FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, and the European Union European Medicines Agency. Developing authorities frequently have fewer clear guidelines and depend largely on their own judgment or on replicating the structure of other nations.[24]

Application Process for Clinical Trial Studies

As for the GCC countries' data requirements, after registration with the country's FDA through the clinical trial registry system, they should follow the guidelines for GCP, the law of ethics of research on living creatures, and its implemented regulation regarding the registration process of local institutional review boards (IRBs). The applicant must follow FDA-accredited phase I unit guidelines for phase I clinical trials on risk identification and mitigation measures for first-inhuman and preliminary experimental studies with experimental treatment medications.[25] Subsequently, the applicant should submit an annual status report after 1 year of approval. This is dependent on the trial duration, which, if less than a year, requires the applicant to submit a progress report every 3 months. Additionally, each trial site's assignment logbook and documentation of the research team's comprehensive GCP training must be submitted. The steps involved to be followed for meeting the clinical trial regulations include registration of clinical studies with a local body, such as the FDA, completion of regulation requirements as per

guidelines, payment of financial fees for clinical trial file evaluation (for phase IV after IRB approval), submission of progress report as per duration, and conduction and reporting of bioequivalence studies and adverse drug reactions with a study monitoring plan.

Navigating the Regulatory Process with Its Limitations

The demanding prerequisite to observe and abide by multiple regulation amendments is one of the difficulties encountered while carrying out clinical trials in nations advancing with research prospects. Clinical research organizations and study funders must continuously track regulatory developments to prevent interruptions or postponements in present studies. Consequently, the absence of continuous follow-up and poor protocol documentation are two significant causes of the delayed start of investigations, which can extend the approval to 60 to 90 days. Furthermore, clinical research organizations with local headquarters have a major edge as they will likely better understand of the regulatory landscape and the logistical requirements unique to the respective nation.[12]

The capacity of a nation to enact and continually implement laws can also be impacted by bureaucracy and financial constraints. A clear, efficient, and impartial procedure cannot be ensured by clear instructions alone if staff members are overworked and unable to adequately analyze intricate paperwork and information. In some situations, corruption also endangers the credibility of the regulatory system.[24] Universal acceptance of licenses can aid in facilitating worldwide access; for instance, the World Health Organization prequalification helps some registrations in impoverished nations be accepted, although regulatory harmonization demands considerable time, skill, and collaboration. Instead of every nation creating new norms, bilateral and multilateral agreements offer another way to leverage other thorough evaluations.[26]

CHALLENGES AND OPPORTUNITIES

The conduction of early phases of oncology clinical trials in the MENA region faces challenges that could hold back the region's contribution to the global effort to develop new cancer treatments. From June 1, 2003, until June 25, 2023, only 8 of 19 countries in the MENA region conducted phase 0, phase I, or phase I/II oncology clinical trials, resulting in a total of 79 clinical trials (Table 2). While conducting early phases of oncology clinical trials face challenges worldwide, including in leading countries like the USA and EU, the MENA region could face additional challenges that limit its contribution. These challenges include limited infrastructure and funding opportunities, patient and community awareness, industry and global research community collaborations, and regulatory challenges.

Personnel Capacity

Medical schools and teaching hospitals in the MENA region do not adequately prepare their graduates to conduct clinical research.[12] This is particularly true for early-phase clinical trials, which are not typically incorporated into the curriculum. Furthermore, postgraduate training, such as early phase trials/drug development fellowships after finishing basic oncology training, is not currently present in the MENA region. In contrast, they are available in North America and large European centers. Additionally, there is a shortage of trained other healthcare professionals, such as nurses, laboratory specialists, and other professionals, who are essential for conducting early-phase clinical research. This shortage further limits the ability of medical schools and teaching hospitals in the MENA region to prepare their graduates for clinical research, as well as limit the mentorship and creating related training program opportunities.[12]

Furthermore, the lack of proper research and manuscript writing education presents another challenge for conducting early-phase oncology research in the MENA region. Such skills are essential for securing funding for clinical trials, collaborating with potential international researchers, and effectively communicating research findings.[12]

Oncologists in the MENA region face time constraints and competing priorities that limit their ability to conduct oncology-related clinical trials.[27] The high prevalence of burnout among oncology professionals in the region, which accounts for 68% according to cross-sectional research conducted in 2020,[28] only exacerbates this issue. Moreover, unlike in other regions, conducting clinical research is not typically supported or promoted by institutions and hospitals in the MENA region. This lack of support and the additional challenges of conducting early-phase trials further limit physicians' ability to engage in clinical research.[29]

Multiple initiatives have been launched by governments and organizations in the region to tackle these challenges, including offering academic programs for conducting clinical trials, providing scholarships for studying and training abroad, and raising awareness of the importance of oncology clinical trials among healthcare professionals. Most of these initiatives are planned by governments of the GCC countries, such as Saudi Arabia. For example, in August 2023, the Saudi National Institute of Health was authorized to launch various initiatives to improve the ecosystem of clinical trials in the country.[30] The primary objective of these initiatives is to enhance the infrastructure, support system, and training opportunities available for researchers in the region.[30]

Specialized Facilities and Access to Equipment

Oncology clinical trials are usually conducted in specialized cancer centers and research institutions. Because

Table 2. Information on early phase and phase I oncology clinical trials from June 1, 2003-June 25, 2023, in the MENA region

Country*	Number of clinical trials	Study Type	Phase	Status	Funding Source *n*, (%), Type**
Total	79	All interventional	11 early phase I 68 phase I or I/II	3 not yet recruiting. 5 recruiting, 1 active, not recruiting. 40 completed, 1 enrolling by invitation 3 withdrawn 26 unknowns	11, (13.9), industry, 73, (92.4), All others (individuals, universities, organizations) (Note: 6 studies were funded by both industry and organization)
Egypt	43	All interventional	8 early phase I 35 phase I or I/II	1 not yet recruiting. 2 recruiting, 1 active, not recruiting. 23 completed, 1 enrolling by invitation 1 withdrawn 14 unknowns	3 industry, 40 all others (individuals, universities, organizations)
Iran	17	All interventional	1 early phase I 16 phase I or I/II	2 not yet recruiting. 1 recruiting, 10 completed, 4 unknowns	2 industry, 17 all others (individuals, universities, organizations) (Note: 2 studies were funded by both industry and organization)
Saudi Arabia	7	All interventional	1 early phase I 6 phase I or I/II	1 recruiting, 2 completed, 4 unknowns	2 industry, 7 all others (individuals, universities, organizations) (Note: 2 studies were funded by both industry and organization)
Lebanon	5	All interventional	5 phase I or I/II	3 completed, 1 withdrawn 1 unknown	2 industry, 3 all others (individuals, universities, organizations)
Jordan	3	All interventional	3 phase I or I/II	1 recruiting, 1 withdrawn 1 unknown	1 industry, 2 all others (individuals, universities, organizations)
Tunisia	2	All interventional	2 phase I or I/II	1 completed, 1 unknown	1 industry, 2 all others (individuals, universities, organizations) (Note: 2 studies were funded by both industry and organization)
Iraq	1	Interventional	1 Early phase I	1 completed	1 all others (individuals, universities, organizations)
Sudan	1	Interventional	1 phase I or I/II	1 unknown	1 all others (individuals, universities, organizations)

Note – Based on information from ClinicalTrials.gov.
*The following countries held no early phases, phase I, or I/II trials: UAE, Algeria, Bahrain, Yemen, Kuwait, Libya, Morocco, Oman, Palestine, Qatar, and Syria.
**Funding could hold 1 or more funding types.

early phases of oncology clinical trials involve the development of new treatments, they require specialized and equipped facilities, such as clinical trial units, specialized laboratories, and related technology.

Unfortunately, the MENA region has a limited number of specialized facilities prepared to host early phases of oncology research.[15] The total number of specialized facilities or centers ready to host early phases of clinical trials is not easily accessed nor published online. This may create a challenge in analyzing the challenges and opportunities that could help increase the number and advance the usage of such places. Moreover, it can create a challenge for interested local and global stakeholders and individuals interested in collaborating to conduct early phases of oncology clinical trials.

Building specialized facilities for conducting early-phase oncology clinical trials has a multifactorial aspect. Its existence is linked to other factors such as support of major cancer centers, available funding, regulatory requirements, and available experienced clinical research professionals. Nevertheless, the number of clinical research units at research institutions and hospitals is rapidly growing in some countries in the region, given that the number of overall conducted clinical trials has increased compared with previous years. For example, in 2018, Egypt achieved the highest growth in research output worldwide, setting a remarkable precedent.[31]

Patient and Communities

Patient and community awareness of the importance of early phases of clinical trials in oncology is crucial to enhancing participation rates. However, the challenge of patient recruitment in the early phases of clinical trials is faced by researchers worldwide, including in the MENA region.[32] A cross-sectional survey about clinical research participation motivators and barriers in a MENA country reported that 70% of participants agreed on the importance of clinical research in health promotion, and 63% were willing to participate in future clinical research, while only 25% were recruited to participate.[33] Participants reported that online information and healthcare staff were the main sources of information for clinical research participation.[33] A similar study conducted in Saudi Arabia showed that 64% reported being knowledgeable about the importance of clinical research, and 69% were willing to participate in clinical trials.[34]

These findings suggest that patients in the MENA region accept the idea of clinical research participation, and this could be an opportunity for stakeholders and oncology researchers to take the initiative to invite, educate, and spread awareness of early-phase oncology medical research. Nevertheless, there is a limitation to the number of available research dedicated to understanding patients' participation experience and unique perspectives of early-phase oncology clinical trials.

Global Research Community and Industry

International collaborations can open doors to many new opportunities for oncology clinical research in the MENA region. These collaborations can provide access to experts and brilliant researchers from around the world, new research and treatment ideas, funds, and resources that can maximize the quantity and quality of clinical trials in the region.[35] However, the MENA region has fewer international collaborations than leading countries, which could be due to factors such as regulatory complexity, political concerns, and language and cultural barriers.[15] Collaborating with researchers in the MENA region can offer promising opportunities such as cost savings in conducting clinical trials, collaboration with brilliant minds in the region, access to a growing population, and opportunities to advance and develop new treatments in a promising and growing region.[36]

Access to Funding

Finding a sponsor for clinical research is a crucial part of the study process that cannot be completed without sufficient funds to cover the study's costs. In the MENA region, the lack of funding is one of the top barriers faced by oncology researchers.[27] Funding for clinical trials can come from various sources, including the government, industry, universities, not-for-profit organizations, and other research institutions. However, obtaining funding from these sources can present challenges, especially for early-phase clinical trials. Such trials necessitate substantial financial resources, and their benefits are often realized only after a considerable period, in contrast to late-phase trials.[29] Nevertheless, there are ongoing efforts to increase funding for oncology research in the MENA region, including the establishment of public–private partnerships and increased collaboration between researchers and industry partners.[15]

A percentage of early phases and phase I clinical trials funding sources were reviewed using ClinicalTrials.gov for both the MENA region and the following five leading countries: the United States, China, Spain, France, and Canada.

Industry fund

The industry contributes to funding most oncology early-phase clinical trials in most leading countries by either being the sole source of sponsorship or with additional other types of sponsoring parties (Table 3). The percentage of industry-sponsored early phases and phase I clinical trials for leading countries were 58.9%, 62.3%, 93.9%, 83.0%, and 72.1% for the United States, China, Spain, France, and Canada, respectively (Table 3), while only 13.9% of the early-phase and phase I clinical trials in the MENA region were industry sponsored (Table 2). This could be due to the limited number of regional-based pharmaceutical companies in addition to regulatory, cultural, and language barriers for interested foreign companies.[15]

Table 3. Information on early-phase and phase I oncology clinical trials from June 1, 2003-June 25, 2023 in the United States, China, Spain, France, and Canada

Country	Number of Clinical Trials	Study type	Phase	Status	Funding *n*, (%), type*
United States	12,604	All interventional	869 Early phase I 11,735 phase I or I/II	220 not yet recruiting. 2641 recruiting, 1433 active, not recruiting. 5595 completed, 1980 terminated 21 enrolling by invitation 95 suspended 369 withdrawn 250 unknown	2641 (21.0), NIH 98 (0.78) other US federal agency 7422 (58.9), industry 6663 (52.9), all others (individuals, universities, organizations)
China	2778	All interventional	275 early phase I 2503 Phase I or I/II	179 not yet recruiting. 1181 recruiting, 145 active, not recruiting. 435 completed, 68 terminated 23 enrolling by invitation 12 Suspended 28 withdrawn 707 unknowns	16 (0.58), NIH 1731 (62.3), industry, 1520 (54.7), all others (individuals, universities, organizations)
Spain	1288	All interventional	16 Early phase I 1272 phase I or I/II	10 not yet recruiting. 384 recruiting, 213 active, not recruiting. 503 completed, 147 terminated 4 suspended 11 withdrawn 16 unknowns	1 (0.08) NIH 1210, (93.9), industry. 171 (13.3), All others (individuals, universities, organizations)
France	1256	All interventional	14 early phase I 1242 phase I or I/II	11 not yet recruiting. 299 recruiting, 166 active, not recruiting. 560 completed, 155 terminated 0 enrolling by invitation 2 suspended 16 withdrawn. 47 unknowns	2 (0.16), NIH 1042 (83.0), industry, 336 (26.8), All others (individuals, universities, organizations)
Canada	1149	All interventional	24 early phase I 1125 phase I or I/II	4 not yet recruiting. 229 recruiting, 166 active, not recruiting. 565 completed, 121 terminated 1 enrolling by invitation 5 Suspended 14 withdrawn. 44 unknowns	96 (8.4), NIH 829 (72.1), industry, 356 (31.0), All others (individuals, universities, organizations)

Note – Based on information from ClinicalTrials.gov.
*Funding could hold 1 or more funding types.
NIH: National Institutes of Health.

Public sector, universities, nonprofit organizations, research institutions, and others

Clinical trials funded by nonindustry sponsors are contributing to numerous successful clinical trials worldwide. Nonindustry sponsors allow for more variety in the types of hypotheses, such as testing new surgery techniques, screening, prevention, and diagnostic strategies, compared with industry-funded clinical trials, where they invest mostly in a drug-centered approach in clinical research.[37]

Although most funds come from nonindustry sponsors in the MENA region, which account for 92.4% of sponsored early phases and phase I clinical trials, it is likely due to the small total number (79) of conducted early phases oncology clinical trials compared with other leading countries (Tables 2, 3).

Other international funding agencies

It is worth mentioning that the National Institutes of Health (NIH) offers international grants to support research conducted by non-US countries. Quoting the NIH information website: "Applications for research grant support from foreign organizations are treated as if they were applications from domestic organizations."[38] NIH funds approximately 2641 early-phase and phase I clinical trials in the United States, and the number of funded trials ranges from 1 to 96 in China, Spain, France, and Canada (Table 3). On the other hand, none of the early phases and phase I oncology clinical trials in the MENA region were funded by NIH (Table 2). This could be due to a lack of awareness of international funding opportunities by regional organizations and researchers. The region offers a comparatively lower cost for conducting clinical trials in comparison to prominent countries. Conducting clinical trials in the MENA region can cut the costs to 59% compared with the US.[12]

This circumstance presents an opportunity to attract international funders inclined to invest in early-phase oncology clinical trials within the region.

CASE STUDIES OF SUCCESSFUL ONCOLOGY PHASE I CLINICAL TRIALS

According to a recent study, despite making up approximately 23% of the total population of the MENA region, investigators from Fragile and Conflict-Affected Settings contributed 6.5% of the region's cancer research output.[39] Iraq, Syria, and Lebanon were the three countries with the largest publishing output at the national level. There was no apparent association between gross domestic product per capita and cancer research in the investigated nations. Strategies should be advocated for creating creative, open-access training possibilities that emphasize improving fundamental, clinical, and qualitative research abilities. Initiatives to build research capacity should promote examining context-specific research issues with the potential to significantly affect cancer prevention in the area.[40] As for oncology phase I studies completed in the region, a few, as presented in Table 1, have been discussed here.

A study conducted in Egypt in 2016 explored the impact of rifampin on the pharmacokinetics (PK) of vemurafenib (Zelboraf) with sponsorship from Hoffmann–La Roche. This open-label, multicenter, three-period, one-sequence study looked at how rifampin influenced the PK of vemurafenib in patients with metastatic, inaccessible melanoma with the *BRAFV600* mutation or other cancers with the mutation with no standard alternatives to therapy.[41] A continuation of vemurafenib therapy was an option for eligible individuals in the extension trial.[16]

Another study posted in 2021, conducted in Lebanon with sponsoring from Novartis Pharmaceuticals, was a phase I/II study of PDR001 in patients with advanced malignancies. This "first-in-human" PDR001 research aimed to investigate the safety, tolerability, PK, PD, and anticancer efficacy of PDR001 when delivered intravenously as one medication to adults with malignant cancers. Phase I and II dose increment parts were both included in the study's multicenter, open-label design. PDR001 was provided every 2 weeks until the patient encountered intolerable side effects, a disease that progressed according to immune-related response criteria, or until the treatment was stopped by the patient or researcher's decision.[42]

A clinical trial study conducted in Saudi Arabia sponsored by King Faisal Specialist Hospital & Research Center in collaboration with AstraZeneca was first posted in 2015, with a last update in 2020. It was about the safe administration and effectiveness of durvalumab in combination with paclitaxel in metastatic triple-negative breast cancer patients. Three dosages of paclitaxel were evaluated on three patients each in the trial's dose-decreasing phase, followed by a dose-increase phase including 25 patients. After a single cycle of weekly Paclitaxel administration, paclitaxel and durvalumab were administered. Durvalumab was given alone once six cycles of paclitaxel were finished until the disease progressed or the toxicity became intolerable. The efficacy was a secondary endpoint, with the toxicity and tolerability of the combination serving as primary endpoints.[43]

FUTURE RECOMMENDATIONS FOR TRIALS IN THE MENA REGION

It is important to recognize the barriers facing researchers in the region to find appropriate solutions that will aid in solving them. Governments, industries, organizations, and individuals in the region are all responsible for recognizing such barriers and constructing initiatives to help overcome these challenges.

Funding Access

Shifting governments' funding priorities to invest in research infrastructure and fund more oncology clinical

research is crucial for advancing cancer treatment and improving patient's quality of life in the MENA region. In particular, investing in early-phase clinical trials is essential, given the region's unique genetics and population niche. By supporting early-phase clinical trials, governments can provide researchers with the resources needed to investigate new treatments and therapies and accelerate the development of new cancer drugs.[44] Furthermore, investing in research infrastructure can help to create a more favorable environment for clinical research in the region and attract more international stakeholders to fund oncology clinical trials. Ultimately, this investment can improve cancer care and outcomes for patients in the MENA region and beyond.

In addition to navigating available traditional funding sources like government entities, industry partnerships, universities, and nonprofit organizations, researchers, research institutions, and organizations must recognize and explore alternative funding sources.

These alternative funding sources included crowdfunding platforms, which helped raise approximately 115 million dollars and have been allocated to multiple research projects.[45] The utility of this approach was deliberated in the context of pilot or phase I studies, considering the decline in funding provided by government agencies for such research endeavors[46]; collaborations with international researchers and funders will help national researchers in the MENA region get access to funds and resources, which in return help cover their study's cost.[47] Leveraging these additional funding sources can provide valuable support for clinical research endeavors within the region.

Collaborations

Collaboration between industrial corporations, local experts, and businesses in the MENA region can benefit clinical research by easing the regulatory process and improving communication. Local experts and businesses can provide valuable knowledge of the regulatory requirements in the region, which can help streamline the process of conducting clinical research and minimize delays. Moreover, collaboration with local partners can help industrial corporations to better understand the region's cultural and linguistic nuances, which can improve communication and enhance the success of clinical trials. By working together, industrial corporations and local partners can establish strong relationships and build trust, which can lead to more effective collaborations and greater success in conducting oncology clinical trials.[48] Such collaborations can facilitate the transfer of expertise, promote innovation, and accelerate the progress of clinical trials. More research is needed in this area, investigating opportunities and challenges regarding collaboration and international funding in the MENA region.

Infrastructure and Sustainability

Large academic centers within the MENA region must encourage and foster clinical research at the highest standards. Additionally, building national clinical and translational research capacity is important to increase the capacity to conduct clinical trials. Centers should have specific considerations about the infrastructure related to creating a clinical trial unit dedicated to conducting early-phase trials with sustainability in mind. These routinely have unique designs with infusion facilities, advanced pharmaceutical capabilities with storing, mixing, and advanced compounding abilities, and others. Additionally, building and sustaining infrastructure will improve local training and professional development.[49] It is recommended to allocate dedicated funding for long-term investments in infrastructure and professional development. Organizational structure, dedicated space and facilities, and the presence of institutional human research infrastructure and standard operating procedures are all important factors to be considered by centers when setting up a clinical trial unit within an academic facility.

Training and Education

Training plays a vital role in the professional development of individuals conducting early-phase oncology clinical trials in the MENA region. In this highly specialized field of clinical research, it is crucial to acquire comprehensive knowledge and practical skills and cultivate the appropriate attitude. Additionally, it is equally important to establish distinct levels of training suited to the specific functional roles of clinical research professionals in this region, such as team leaders, physicians, pharmacists, nurses, and data handlers.

Including clinical trial education within the medical school curriculum has resulted in enhanced comprehension of clinical research among students, improved communication skills regarding the clinical trials process, and increased confidence in conducting, referring to, and identifying clinical trials.[50] This is a crucial step, specifically in the context of early-phase oncology trials conducted in the MENA region.

Further epidemiologic and qualitative research regarding the quantity and quality of programs offering early-phase clinical trials in the MENA region is needed.

Regulatory Aspect

Easing the process of national pharmaceutical production and encouraging local pharmaceutical companies to fund oncology clinical trials is important to advance oncology patient care. Additionally, unifying and easing regulatory processes for interested foreign companies to invest in oncology medical research in the MENA region is crucial. The complexity and slow approval process for clinical trials can discourage interested production companies from investing in research in the region. By reforming regulatory processes and

increasing transparency, the region can attract more international stakeholders to fund oncology early-phase clinical trials, ultimately advancing the development of new cancer treatments. Regulatory reform has the potential to not only improve the funding landscape for clinical research in the MENA region but also to stimulate economic growth and create new job opportunities in the healthcare sector.

Study start-up time is a critical step and is routinely measured from submitting the clinical trial to the first enrolled patient. Competitive centers in North America and Europe have short start-up times, which gives them a major advantage when being considered for early-phase trials by industry and other trial sponsors.

Streamlining regulatory and ethical reviews to coincide will certainly be advantageous. This has to occur, however, with a careful and robust review process. Applying for a central institutional review board (IRB) instead of a local IRB for study approval results in faster decisions.[51] The central IRB took 7 days on average to reach a decision compared with 35 days for the local IRB.[51] Furthermore, independent and private practice sites were found to have less cycle time compared with academic and hospital-based sites in the United States.[51] There is a need for similar studies to be conducted in the MENA region to effectively address challenges and capitalize on opportunities in early-phase oncology clinical trials. These studies would provide valuable insights and serve as a guide for future trial start-up implementation within the region. Also, providing a "fast-track" priority for trials that need a rapid research ethics review, such as what has occurred during the COVID-19 era for vaccine trials and what is currently occurring for Monkey Pox studies, should be considered for phase 1 trials in the MENA region.

Patient Enrollment

Centers being considered for early-phase trials in the MENA region should have a strategy for patient enrollment to ensure that this occurs without delay. Dose-escalation phase Ia trials, which use specific dose-escalation strategies, commonly use competitive patient enrollment slots where when a patient is enrolled, another may be enrolled at a different time point, and likely once the dose level is cleared. This means that there are carefully selected time points where enrollment can happen for a very small number of patients, and hence, this becomes competitive between active centers. Whereas dose-expansion phases (e.g., Phase Ib) that use certain biomarkers as prerequisites for enrollment may need different strategies to help enroll patients. These may include local hospital patient database interrogation, if feasible, and engaging neighboring hospital physicians and encouraging them to do early referrals for these patients.

Advertising locally for such trials may also increase uptake. Engaging patient advocacy groups will also certainly be advantageous as it encourages participation and may help recruitment when patients of certain diseases/histologies are needed.

Increasing consumer understanding and awareness of clinical research is also needed for the success of oncology trials in MENA. Educating the public about the importance of clinical trials and their potential benefits and dispelling misconceptions can encourage greater participation. This can be achieved through community outreach programs, public awareness campaigns, and engaging with patient advocacy groups.

However, there is a need for more studies regarding participants' perspectives and awareness dedicated to participation in oncology early-phase clinical trials. Furthermore, more research is needed to investigate cultural and social challenges related to patient recruitment in the MENA region. Also, further research investigating the number of patients evaluated for clinical trials is needed. Such studies could help identify additional barriers to participation to enhance patient recruitment and increase the success of early-phase clinical trials in the MENA region.

In-House Molecular Profiling and Precision Oncology Team

Initiating an individualized molecular profiling program in countries of the MENA region and establishing an in-house capability for molecular profiling can have significant benefits for early-phase oncology clinical trials in the region. In-house molecular profiling helps enhance patient selection for clinical trials. Identifying patients with specific genetic profiles that match the targeted mechanisms of investigational drugs increases chances of observing positive treatment responses.[52] This improves patient selection for clinical trials and enhances the overall success rates of early-phase oncology trials in the MENA region.

Furthermore, individualized molecular profiling data can provide valuable insights into tumor heterogeneity and prevalent molecular subtypes in the MENA region. This information can aid in designing more precise and effective clinical trials, ensuring that the investigational therapies align with the specific molecular characteristics of the patient population. Consequently, this can lead to more successful trial outcomes, improved patient outcomes, and a better understanding of the regional oncology landscape.[52]

Implementing an in-house individualized molecular profiling program in the MENA region also facilitates collaborative research. By sharing molecular profiling data and findings, researchers, clinicians, and institutions within the region can form partnerships and collaborations that promote knowledge exchange, accelerate research efforts, and strengthen the early-phase oncology clinical trial ecosystem in the MENA region. Additionally, it can attract global sponsorship and pharmaceutical companies to the MENA region. The availability of

comprehensive molecular profiling data instills confidence in sponsors, providing a solid foundation for patient selection and treatment decision-making.

Incorporating precision oncology team support is of utmost importance in early-phase oncology clinical trials, specifically in the context of molecular profiling. These teams include experts from various disciplines, such as trained oncologists, molecular biologists, geneticists, and bioinformaticians, who collaborate to ensure accurate and reliable molecular profiling data. Their expertise in molecular technologies, data interpretation, and standardization is crucial for identifying actionable mutations and genetic alterations, correlating biomarkers with potential treatment responses, and optimizing patient selection. Precision oncology teams also contribute to trial design, ongoing monitoring, and treatment modifications based on molecular changes, enhancing the overall success and efficacy of early-phase oncology clinical trials.[53]

CONCLUSION

The MENA region faces challenges but also offers opportunities in oncology clinical trials. Efforts should be made to address regulatory and funding challenges, improve research infrastructure, enhance access to medical facilities, promote consumer understanding, foster collaborations, and focus on areas for improvement. By doing so, the region can become a hub for oncology clinical trials and contribute to global cancer research and treatment.

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