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## **Regulations and Recruitment**

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# Regulations and Recruitment: Experiences in the Middle East



The potential for the pharmaceuticals industry in the Middle East is vast, and growing. Clinical research is also growing, alongside pharma, in the region, despite variations in situation from country to country, and despite certain barriers that still need to be solved. The challenges of regulations and patient recruitment, in particular, are analysed. We take a specific look at one of the most established countries in the region for clinical trials, Turkey, to see how it might act as a model for the rest of the region.

Home to 410 million people,<sup>1</sup> or 5.6% of the world's population, the countries of the Middle East form a small but significant patient cluster, not yet fully explored for the purposes of clinical research. The region actually runs 5.1% of the trials registered on clinicaltrials.gov, but Israel, which has a developed clinical infrastructure, takes a large proportion of this. Taking out Israel, the rest of the Middle East performs 2.5% of the trials, despite having a population which is 5.5% of the world's.<sup>2</sup> Of the remaining countries, the standout star, with a high number of trials and a high level of trials per capita, is Turkey. Table 1 shows the relevant numbers for each country, as well as for the region as a whole.

	Pop '000 (UN, 2015)(1)		#trials (clinicaltrials.gov, 2017)(2)		Trial share vs population share	Pharmaceuticals market (3) (4)
<b>WORLD</b>	<b>7 349 472</b>		<b>240 154</b>			<b>1 200</b>
Bahrain	1 377	0.02%	56	0.02%	4.81%	147%
Cyprus	1 165	0.02%	56	0.02%	4.81%	147%
Egypt	91 508	1.25%	1 442	0.60%	1.58%	48%
Iran (Islamic Republic of)	79 109	1.08%	828	0.34%	1.05%	32%
Iraq	36 423	0.50%	19	0.01%	0.05%	2%
Israel	8 064	0.11%	6 076	2.53%	79.59%	2300%
Jordan	7 595	0.10%	134	0.06%	1.76%	54%
Kuwait	3 892	0.05%	64	0.03%	1.64%	50%
Lebanon	5 051	0.07%	322	0.13%	5.00%	168%
Oman	4 491	0.06%	28	0.01%	0.62%	19%
Qatar	2 235	0.03%	80	0.03%	3.58%	110%
Saudi Arabia	31 540	0.43%	474	0.20%	1.50%	46%
State of Palestine	4 668	0.06%				
Syrian Arab Republic	18 502	0.25%	53	0.02%	0.29%	9%
Turkey	78 666	1.07%	2 440	1.02%	3.10%	95%
United Arab Emirates	9 157	0.12%	149	0.06%	1.63%	50%
Yemen	26 832	0.37%	2	0.00%	0.01%	0%
<b>Middle East</b>	<b>411 077</b>	<b>5.6%</b>	<b>12 167</b>	<b>5.1%</b>		<b>23</b>
<b>Middle East minus Israel</b>	<b>403 013</b>	<b>5.5%</b>	<b>6 091</b>	<b>2.5%</b>		
ME minus Israel, minus Egypt	311 505	4.2%	4 649	1.9%		
ME minus Israel, minus Turkey	324 347	4.4%	3 651	1.5%		
ME minus Israel, Turkey, Egypt	232 839	3.2%	2 209	0.9%		

Table 1: Population, clinical trials and pharma size by country in the Middle East.

It should be noted that these statistics only reflect trials which are reported on clinicaltrials.gov. The authors' own research has found that Iran, for example, is currently running up to 13,500 trials, reported in the country's own registries, and run as investigator-initiated trials.

## The Growth of the Pharma Market in the Middle East

The global pharmaceuticals market is USD 1.2 trillion in size and is projected to grow to USD 1.5 trillion by 2021.<sup>3</sup> Of that amount, USD 26 billion is projected to be spent in the Middle East in 2017. This is less than 2% of the total, but the Middle East share is growing at 12–14%, one of the highest growth rates in the world.<sup>4</sup>

In the Middle East, growth is driven by a number of factors. First, population growth has led to an increasing population requiring medical treatments. The area reportedly has a high prevalence for some rare and genetic diseases, with an estimated

more than 2 million people in the Middle East suffering from a rare disease.<sup>4</sup>

Second, the high rate of economic growth has increased access to better healthcare, which has a number of consequences. Better healthcare in itself costs money, but the health benefits are improved mortality rates and longer life expectancy, meaning people have more years of treatment and drug consumption. Longer life expectancy also leads to higher incidence of lifestyle diseases, for example those associated with smoking and alcohol. Obesity, diabetes and cardiovascular disease are on the rise, and six countries of the Middle East are among the top 10 globally in terms of prevalence of Type-2 diabetes.<sup>5</sup>

Increased affluence also creates a more selective, health-conscious and treatment-aware population, with sophisticated healthcare needs. The Middle East shows a marked predilection for innovative treatments. In her essay "Diabetes in the Middle East and North Africa: a high growth pharmaceutical market receptive to innovation", Carolyn Gauntlett reports: "... a strong share of spend on the modern insulins, and the newer innovative classes of pre-insulin diabetes treatments, the DPP-IVs and the GLP-1s. In Kuwait, spend on innovative treatments accounts for 73% of all diabetes IMS audited diabetes spend; in the UAE this is 68%".<sup>6</sup>

Governments across the region encourage strong healthcare programmes, backed up by reimbursement for rare disease treatments.<sup>4</sup> Improvement of infrastructure increases the patient base by improving diagnosis rates, in turn. A combination of weaker IP protection and an encouragement of the development of local industry has gone hand in hand with a push for affordable, lower-priced medication, meaning that generics will be a major market driver (and that market growth will come from volume growth).<sup>7</sup>

## Drivers for Clinical Research in the Middle East

There are clear, high expectations for the growth in clinical trials in the Middle East. Quintiles has estimated a market of about USD 1 billion by 2022 in the whole MENA region.<sup>8</sup> This growth will be driven by many factors.

First, the region has a high and growing population. MENA had the highest rate of population growth of any region in the world in the 20<sup>th</sup> century, and the region is projected to increase by a further 87% again between 2001 and 2050.<sup>9</sup>

Both the growth of the population and the growth of the pharma market are drivers for the growth of clinical research in the region. With the growth of pharma comes the increased relevance of drugs developed for local genotypes, growth in local manufacture, and the efficiency savings of early regulatory approval.

As we have seen, the Middle East has a high incidence of some rare diseases. According to the Center of Arab Genomic Studies (CAGS), there are 774 genetic disorders caused mainly by recessive genes, possibly as a result of a high rate of consanguineous marriages.<sup>4,8</sup> These diseases include diabetes mellitus (for which people in MENA exhibit the second highest prevalence), and orphan

diseases such as Gaucher's disease, Fabry disease, Behçet's disease, thalassemia and sickle cell anaemia. The region also has high levels of hepatitis, chronic respiratory diseases, such as asthma, cancer, cardiovascular disease, obesity and psychiatric diseases.<sup>8,10,11</sup> Studies have shown that 3% of pregnancies result in a child with a significant genetic disease.<sup>11</sup> As a result, governments in the Gulf region reimburse for rare diseases.<sup>4</sup>

Running clinical trials in countries with high prevalence of certain diseases also allows a headstart in regulatory registration: trial results can be designed for relevance to local regulations. Marketing authorisation approvals and subsequent reimbursement gain extra leverage when clinical research was done on a country's own population.

Looking at patients, there is a high willingness to join trials in the Middle East. Quintiles' research shows that "data collected on patient recruitment-related site productivity—defined as the average number of patients recruited per site in a country—indicated that MENA, in terms of patients recruited per site, is more productive than the US. In fact, some parts of MENA proved incredibly productive: for example, the combination of Egypt, Jordan, Lebanon and Syria produced a patient recruitment-related site productivity of 475 per cent of US levels."<sup>8</sup>

At the same time, the region has developed a very good infrastructure to run international clinical trials. There has been a rapid adoption of a high level of technology, e.g. Turkey's new digitised submission process, which promises first feedback within 48 hours, making some medical facilities in the region world-leaders. Highly qualified investigators are available, many Western-trained and with excellent English language skills, which smoothens communications for international trials. Alongside that, there are highly centralised healthcare systems and strong levels of governmental support, with a clear focus on attracting research.<sup>8,10</sup>

Arabic is spoken most commonly in the Middle East, and this supports a uniform systems language, across the whole region. A similar harmonised approach has been put in place for regulatory requirements<sup>10</sup> These factors result in a region that can be approached in an efficiently consistent way.

Recouping costs from ever greater efficiencies is, of course, a key driver for pharma companies. Studies show that trial costs in the countries of the GCC and MENA are 59% of equivalent trials in the US,<sup>11</sup> making the siting of trials in the Middle East eminently sensible, economically, with companies ever looking for new ways to reduce cost per patient. The high level of patient acceptance in joining trials also allows the acceleration of trial timelines, boosting productivity, and reducing the overall cost per patient.

As we have seen, there is currently a very low density of trials in the Middle East, which means there is a wide-open field for growth.

### Barriers to Clinical Research: Regulations

Strong governmental support notwithstanding, we do note hindrances arising from the regulatory landscape in the Middle East. Guidelines and procedures are not up to international standards, but rather just administrative. There is an inadequacy of resources and coordination between authorities; trials refused by one committee may be approved by another with no change in submission.

Various sources define challenges still to be hurdled for clinical trials to take off in the region, standards and practices for trials among them.

In their paper "Clinical trials in the Middle East and North Africa (MENA) Region: Grandstanding or Grandeur?" the authors outline a few challenges, including that of familiarity with local regulatory rules and processes, which may vary wildly between different countries in the region. They also mention the need for monitoring and oversight, following Good Clinical Practice (GCP) requirements. Informed consent is also raised, citing issues of language and understanding, among a local population which needs translation into Arabic, and a migrant population who might speak one of many other languages where translation may not be easy, or might even have marginal literacy. Lastly, in standards of medical teaching, while the region is home to many excellent medical schools and teaching hospitals, the authors worry that research design is not taught and scientific research itself is undervalued.<sup>11</sup>

Quintiles quotes an EMA paper, which states: "There is growing concern both among regulators and in public debate about how well these trials are conducted from an ethical and scientific/organisational standpoint (including GCP compliance) and about the available framework for the supervision of these trials."<sup>8</sup>

We see a trend to shift regulatory responsibilities from Ministries of Health to independent authorities (for example, SFDA in Saudi Arabia, FDO in Iran, MCC in South Africa). Meanwhile, site administration and registry applications are separate processes in many countries. Countries such as Lebanon do not require a Ministry of Health registry, or approval, site approval is sufficient to initiate a trial. Although this is preferable by companies who would appreciate a fast start, it is questionable from quality and safety perspective.

Compatibility, or harmonisation, with international regulations is a mixed bag. Francophone countries are generally tied to French regulations. Turkey, meanwhile, has taken major steps towards harmonising with EU legislation. The GCC has had a central committee since 1999 to oversee the setting up of a uniform set of regulations for the seven member countries: the Kingdom of Saudi Arabia, the United Arab Emirates, Kuwait, Qatar, Bahrain, Oman, and Yemen. Likewise, African states are creating their own standards for harmonisation and cooperation, via the Africa Medicine Regulatory Harmonisation (AMRH) programme.

### Barriers to Clinical Research: Patient Recruitment

The barriers to patient recruitment in the Middle East are a lack of awareness about clinical trials in patients, the complexity of study protocols, and social and cultural issues related to trial participation.<sup>12</sup> Patients entering the process will have fears of being guinea pigs and have anxieties about the side-effects of the medication. They will have trust issues with physicians who may not offer effective services to patients during the trial.

Potential strategies to enhance subject recruitment, therefore, include:

- engaging a dedicated clinical research coordinator to manage the running of each trial
- arranging for patient transport to trial site for study visits
- designing a recruitment strategy prior to study initiation
- interacting with the medical community in the local area regarding clinical trial recruitment
- educating subjects on the clinical trial during routine outpatient department (OPD) visits
- creating positive awareness about clinical trials among people through press and mass media
- using technological tools to select sites with high numbers of

qualifying patients and to identify potential patients

- using technological tools to engage patients and to increase the retention rate
- creating professional centers using a software-driven, full process management system, which allows the definition and measurement of key performance indicators.

## Country Insights

As we have seen, countries in the Middle East each have their own disease profile. The UAE and Jordan, for example, have high prevalence of diabetes (the UAE has the second highest in the world).<sup>11</sup> Egypt has a high incidence of hepatitis C.<sup>10</sup> Saudi Arabia has the fifth highest incidence in the world for obesity.<sup>5</sup> Just under a third of Saudis are classified as overweight, just under a quarter are habitual smokers, and just under a fifth suffer from diabetes.<sup>13</sup>

Authorities in Saudi Arabia are aware of this and have given free health plans for everyone in the Kingdom, creating a model healthcare system.<sup>5,13</sup>

## Country Insights: Turkey

Of all the countries of the Middle East, the authors have had the most experience with Turkey.

Turkey has well-structured processes and systems in place for clinical trials and has had a long history in running them. In this way, it is seen as a model for countries such as Egypt and Saudi Arabia, who are trying to close the gap. The country's clinical research profile is developing, supported by new regulations that are in accordance with international standards and European directives. As a country with a population of nearly 80 million, with high genetic diversity, Turkey is a country that offers great, new opportunities for clinical trials.

The number of hospitals in Turkey shows an increasing trend. In 2012, the country had 62 university hospitals, 489 private hospitals and 843 government hospitals. By 2016, these numbers had risen to 70 university hospitals, 560 private hospitals and 874 government hospitals.<sup>14</sup> The number of researchers in the hospitals is increasing day by day, with Good Clinical Practice (GCP) training throughout the country, instigated at ministry level. Beyond all of these advantages, trial costs are comparatively low relative to European Union countries and the United States of America.

## Turkey: Challenges

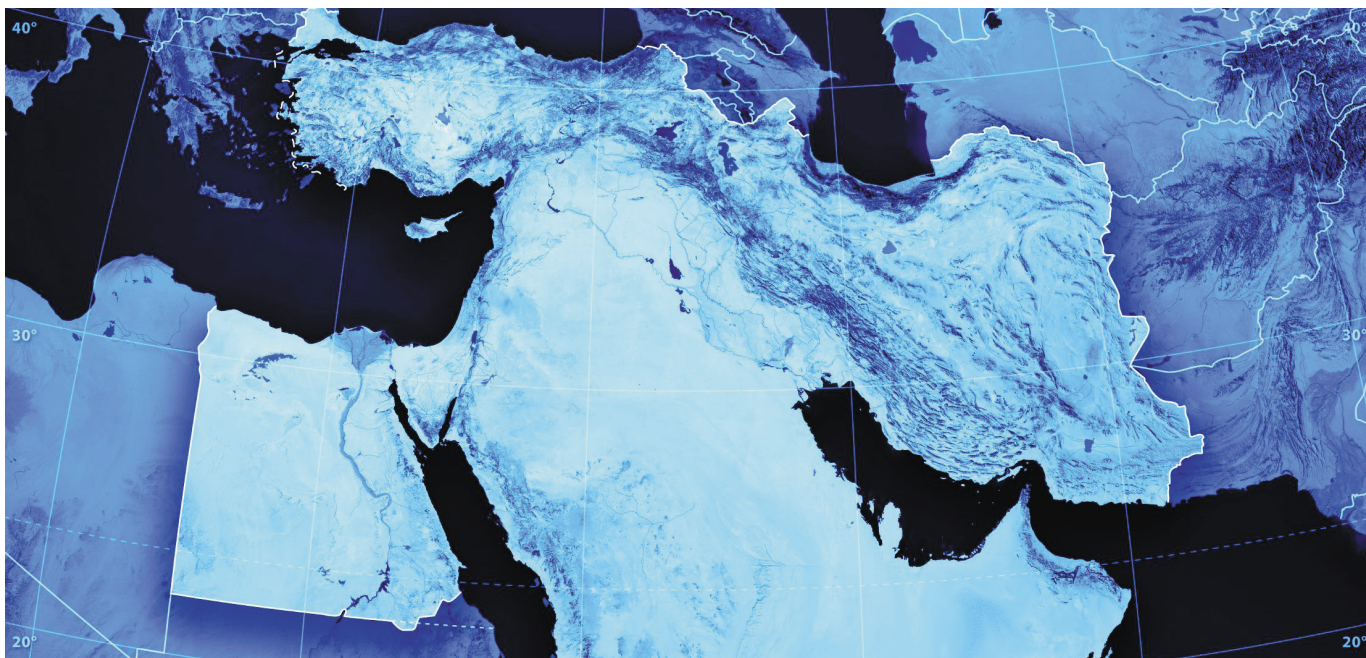
In Turkey, the most important problem in the clinical research process is the lack of administrative integrity. Institutions act independently, budgets are unpredictable, and there are significant differences in administrative evaluation processes. The Ministry is continuing work on this issue.

Other restrictions that may impede site and patient enrolment include the fact that no payments can be made to assistant personnel (leading to low motivation on their part to enroll more patients than they have to), no advertising can be done to recruit patients for clinical trials and no payments can be made to patients in return for their study participation (except Phase I). One further limiting factor is that investigators cannot be paid directly for their trial involvement; payments must be made to the circulating capital department of the relevant institutions. Researchers receive around 60% of the trial-related payments.

In particular, with the increasing number of ethical committees over the last two years, both inexperienced committees and increased opportunities have emerged. Now it is easier to conduct a study without worrying about application timelines.

But the major issues in clinical trial patient recruitment are the same issues felt elsewhere, around the world:

- Finding the right sites, with high potential, for trials.
- Reaching the targeted number of patients. To avoid this, trial principal investigators (PIs) give very low estimates. The numbers for recruitment in the country as a whole are very low.
- It is not possible to identify non-diagnosed rare disease patients.
- Hospitals do not have dedicated staff for trials. PIs have the initiative. This gives a lack of reputation among international studies. Only PIs with some degree of reputation are able to conduct trials. The rest of the researchers may have ambitions to run trials, but do not know how to get access to them.
- Currently, hospitals have no idea about their own numbers for ongoing studies, completed studies, recruited patients, budgets used/missed, patients dropped/completed.
- No transparency in trial revenues (cf. US Sunshine Act).



## Solutions?

Ostensibly about research, conducting sponsored trials requires professionalism to thrive in a competitive world. This is valid for physicians, clinical trial centres, and even countries. Physicians should be GCP-certified. They should be encouraged to conduct trials. Universities should have programmes related to clinical trials. Processes should be in line with international standards, and transparent.

Technology should be in place in every step of the process, starting from feasibility, until the end of the study, to take advantage of the technological improvements and speed up the clinical trials management process, in addition to reducing human error rate.

Given Turkey's high rate of patient record digitisation and excellent and consistent data quality, it would make sense to leverage hospital databases for checking trial feasibility and for patient identification during trial recruitment. Big-data-style analytics allow queries to be performed which can identify eligible patients fitting complex sets of inclusion and exclusion criteria. This means that even patients with conditions that have gone undiagnosed may still be found by triangulating on combinations of other diagnoses, lab values, demographic data, and so on. With a large enough database, patients with rare diseases may easily be found.

We would also suggest that centres should be built for clinical trials. The whole process workflow of a clinical trial at hospitals could be coordinated by these centres electronically. This would give transparency and efficiency. Clinical research centres have the potential to be a lightning rod to attract new studies to their local regional hospital cluster, by showcasing the clinical potential of their local population. PIs associated with these centres would also have a platform to present their clinical expertise and capabilities.

## Conclusion

The countries of the Middle East have a unique profile which makes them an ideal ground for running sponsored, international clinical trials. An expansion within the region would bring benefits both to patients and physicians in the form of better access to new and advanced healthcare options, as well as to the pharmaceuticals industry seeking better, more cost-effective, high quality clinical trials.

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