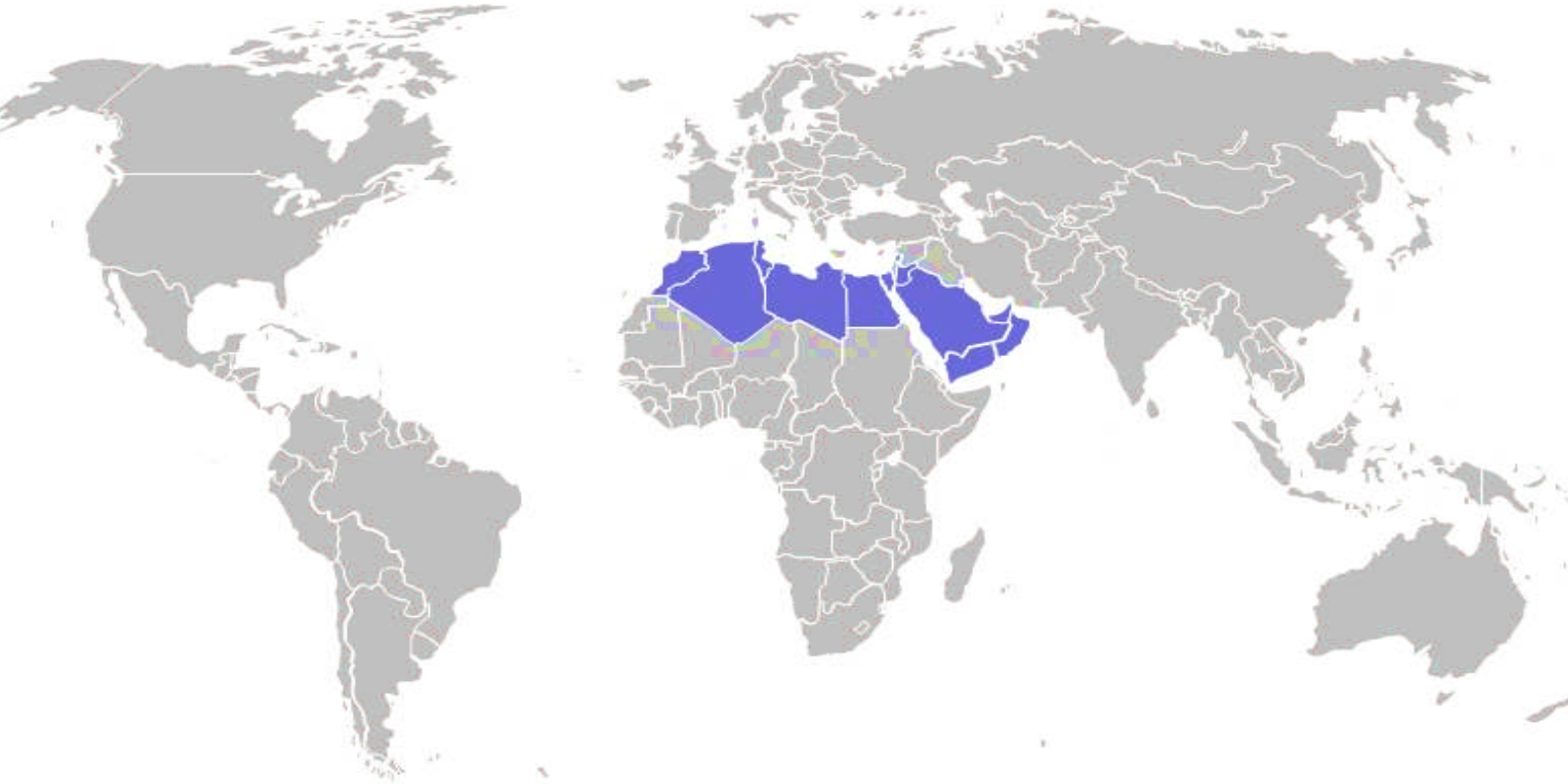
March 2019

Rare Disease Clinical Research
Untapped potential in MENA



A White Paper by Clinart MENA in collaboration with LongTaal

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Rare Disease Landscape

Around the turn of the century, the tidal wave of success from numerous "blockbuster" treatments available on the market began to lose its momentum. The so-called patent cliff, with patents on highly profitable drugs expiring around the same time, a drought in products in the pipeline and soaring clinical trials costs (1), clinical research and development has increasingly started to shift focus to the "niche buster" approach, targeting the plethora of rare diseases with very small subject populations. It is generally believed that the number of known rare diseases has reached roughly 6-8,000 (2), with 85-90% of the cases being serious or life-threatening (3). However, only 5% of all rare diseases have treatments available for use (4).

In the United States, a rare disease is defined as a condition affecting less than 200,000 (5) (translating to roughly 1 out of 1,600 in 2018) and fewer than 5 out of 10,000 in the European Union (6). Some rare diseases are so scarce they fall into the ultra-rare category, defined as less than 20 per million population, with some as low as less than 1 per million (7). Although the number of individuals afflicted by each distinct rare disease is low, the cumulative impact of rare diseases on the global scale is far reaching, believed to affect around 10% of individuals worldwide (8). Furthermore, a disease may be considered rare or ultra-rare in one region of the world, however, may be highly prevalent in another.

Eight in ten rare diseases result from a form of genetic mutation, however each rare disease has such complexity that within just one disease there can be many variations or subtypes resulting in different clinical manifestations and disease progression (4, 9). The scarcity of a particular rare disease, combined with the limited knowledge of the disease itself by the scientific community and/or the health care provider, often leads to misdiagnosis and delayed care, which in many cases can be fatal.

In addition to the confounding biological makeup of a rare disease, there are a number of challenges to successfully carrying out clinical research in search of treatment. Development of medicinal products intended for the treatment, diagnosis or prevention of rare disease (orphan drugs) can be very challenging due to distinct rare disease features, such as small patient populations, low event rates, inadequate understanding of disease natural course, and a lack of previous clinical trials (10). However, in spite of these challenges, there has been a consistent upward trend of clinical trials targeting a rare disease (average 7% increase year on year), with 6,084 active trials as of February 2019 (Figure 1).

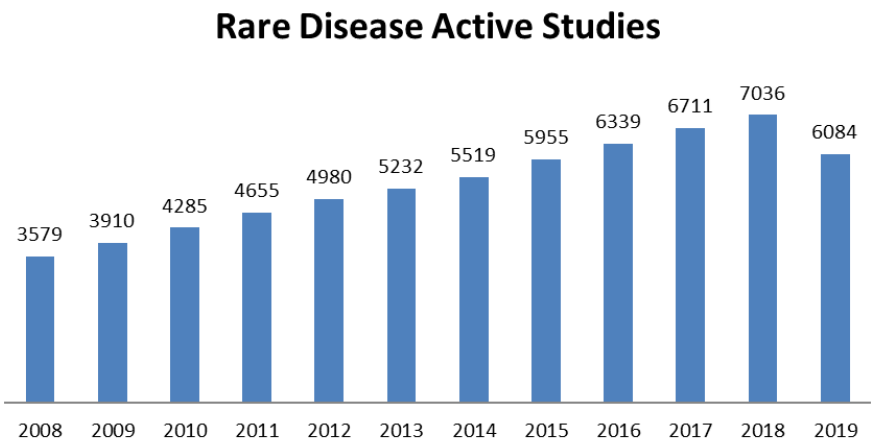


Figure 1: The above table shows all initiated and ongoing rare disease clinical trial studies in a given year, excluding studies that have been withdrawn or terminated. Data include Industry and non-Industry sponsored trials (See Appendix 1 for methodology and Appendix 2 for additional analysis. Additional data can be found via the online dashboard at bit.ly/rare_disease_dashboard

This surging interest in clinical research into rare diseases can be attributed to a number of factors: 1) Economically viable government incentives to promote rare disease research in the US (1983), Japan (1993), Australia (1997), EU (1999), Taiwan (2000) and South Korea (2003) (1,8,11), 2) better availability and understanding of diagnostic tools to detect diseases (9), and 3) growth of patient advocacy groups' privately funded research (5). Since 2008, 4,350 sponsors have conducted clinical trials in rare diseases with increasing interest among biopharmaceutical industry sponsors (Industry) (Figure 3). In fact, among Industry sponsors as a whole, the average year on year growth rate of active rare disease clinical trials of 9% is double the average growth rate for their entire global portfolio of 4%. Table 1 shows the top 20 sponsors in global clinical trials for rare disease and the total number of studies since 2008.

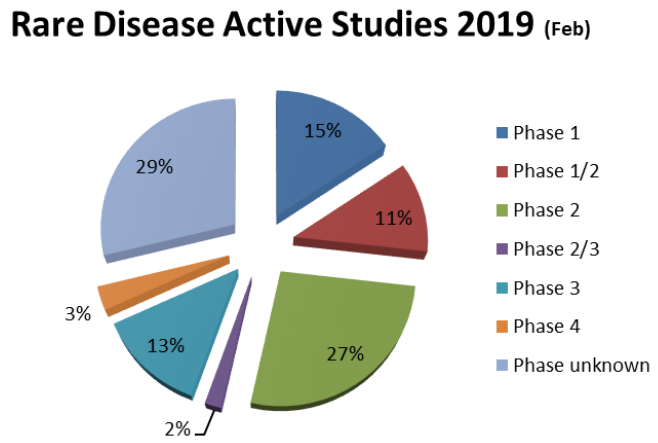


Figure 2: The 6,084 rare disease studies active in Feb 2019 by trial phase, with 29% of studies not listing trial phase in online databases. Data include all Industry and non-Industry sponsors. Additional data can be found via the online dashboard at bit.ly/rare_disease_dashboard

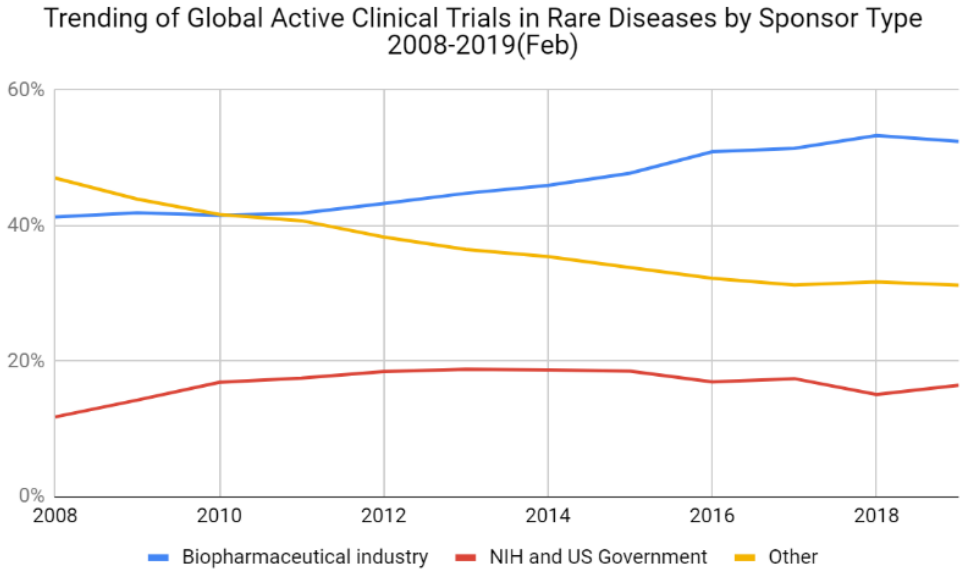


Figure 3: Trending of all active clinical trials in rare diseases by sponsor type during 2008-2019 (Feb) shows continuously increasing interest from Industry sponsors. Additional data can be found via the online dashboard at bit.ly/rare_disease_dashboard

Table 1: Top 20 sponsors of global clinical trial research into rare diseases. Data is an aggregate of the number of studies active in each year during the 2008-2019 (Feb) period. Industry sponsors are shown **in bold**. Additional data can be found via the online dashboard at bit.ly/rare_disease_dashboard

Rank	Parent Sponsor	Total Rare Disease Portfolio 2008-2019 (Feb)	Total Sites	%Studies for rare diseases vs. whole portfolio
1	National Cancer Institute (NCI)	785	6,280	44%
2	M.D. Anderson Cancer Center	362	2,896	23%
3	**Novartis**	357	8,425	17%
4	Memorial Sloan Kettering Cancer Center	274	2,192	25%
5	**GlaxoSmithKline**	265	6,254	12%
6	Assistance Publique - Hôpitaux de Paris	258	2,064	18%
7	**Pfizer**	191	4,508	10%
8	National Institute of Allergy and Infectious Diseases (NIAID)	190	1,520	20%
9	Mayo Clinic	186	1,488	13%
10	**Celgene**	185	4,366	57%
11	**Sanofi**	183	4,319	18%
12	**Hoffmann-La Roche**	180	4,248	13%
13	Massachusetts General Hospital	166	1,328	13%
14	Children's Oncology Group	150	1,200	68%
15	Dana-Farber Cancer Institute	145	1,160	30%
16	Washington University School of Medicine	143	1,144	17%
17	Fred Hutchinson Cancer Research Center	133	1,064	55%
18	University of California, San Francisco	131	1,048	12%
19	**Johnson & Johnson**	130	3,068	10%
20	**Bayer**	121	2,856	12%

Rare Disease Landscape Across Middle East, North Africa (MENA)[1]

Due to the low population and geographic spread of any individual rare disease subject pool, multicenter and multinational collaboration is often required (10). Countries across the MENA have historically often been overlooked for clinical trial participation (12) however, particularly when considering locations to conduct rare disease studies, there are a number of reasons to reverse this trend.

Cultural Factors and Rare Disease profile - Across MENA, the common practices of large family size, high maternal and paternal age, and high consanguinity rates (marriage between close relatives) in the range of 25-60% are strong contributing factors for higher levels of congenital and genetic disorders present in this region (13). This high prevalence of common genetic disorders (over 900 have been catalogued) has led to a plethora of rare diseases, many with orphan status, including Gaucher's disease, Fabry disease, Behcet's disease, thalassemia and sickle cell anemia (14). In Bahrain, Kuwait, Oman and Qatar congenital malformations are the second leading cause of infant mortality and in Saudi Arabia account for about 30% of perinatal deaths (15). According to the Center for Arab Genomic Studies (CAGS), diabetes, sickle cell disease, hypertension thalassemia (particularly alpha-thalassemia) are continually growing concerns, soon reaching epidemic status (16). Consequently, the historical underrepresentation in clinical trials has positioned this region to provide a significant untapped and often treatment-naïve patient population.

World-class infrastructure - The tremendous wealth accumulated through the production of natural resources and subsequent rapid growth of the majority of the regional economies, combined with the vision of local governments to shift investment into the healthcare sector, has resulted in a burgeoning landscape of modern hospital facilities and centers of excellence with state-of-the-art equipment. In the United Arab Emirates (UAE), the opening of Dubai Science Park and the Dubai Healthcare City have significantly garnered the attention of Industry sponsors to the region through offering tax exemptions, 100% foreign ownership and opportunities for strategic collaboration across industry and academic institutions (14). Since 2009, the American University in Beirut has offered neurological and genetic diagnostic and treatment services to Lebanon and the region through their Neurogenetics center of excellence as well as state-of-the-art research facilities for regionally relevant genetic disorders (17). The National Heart, Lung and Blood Institute, one of the largest institutes within NIH, has a collaborative center of excellence partnership with the University Hospital Farhat Hached in Tunisia to develop research and training to conduct clinical research (18). The Oriental Al Kindy, a center for medical imaging and oncology in Morocco, has opened this year offering some of the most advanced technologies to treat cancer and can host up to 6,000 patients a year (19). The Children's Cancer Hospital Egypt is the largest pediatric oncology center in all of MENA (320 beds) offering a wide range of diagnostics and treatments (20).

International standards –

Education and Training: Countries across the region have made strategic investments into higher education and in particular into forging partnerships with Western educational institutions to match rigorous international standards and expand the growing pool of highly motivated and talented medical teams (21) Numerous institutions in the UAE have forged strategic collaborations with Harvard Medical School, Johns Hopkins University and Cleveland Clinic to develop centers of excellence and residency

[1] For the purposes of this paper, MENA includes Algeria, Bahrain, Egypt, Jordan, Kuwait, Lebanon, Morocco, Oman, Qatar, Saudi Arabia, Syria, Tunisia, United Arab Emirates (UAE) only. Israel was excluded due to its market differences in the wider region.

exchange programs (14). Similarly, through partnership with the Weill Cornell Medical College in Qatar, an all-digital specialty teaching hospital was established in 2008 with particular expertise in women's and children's health (22). In Saudi Arabia, significant investment has been made into the education sector with the opening of numerous universities focused on biotechnology creating a pipeline of talent for the future. According to one report, Egypt has 41 universities and 94 health-related faculties and medical schools, where experience in clinical research (including clinical trials) is required before obtaining a masters or doctorate degree (23).

Regulatory environment: In many countries around the world the initiation of a clinical trial can often experience unforeseen delays due to the onerous and often time-consuming submission processes to the necessary regulatory authorities. Effort has been made in countries across MENA to mitigate these bottlenecks. In 2008, the Egyptian Network of Research Ethics Committees was established to bring harmonization and simplify procedures and standards among the country's 56 Regulatory and Ethics Committees and Institutional Review Boards (23). In 2001, Jordan became the first Arab country in MENA to enact clinical regulations and in 2003 both the Jordan and Saudi Food and Drug Administrations were established, adhering to ICH-GCP compliance and aligning regulations to the US FDA and European Medicines Agency with respect to clinical trials, bolstering its credibility and matching processes familiar to Industry sponsors (14, 24). ICH-GCP compliance has since become well established in all countries across MENA. Furthermore, start-up timelines from submission to trial initiation on average takes 4-6 months in sharp contrast to other developing markets such as Russia or China that can take twice as long (21). In the UAE, new guidelines allow submissions to the Ministry of Health and Ethics Committee to be done in parallel, thus shortening timelines even further.

There is a growing number of regionally-based Clinical Research Organizations with proven track records in navigating the submissions process and experience in conducting clinical trials.

All eight Industry sponsors listed in Table 1 (Top 20 sponsors globally) cumulatively have conducted 68 clinical trials involving at least one country from MENA in the last eleven years (See Appendix 3). Clearly the capacity is available, only the potential has yet to be further utilized.

Missed Opportunities in MENA

The lack of participation in clinical trials across the MENA region has resulted in significant missed opportunities for all stakeholders. From the patient perspective, participation in a clinical trial may be the only potential option for treatment or ease of symptoms for a rare disease. Patient participation contributes as well to relieving the financial burden on national healthcare systems left with the cost of disease management. For investigators and healthcare professionals, participation in the trials provides invaluable first-hand experience with the intervention, thus making them more likely to recommend the treatment. This provides an additional financial incentive for sponsors, as recommendations from a treating physician or major public hospital allows an orphan drug to be made available prior to registration and applicable for government subsidy in many MENA countries (21). With pharmaceutical market sales expected to grow 9-11% across the region in the next few years, there is tremendous opportunity to recover on investment. As mentioned previously, the availability of a large, unilingual, often treatment naïve, patient population, has the potential to cut down timelines through faster patient enrollment, fewer sites, and fewer regulatory submissions. Below are three case studies highlighting the contrast between the high prevalence of a particular rare disease and the low/absence of participation in clinical trial research in the region.

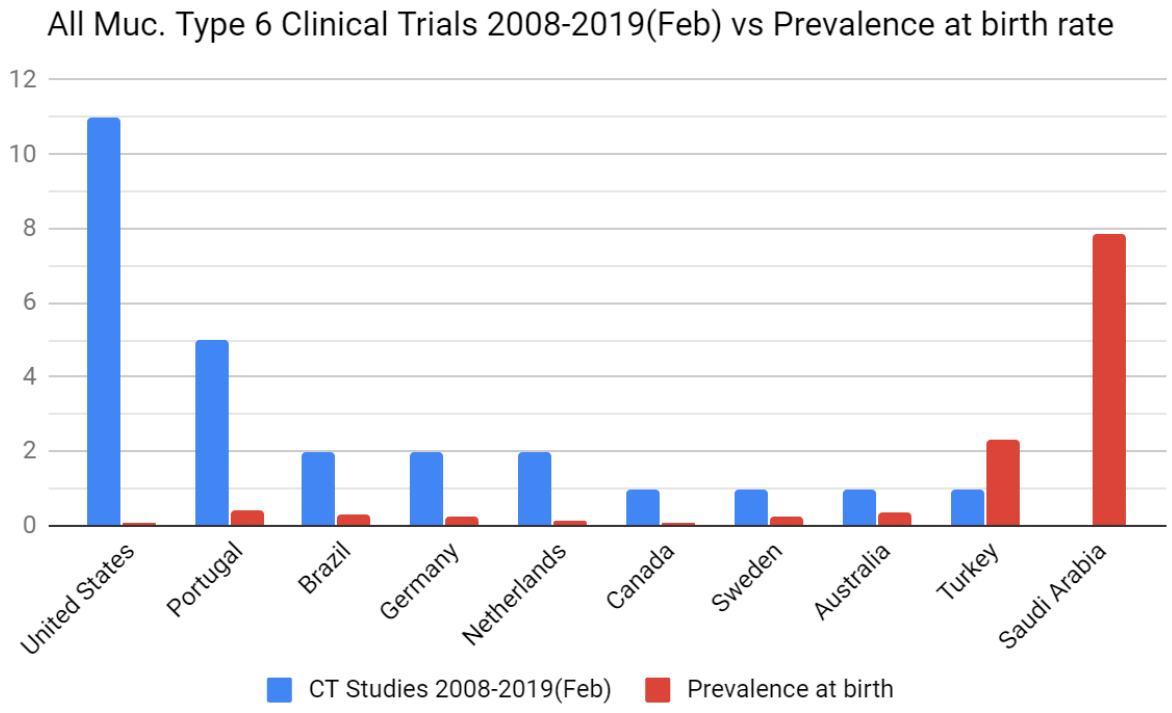
Case Study 1: Mucopolysaccharidosis Type 6

11 studies, 18 countries, 8 sponsors - Saudi Arabia not included despite highest prevalence globally

Mucopolysaccharidosis is clustering of seven distinct inherited conditions in which the body is unable to properly breakdown mucopolysaccharides resulting in these sugars building up in cells, blood and connective tissue which can lead to a variety of health problems (25). Type 6, also known as Maroteaux-Lamy syndrome, causes damage to many tissues and organs and often causes skeletal abnormalities. Without treatment, severely affected individuals may survive only until late childhood or adolescence (26).

According to published data, Saudi Arabia has the highest global prevalence-at-birth rate in the world at 7.85 per 100,000, yet has not been included in even one of the 11 clinical trials in the last 10 years (Figure 5). This is particularly striking when comparing the prevalence rates with countries that have participated in clinical trials: x157 greater than the US (0.05), x79 than Canada and x34 than Germany to name a few (complete list in Appendix 4). A higher national prevalence rate can translate into a larger potential pool of subjects for enrollment thereby reducing timelines and cost through faster enrollment, fewer sites and potentially shortened time to market.

Furthermore, of the 11 studies for Mucopolysaccharidosis Type 6, seven included more than one Type for research. Saudi Arabia also has one of the highest prevalence at birth rates globally for Type 1, 3 and 4 (Appendix 4), further enhancing the potential contribution to ongoing clinical research.

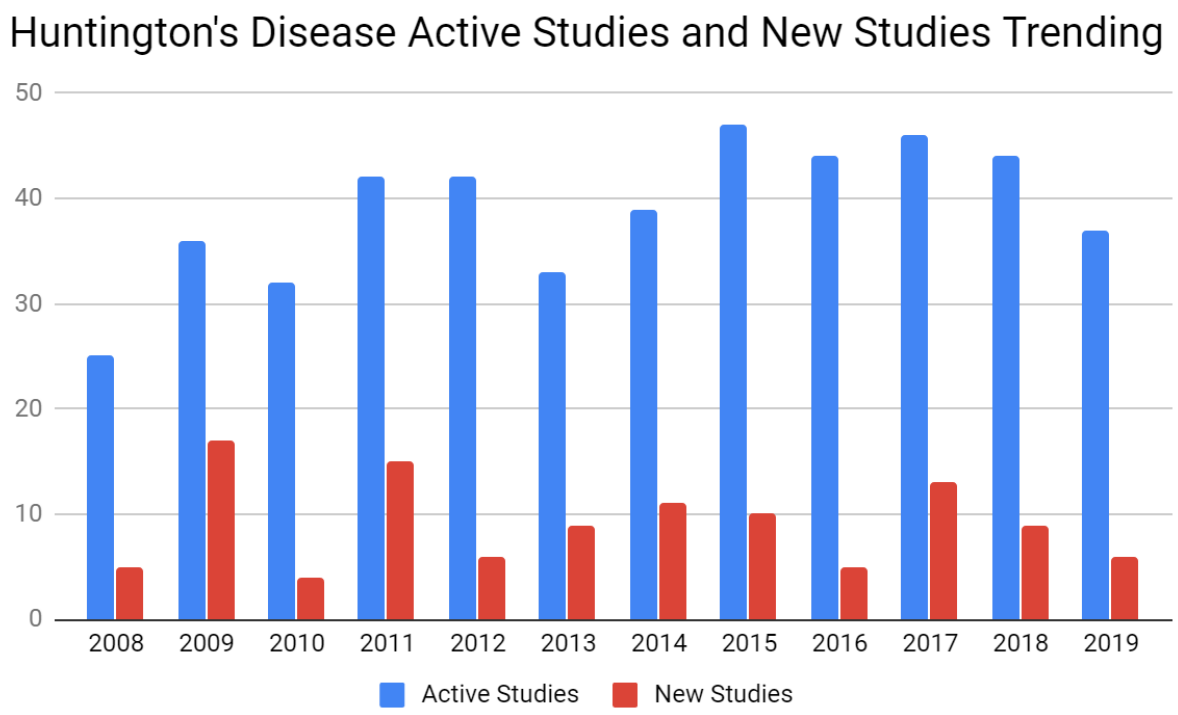


Case study 2: Huntington's Disease

130 studies, 30 countries, 67 sponsors - Egypt not included despite highest prevalence globally.

Huntington's Disease is a fatal genetic disorder that causes the progressive breakdown of nerve cells in the brain, deteriorating an individual's physical and mental abilities, with onset between 30-50 years of age (27). According to published research, the global point prevalence is 2.7 per 100,000 and Europe as a whole reaching to 10 per 100,000. Egypt has the highest global point prevalence at 21 per 100,000, at a rate twice as high as Europe and 11 times higher than the United States (1.9) (Appendix 5).

It is understandable for sponsors to focus their clinical trial efforts in Western Europe, both due to the high prevalence rates and the extensive past experience working in these countries. However, it is surprising to find that at least 4 new trials are initiated each year and yet Egypt, or another country in MENA, has not once been included in a study in the last 10 years. Similar to Saudi Arabia mentioned above, this presents a tremendous missed opportunity, both for the sake of clinical research and future understanding of this disease, but also for the thousands of patients (and families) with no access to potential relief or cure for their declining quality of life.



Case study 3: Single Gene Blood Disorders

As mentioned earlier, the cultural and lifestyle habits across Arab MENA are viewed as strong contributing factors for the high levels of genetic and congenital disorders. Attempts to capture the scope of genetic disorders among Arab populations in the late 1990s, then cataloguing 374, were quickly outdated as refined research resulted in classifying 752 Mendelian characters in Arabs just five years later in 2004 and further grew to 774 in 2006 (15, 16). Government initiatives focused on prevention, awareness and early recognition through genetic screening initiatives throughout the region (Oman, Saudi Arabia, UAE, Jordan, Lebanon, Tunisia, Bahrain, Egypt, and Qatar), have made significant strides in raising awareness of the risks of consanguinity and its genetic impact, however studies show that this practice is still widely continued (16). Some of the disorders recorded are Arab specific syndromes or are localized within specific regions or communities, however most are of global significance (15). Of particular concern for the region are blood disorders that can be attributed to high consanguinity rates as well as the history of malaria endemicity in the case of Sickle Cell Disease. Hemophilia A is also of particular concern with point prevalence rates ranging from 0.5 (Saudi Arabia) to 7.9 (Qatar) per 100,000. Table 2 highlights the number of global studies for Hemophilia A, Sickle Cell Anemia and Beta-Thalassemia and the regional and national participation in those studies. MENA has been included in a number of trials however, considering the high prevalence rates, has the potential to contribute much more to clinical research.

Table 2: Breakdown of MENA participation in global studies across three very common blood disorders in the region: Hemophilia A, Sickle Cell Anemia and Beta-Thalassemia. Data is an aggregate of the number of studies active in each year during the 2008-2019 (Feb) period. Additional data can be found via the online dashboard at bit.ly/rare_disease_dashboard

	Hemophilia A	Sickle Cell Anemia	Beta-Thalassemia
	192 global studies, of which **10** include at least one MENA country	**64** global studies, of which **6** include at least one MENA country	**59** global studies, of which **20** include at least one MENA country
Algeria			
Bahrain	1	1	
Egypt	2		12
Jordan	1		
Kuwait	1		
Lebanon	4	3	8
Morocco	2		
Oman	2	1	1
Qatar	1		1
Saudi Arabia	3	4	1
Syria			1
Tunisia	1		1
United Arab Emirates	1		

Looking Forward

For the millions of people suffering from a rare and often debilitating disease, this is a hopeful time in modern medicine. Due to improved technology, breakthroughs in personalized medicine and the understanding of disease pathologies combined with financially viable incentives for research, there is a continuously growing awareness of and interest in developing treatments for these patients. The challenges for carrying out clinical trials for rare diseases, including geographic spread and size of these often small patient pools, can be mitigated through increasing clinical trial enrollment across the MENA region. The availability of highly trained doctors, world-class facilities and some of the highest prevalence globally for numerous rare diseases will aid in cutting down the cost of research and shorten timelines in bringing treatments to market. The historical lack of participation in clinical trials is now an opportunity with a significant untapped and often treatment-naïve patient populations.

Customized clinical trial analytics for this paper were provided by Clinart MENA in collaboration with LongTaal.

Access to the online Rare Diseases Dashboard - MENA Region will be available at bit.ly/rare_disease_dashboard until May 31st 2019. After this point, access will be provided through Clinart MENA: business@clinart.net

References

1. Kakkar, A. K., & Dahiya, N. (2014). The Evolving Drug Development Landscape: From Blockbusters to Niche Busters in the Orphan Drug Space. *Drug Development Research,* 75(4), 231-234. doi:10.1002/ddr.21176
2. Pharma intelligence. (2013). *Rare Disease Landscape: Will the Blockbuster Model Be Replaced?* [Brochure]. Stephens, Johnathan, Blazynski, Christine. Retrieved 10 March 2019, from https://pharmaintelligence.informa.com/resources/product-content/will-the-blockbuster-model-be-replaced
3. Department of Health and Human Services. (Fiscal Year 2017). *Food and Drug Administration: Justification of Estimates for Appropriations Committees.* Retrieved 8 March 2019, from https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/BudgetReports/ucm488357.htm
4. PhRMA. (2017). *Spurring Innovation in Rare Diseases: 2017 Update.*[Brochure].Retrieved 3 March 2019, from https://www.phrma.org/fact-sheet/spurring-innovation-in-rare-diseases
5. Griggs, R. C., Batshaw, M., Dunkle, M., Gopal-Srivastava, R., Kaye, E., Krischer, J., Nguyen, T., Paulus, K., Merkel, P. A., Rare Diseases Clinical Research Network (2008). Clinical research for rare disease: opportunities, challenges, and solutions. *Molecular genetics and metabolism*, *96*(1), 20-6.
6. Council of the European Union. (2009, July 3). *Council Recommendation of 8 Jun 2009 on an action in the field of rare diseases* (2009/C 151/02). Retrieved 10 March 2019, from https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF
7. Alexion. (2018). *Rare and Ultra-Rare Diseases.* [Brochure]. Retrieved 10 March 2019, from https://news.alexionpharma.com/sites/alxn.newshq.businesswire.com/files/doc_library/file/ALXN-FS-UltraRare-US-082118_3.pdf
8. Song, P., Gao, J., Inagaki, Y., Kokudo, N., & Tang, W. (2012). Rare diseases, orphan drugs, and their regulation in Asia: Current status and future perspectives. *Intractable & rare diseases research*, *1*(1), 3-9.
9. EURORDIS. (2005). *Rare Diseases: understanding this Public Health Priority.* [Report]. Retrieved 12 March 2019, from https://www.eurordis.org/sites/default/files/publications/princeps_document-EN.pdf
10. Logviss, K., Krievins, D., & Purvina, S. (2018). Characteristics of clinical trials in rare vs. common diseases: A register-based Latvian study. *PloS one*, *13*(4), e0194494. doi:10.1371/journal.pone.0194494
11. Almalki, Z. S., Alahmari, A. K., Guo, J. J., & Kelton, C. M. (2012). Access to orphan drugs in the Middle East: Challenge and perspective. *Intractable & Rare Diseases Research*, 1(4), 139-143. doi:10.5582/irdr.2012.v1.4.139
12. Misik, Vladimir, Bolecek, Martin, Brady, Rachel V. (2017). Ethical Considerations of Industry-Sponsored Clinical Trials in the Arab Region. In Henry Silverman (Ed.), *Research Ethics in the Arab Region* (161-170). Switzerland: Springer.
13. Al-Gazali, L., Hamamy, H., & Al-Arrayad, S. (2006). Genetic disorders in the Arab world. *BMJ (Clinical research ed.)*, *333*(7573), 831-4.
14. Quintiles in collaboration with Saudi Ajal. (2013, October). *White Paper: The Value of Industry-Sponsored R&D Clinical Trials to Saudi Arabia*. Misik, Vladimir, Al-Sultan, Mohammed, Brady, Rachel V.
15. Tadmouri, Ghazi Omar. (Date unknown). *Genetic Disorders in Arab Populations*. Retrieved 15 March 2019, from http://www.cags.org.ae/cbc02ga.pdf
16. Genpharm. (Date unknown). *MENA Market: An Attractive Opportunity for Rare Disease and Healthcare Companies.*[White Paper]. Retrieved 29 March 2019, from https://www.genpharmservices.com/docs/Final%20MENA%20Region%20-%20White%20Paper-OrphanDrugMeeting.pdf
17. American University of Beirut. (Date unknown). *Faculty of Medicine: Pediatrics: Centers of Excellence*. [Website]. Retrieved 29 March 2019, from https://www.aub.edu.lb/fm/Pediatrics/Pages/CentersofExcellence.aspx
18. National Heart, Lung and Blood Institute. (Date unknown). *UnitedHealth and NHLBI Collaborating Centers of Excellence*. [Website]. Retrieved 29 March 2019, from https://www.nhlbi.nih.gov/about/globalhealth/centers/index
19. Saga, Ahlam Ben. (2019, March 7) Morocco Opens Large Cancer Treatment Center in Oujda. *Morocco World News.* Retrieved 29 March 2019, from https://www.moroccoworldnews.com/2019/0

3/267389/morocco-cancer-treatment-center-oujda/
20. Children's Cancer Hospital Foundation – Egypt. (2019) [Homepage]. Retrieved 29 March 2019, from https://iba-worldwide.com/proton-therapy/proton-therapy-centers/egypt-childrens-cancer-hospital-foundation-egypt
21. Clinart MENA. (2016 April). *From Patient Access to Commercialization: The MENA Opportunity for Orphan Drugs* .[White Paper]. Retrieved 29 March 2019, from http://www.orphan-drugs.org/2016/04/18/whitepaper-patient-access-commercialization-mena-opportunity-orphan-drugs/
22. Weill Cornell Medicine, Office of External Affairs. (2004, August 16). *Specialty Teaching Hospital to be Built in Education City in Qatar* [Press release]. Retrieved 9 March 2019, from https://news.weill.cornell.edu/news/2004/08/specialty-teaching-hospital-to-be-built-in-education-city-in-qatar
23. Shehata, Sherif M., ElMashad, Nehal M., Hassan, Azza M. (2017, April 26). Current Review of Medical Research in Developing Countries: A Case Study from Egypt. In Seth Appiah-Opoku (Ed.), *International Development* (Chapter 3). IntechOpen.
24. Arouri, Ahmad, Al-Mahrouq, Saleem, Al-Ghazawi, Mutasim, Russmann, Dieter. (2015 April). The evolving clinical research environment in Jordan. *Regulatory Rapporteur*, 12(4), 16-21.
25. NIH: Genetic and Rare Diseases Information Center. (2016, May 24). *Mucopolysaccharidosis*. [Website]. Retrieved 12 March 2019, from https://rarediseases.info.nih.gov/diseases/7065/mucopolysaccharidosis
26. NIH: Genetics Home Reference. (2019, March 12). *Mucopolysaccharidosis type VI*. [Website]. Retrieved 12 March 2019, from https://ghr.nlm.nih.gov/condition/mucopolysaccharidosis-type-vi
27. Huntington's Disease Society of America. (Date unknown). *What is HD / Overview of Huntington's Disease* [Website]. Retrieved 29 March 2019, from https://hdsa.org/what-is-hd/overview-of-huntingtons-disease/
28. Misik, Vladimir, Brady, Rachel V., Bolecek, Martin, Klech, Heinrich. (2014). Current Trends in Globalization of Industry-Sponsored Clinical Trials. *Applied Clinical Research, Clinical Trials & Regulatory Affairs* 1, 56-66.
29. Karlberg, JPE. (2010). Clinical trials overseen by US FDA. *Clinical Trial Magnifier* 3(4), 279-96.
30. Karlberg, JPE. (2011). The Establishment of Emerging Trial Regions. *Clinical Trial Magnifier* 4(1), 7-23.

Appendix 1: Methods, data sources, and model assumptions

For the purposes of this analysis, the following data sources and assumptions have been used:

The US clinical trial registry (ClinicalTrials.gov) database has proven to be a reliable data source for analyzing global industry-sponsored clinical trial trends (28-30). Suspended, terminated or withdrawn trials have been excluded from analysis.

To improve data accuracy, we have also included data downloaded from EU Clinical Trials Register and utilized proprietary algorithms to eliminate duplicate entries and enrich data content.

Orphanet (http://www.orpha.net): an online database of rare diseases and orphan drugs has been used to cross-match list of rare diseases with clinical trials by utilizing MeSH terms (https://meshb.nlm.nih.gov/).

Data on disease epidemiology has also been sourced from Orphanet.

Appendix 2: Global overview of studies and sites in rare diseases

Table lists total number of new studies and sites initiated each year and total number of active studies and sites (new and ongoing) each year for all rare diseases across all sponsors globally. Additional data can be found via the online dashboard at bit.ly/rare_disease_dashboard

Year	Rare Disease Clinical Trials Only					
	New Studies	New Sites	New studies growth yoy	Active Studies	Active Sites	Active Studies growth yoy
2008	797	13,330		3,579	54,501	
2009	872	15,437	9.41%	3,910	64,682	9.25%
2010	980	13,998	12.39%	4,285	72,729	9.59%
2011	1,042	15,141	6.33%	4,655	81,122	8.63%
2012	972	14,138	-6.72%	4,980	87,552	6.98%
2013	1,079	17,805	11.01%	5,232	96,331	5.06%
2014	1,166	17,306	8.06%	5,519	102,244	5.49%
2015	1,280	20,032	9.78%	5,955	109,849	7.90%
2016	1,329	15,894	3.83%	6,339	113,235	6.45%
2017	1,436	18,407	8.05%	6,711	116,749	5.87%
2018	1,439	11,038	0.21%	7,036	113,710	4.84%
2019	342	1,721		6,084	98,314	

Appendix 3 : Industry sponsors only, ranked by number of rare disease trials globally and in MENA, and Global portfolio of all clinical trials (rare and non-rare). Data is an aggregate of the number of studies that were active in each year during 2008-2019 (Feb). Additional data can be found via the online dashboard at bit.ly/rare_disease_dashboard

Rare Disease Portfolio							% Studies in MENA countries	Global Portfolio: Rare and Non-Rare Diseases			
			Global		MENA			Global - all indications			% Studies in Rare Diseases
Global Rank	MENA Rank	Industry Sponsors only 2008-2019 (Feb)	Studies	Sites	Studies	Sites		Rank	Studies	Sites	
1	1	Novartis	357	8,425	32	80	9%	2	2,046	39,897	17%
2	2	GlaxoSmithKline	265	6,254	10	25	4%	1	2,262	44,109	12%
3	10	Pfizer	191	4,508	4	10	2%	4	1,888	36,816	10%
4	7	Celgene	185	4,366	5	13	3%	22	322	6,279	57%
5	25	Sanofi	183	4,319	1	3	1%	9	993	19,364	18%
6	2	Hoffmann-La Roche	180	4,248	10	25	6%	5	1,400	27,300	13%
7	12	Johnson & Johnson	130	3,068	3	8	2%	6	1,269	24,746	10%
8	12	Bayer	121	2,856	3	8	2%	8	1,032	20,124	12%
9	19	Takeda	107	2,525	2	5	2%	14	560	10,920	19%
10	25	Bristol-Myers Squibb	103	2,431	1	3	1%	11	740	14,430	14%
11	7	Shire	98	2,313	5	13	5%	27	263	5,129	37%
12	19	Amgen	96	2,266	2	5	2%	21	361	7,040	27%
13	5	Novo Nordisk AS	89	2,100	7	18	8%	12	623	12,149	14%
13	19	Eli Lilly and Company	89	2,100	2	5	2%	7	1,095	21,353	8%
15	12	AstraZeneca	77	1,817	3	8	4%	3	1,944	37,908	4%
15	25	AbbVie	77	1,817	1	3	1%	17	476	9,282	16%
17	-	Vertex	75	1,770	0	0	0%	47	109	2,126	69%
17	6	Genzyme, a Sanofi Company	75	1,770	6	15	8%	40	143	2,789	52%
19	25	Boehringer Ingelheim	60	1,416	1	3	2%	10	880	17,160	7%
20	-	Eisai	51	1,204	0	0	0%	20	367	7,157	14%
51	2	Centogene AG Rostock	15	354	10	25	67%	118	38	741	39%
25	7	Alexion	44	1,038	5	13	11%	70	60	1,170	73%

Appendix 4: Saudi Arabia has the highest prevalence at birth rate (per 100,000) for Mucopolysaccharidosis Type 6, however, has never been included in clinical trials in the last eleven years. Additionally, Saudi Arabia experiences some of the highest prevalence at birth rates for Type 1, 3 and 4. No prevalence data available for Saudi Arabia for Type 2 and 7, and no data globally for Type 5. Additional data can be found via the online dashboard at bit.ly/rare_disease_dashboard

	Mucopolysaccharidosis Type 1		Mucopolysaccharidosis Type 3		Mucopolysaccharidosis Type 4		Mucopolysaccharidosis Type 6	
	Prevalence at birth	Factors greater in SA	Prevalence at birth	Factors greater in SA	Prevalence at birth	Factors greater in SA	Prevalence at birth	Factors greater in SA
Saudi Arabia	3.62	-	1.8	-	3.62	-	7.85	-
United States	0.34	x11	0.38	x5	0.09	x40	0.05	x157
Canada	0.58	x6	0.29	x6	0.39	x9	0.1	x79
Netherlands	1.19	x3	1.89		0.36	x10	0.15	x52
Germany	0.69	x5	1.57	x1	0.38	x10	0.23	x34
Sweden	0.67	x5	0.84	x2	0.07	x52	0.23	x34
Brazil	0.24	x15	unknown	-	0.11	x33	0.31	x25
Australia	unknown	-	1.42	x1	0.59	x6	0.37	x21
Portugal	1.33	x3	0.84	x2	0.6	x6	0.42	x19
Ireland	3.8		0.36	x5	1.31	x3	unknown	-

Appendix 5: Egypt has the highest point prevalence (per 100,000) for Huntington's disease globally, however has not been included in even one of the 130 studies conducted over the last ten years (2008-2019 Feb). Additional data can be found via the online dashboard at bit.ly/rare_disease_dashboard

	Point Prevalence	Total Huntington's Disease Studies (2008-2019 Feb)
Egypt	21	0
Ireland	10.6	1
Norway	6.7	3
Italy	6.35	7
Australia	6.3	6
Denmark	5.8	6
United Kingdom	5.4	24
Slovenia	5.2	1
Sweden	4.7	5
United States	1.9	66
Finland	0.5	1
Taiwan	0.42	2
France	unknown	30
Canada	unknown	27
Germany	unknown	22
Spain	unknown	9
Netherlands	unknown	9

About Clinart MENA

Clinart MENA is a leading regional and innovative contract research organization, offering Full Service End-to-End Solution for Phase I to IV / NIS / RWE studies in the Middle East and North Africa region. Clinart offers direct access to 16 + MENA countries and other African countries through qualified partners, in line with global standards, local cultures and regulations. Our local and international experience, as well as our proven track record of successful trials since 2001 assures our clients that Clinart MENA is their reliable partner for the MENA region. Clinart MENA HQ located in the Dubai Healthcare City in UAE, offering direct coverage to the Gulf region. In addition, our local offices in Saudi, Kuwait, Lebanon and Egypt and home-based CRAs offer extensive direct coverage across the region, ensuring that minor cultural differences across the MENA region are well managed by our local professional and qualified teams.
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About LongTaal

LongTaal has been providing advanced clinical trials analytics since 2012 using its proprietary big data technology (www.longtaal.com). Analyses and bespoke reports prepared by LongTaal have been utilized by executives of large pharmaceutical companies, global CROs, policy advocates, investors and media to gain unique insights into the world of global industry clinical trials. Customized reports and market trend analyses were presented at international conferences, and published in peer-reviewed journals (see e.g. Refs 12 and 28 in this report