A roadmap for Phase IV, observational, and registry studies in the Middle East

The need to access larger numbers of patients and qualified investigators for expanded late phase trials, combined with an already saturated field for patient recruitment, has created demand for a truly global approach to site recruitment. Ease of patient enrollment and high-quality, yet lower-cost clinical resources make the Middle East and Turkey a truly attractive region for late phase studies.
THE MIDDLE EAST

TURKEY

LEBANON

JORDAN

KUWAIT

BAHRAIN

QATAR

UNITED ARAB EMIRATES

SAUDI ARABIA

OMAN

EGYPT

YOUR JOURNEY. OUR MISSION.
Why Conduct Trials in the Middle East and Turkey? Access and Eagerness

The Middle East is an emerging region that is welcoming, sophisticated, and home to varied and accessible patient populations. In this white paper we will discuss the winning factors for study start-up, site initiation, and site management in the Middle Eastern region.

Excellent Study Opportunities That Meet Urgent Medical Needs

The countries of the Middle East are home to treatment-naïve patients with a diversity of profiles including common indications such as diabetes mellitus, cardiovascular disease, and psychiatric diseases. Additionally, there is a strong potential for genetic sub-studies. From a high incidence of Hepatitis C in Egypt to Diabetes in the United Arab Emirates and Jordan, trials can provide adequate treatment that may not be available otherwise. This provides an incentive for enrollment in a landscape of very few competitive studies.

Enthusiastic Investigators and Sites

Investigators are fully qualified medical professionals with international accreditations and excellent English language skills. Most investigators meet the opportunity to participate in a study with eagerness to be a part of the international trial community and operate in an atmosphere of mutual endeavor. This attitude sets a strong foundation for successful sites.

Rapid Adoption of New Technology

While there are still some sites with inconsistent internet access, the true story of technology in the Middle East is one of rapid modernization. Technology infrastructure is being developed across the whole region, to the highest standards. Sites in Abu Dhabi and Dubai are often more highly equipped than Western sites. Electronic systems are also being implemented, with Turkey’s newly digitized submission process promising first feedback within 48 hours.

Regional Coherence

With Arabic as the Middle East’s most common language, cross-border monitoring is easier and translation costs are greatly reduced compared to other regions.

There is a concerted effort to harmonize regulatory requirements across Arab states. Currently clinical trial regulations are in place for Jordan. Established processes are in place in Egypt, Lebanon, Saudi Arabia and United Arab Emirates. Regulatory approvals are generally quicker in the Middle East than in countries like China, Brazil and India.
3 STEPS TO SUCCESSFUL LATE PHASE TRIALS IN TURKEY AND THE MIDDLE EAST

Before beginning late phase trials in the Middle East or Turkey, sponsors and their research partners should closely scrutinize three key aspects of studies in this region: study start-up, site initiation, and study management.

1. Critical factors affecting study start-up

OPERATIONAL FACTORS

Awareness of cultural differences and sensitivities is important in all areas of the engagement. From planning and organizing work around different working calendars, awareness and respect of customs and religious laws, to stating the correct justifications of requirements—local knowledge is the key to successful engagements.

Face-to-face interaction is the most effective route for communication. This is true in all stages of the trial and Electronic Data Center (EDC) sites should expect to provide ongoing support to the sites through local staff and helpdesks.

Involvement in an emerging region also presents the opportunity to positively contribute to its development. PAREXEL has been a pioneer in many emerging markets, having participated in the development of South Africa, Eastern Europe, India and Southeast Asia. Constructive and necessary actions include entrenching solid processes and developing local partners for logistics including import and export, providing training courses for health care professionals, to further Good Clinical Practice (GCP) awareness and collaborating with regulators on the formulation of regulations and laws.

Early logistics planning leads to stronger trials and Turkey and the Middle East are easily integrated into global clinical logistics strategy and management. Multinational trials require a combination of trial-wide systems and practices with country- and site-specific expertise such as drug import and sample export regulations. Moreover, real-time trial supply intelligence can optimize supply levels and delivery timetables. PAREXEL® Clinical Logistics Service’s experience in the Middle East and Turkey can help to accelerate site readiness, minimize supply chain and safety issues, access business intelligence, and maximize trial efficiencies.

SITES IN THE MIDDLE EAST

- Are cost effective
- Offer a variety of both common and rare indications
- Have high patient enrollment rates
- Are led by enthusiastic investigators
- Draw on a wide and deep patient pool
- Possess the technology to aid sites
ADMINISTRATIVE REQUIREMENTS

**Informed Consent Form (ICF):**
Informed consent forms should be in Arabic and must include the site address and PI / EC contact details. For Psychiatric indications it is recommended to include the signature of the legally responsible representative or guardian. ICH-GCP guidelines for ICF are followed and a reference to patient insurance and reimbursement of study visit costs are required.

**Clinical Trial Agreement (CTA):**
The tripartite agreement is to be signed by the sponsor, the institution representative and Principal Investigator. The CTA is usually accepted in English. In some specific cases indemnification may be required by the site.

**Budget:**
Payments are acceptable in EGP, USD or EUR and the agreement is site-specific.

**Ethics Committee (EC) / Institutional Review Board (IRB) Approval:**
Administrative fees can differ significantly for IRB approval. Meetings are usually held monthly or ad-hoc, though some ECs meet bimonthly.

**Regulatory Approval:**
Application for approval may be submitted by sites or by a local representative (affiliate, CRO) and remains valid for 1 year. It is then renewed based on the progress report and safety information. There are three Ministry of Health (MoH) departments involved for study evaluation, import license and customs clearance permitting.

**Insurance Policy:**
An insurance policy is required as part of a Dossier. Minimum acceptable insurance is 250,000 EUR per patient.

**Import / Export Licenses:**
An import license is needed for investigational product (IP) as well as for lab kits. No study material may be imported before study approval is granted and no blood sample and genetic material export is allowed without special permit. The import license is valid for 1 MoH financial year, which ends 30 June.

**Logistics:**
An authorized / delegated importer is needed for customs clearance. Once cleared, IP is delivered to the site directly, usually in about 3-4 weeks. The use of the local lab is without limitation.

**Local Sponsorship:**
A local sponsor representative is required for patient insurance and only a locally registered company may submit to MoH.

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Primary Objective
Among the population at risk of atherothrombotic events, the study sought to evaluate the long-term risk (yearly event rate) of atherothrombotic events in global population subgroups.

The Study:
• Compared long-term outcomes within different subject profiles
• Evaluated the importance of cross-risks of subjects at risk
• Defined predictors of risk for subsequent atherothrombotic events

Program Design
A multi-center, observational, quality assurance, disease cohort study of the management of patients treated in the hospital for acute heart failure.

Sites / Patients
• 64,000 patients
• Approximately 5,500 sites in 38 countries

Advantages of using the Middle East region
Faster regulatory approval and low competition from other clinical studies led to early completion of patient recruitment at sites. Communication and teamwork between the CRO and sites are major drivers to a successful recruited study.

PAREXEL Innovation
• eClinical suite
• Peri/Post-Approval Technology Solution
• Direct-to-patient strategies
• Social media application
• Electronic Health Records (EHR)

2. First site ready for initiation strategy

PAREXEL relies on extensive databases of pre-qualified patients and investigators to select well-organized sites that are cooperative with functional ECs.

Negotiations of Clinical Trial Applications (CTA) should be entered into as soon as possible. Sites will usually sign after Ethics Committee (EC) approval, though some prefer to wait for MoH approval. Once study approval and import license is granted, sites should be alerted and staff can begin to oversee and coordinate the import of investigational product.

A dedicated logistics site manual that describes the processes around clinical trial materials (CTM) is essential for a smooth study start-up. For instance, it should define the handling of investigational products and any other add-on or rescue medication and application materials, as well as other materials such as lab kits and medical and testing equipment. Due to extreme warm temperatures in the Middle East region, special focus should be on storage and distribution aspects for cold chain products (e.g., 2-8°C sensitive IMPs and ambient lab samples). IATA regulations for dry ice transportation and roles and responsibilities of the site as well as the transportation companies should be clarified.

Patient / Investigator Insurance:
Local insurance listing all participating sites and investigators is required for patients. Additionally, investigator liability insurance may be required for some studies.

Indemnity Letter:
Indemnity letter is not usually required by the sites.
Final protocol to first site initiation visit (SIV) overview: sequential process

Start of Activities:
Final Protocol and Approved Model Informed Consent Form (ICF) Received

Translation of some study documents into Arabic
Send Reg. Docs. to sites after QV. Regulatory documents collection for EC and JFDA submission and IP release

Country and/or Site-Specific ICF Customization
Country and/or Site Specific ICF Approved
Translation Required

ICF

Simple Site: 30 Days
Complex Site: 60 Days

Site EC/IRB Submission
Site EC/IRB Approval
Import License Obtained with Approval
Draft CTA to PI
PI CTA Fully Executed
Draft CTA to Institution and PI
CTA Fully Executed

Regulatory [JFDA] Submission
Regulatory Approval

Timelines from Final Protocol to First SIV: Both Simple and Complex Sites 110 days

IP Release
SIV

All Sites Approved by Sponsor

QV

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<td>110</td>
<td>Timelines from Final Protocol to First SIV: Both Simple and Complex Sites</td>
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3. Site Management in the Middle East

THE IMPORTANCE OF LOCAL STAFF
Local expertise and the positive attitude of the sites will lead to good working relationships and results. PAREXEL’s on-the-ground staff are experts in our global systems and work practice, which ensures that Middle Eastern sites are seamlessly integrated into global studies. They are also local and at home in their culture.

IN-PERSON CONTACT FACILITATES COMMUNICATION
In the Middle East, as well as in our previous emerging region experience, in-person contact is the key to successful sites. CRAs and CMAs need to interact with site coordinators face-to-face to build relationships and identify misunderstandings through dialogue and by observing body language, since site staff will not always ask for clarification.

THE IDEAL SITE
Sites in the Middle East are usually less experienced and under-staffed compared to those in mature markets. Ongoing in-person support from CRA and CMAs for all aspects of the trial is to be anticipated at all sites. The ideal for a well-recruited trial and high quality of data, is a site that is well-versed in GCP and is staffed with a site coordinator. Site coordinators do not only perform the data entry but also act as technology super users; they serve as site experts for the global web platform and proactively solve issues related to malfunctioning technology.

QUALIFICATION VISITS
Qualification visits are essential and ample time should be allowed. The feasibility specialist should also be in charge of the risk management plan. To identify as many issues as possible, the qualification must go beyond measuring the recruitment potential for the site to encompass logistical and technology issues. This is best done on-site. A thorough visit will not only review but also troubleshoot and assess the ongoing support needs of site. For example, a recent study investigating metastatic tumors required a test scan as part of the qualification visit. The scans far exceeded expectations and were not only helpful as a proof of concept but also in setting expectations for the trial.

CASE STUDY 2

Primary Objective
Evaluate long term risk (yearly event rate) of atherothrombatic events in the global population and in different population subgroups.

Compare outcomes within different subject profiles in order to evaluate the importance of cross-risk of subjects at risk, and define predictors of risk for subsequent atherothrombatic events.

Program Design
An international prospective observational registry with long term (45 month) follow-up in subjects at risk of atherothrombatic events.

Sites / Patients
- 65,000 patients globally
- Approximately 5,000 sites in 45 countries

Advantages of using the Middle East region
Well-communicated trial information leads to a smooth recruitment phase. The qualification and initiation phase must be covered in depth, so the site is aware that there is both in-house technological and CRA support. Technology support is key.

PAREXEL Innovation
- eClinical suite
- Peri/Post-Approval Technology Solution
- Direct-to-patient strategies
- Social media application
- Electronic Health Records (EHR)
CASE STUDY 3

Primary Objective
In a real-world setting, this study sought to assess treatment response and safety profiles of oral anti-diabetic drugs in patients with Type 2 diabetes.

Program Design
• A multinational, multicenter, post-authorization prospective observational 12 month cohort study.
• Anti-diabetic treatment is chosen at physician’s discretion.
• The treatment choice is expected to be driven by a variety of factors, e.g., patient demographics, life-style factors, socio-economic status, body mass index (BMI), country-specific treatment guidelines, co-morbidities, co-medication.

Sites / Patients
• >50,000 patients
• Approximately 4,600 sites in 28 countries

Advantages of using the Middle East region
Enthusiastic site participation led to high recruitment and retention rates. All sites were free of quality issues. In-house and onsite support is essential to a successful trial in the Middle Eastern region.

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SUMMARY

The Middle East is an emerging region that is welcoming, sophisticated and home to a varied and accessible patient population. Investigators are qualified and enthusiastic, they adopt new technology rapidly, and they largely share language and customs for regional coherence in work patterns.

To get the most value from late phase trials in Turkey and the Middle East, sponsors and their research partners should observe three key principles:

1. **Study start-up**: Sensitivity to regional cultures, working patterns and preferences, and familiarity with administrative requirements, can make the most of investigators and patients eager to participate in research.

2. **Site initiation**: Trial approval concurrent with site and materials preparation makes rapid patient recruitment possible.

3. **Study and site management**: Personal interaction, support, and oversight with investigators and sites help to avoid problems and to respond quickly to opportunities.

PAREXEL has conducted trials in Turkey and the Middle East since 2002 in a wide variety of therapeutic areas. Sponsors benefit from PAREXEL’s extensive databases of pre-qualified patients and investigators, deep regional and local regulatory and marketing experience, and in-depth understanding of local medical practices and culture. PAREXEL’s on-the-ground staff, while local and at home in their culture, are also experts in our global systems and work practice, which ensures that Middle Eastern sites are seamlessly integrated into global studies. Our integrated technology and clinical logistics solutions effectively manage trials by eliminating risk and ensuring quality. PAREXEL offers global knowledge deployed locally and harmonized practices that maintain quality and data integrity across multinational trials.

Visit our website to learn how partnering with PAREXEL will help you achieve your ambitions.

www.PAREXEL.com

Our regional leads are always available for a conversation.

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PERI/POST-APPROVAL SERVICES

PAREXEL’s Peri/Post-Approval Services group is a dedicated unit of late phase specialists providing a full scope of peri/post-approval services that help our client’s collect the data needed to successfully prove the value, safety and effectiveness of products transitioning from development to commercialization.

As pioneers in late phase research we have extensive experience in the design and conduct of late phase trials and non-interventional programs. Our services include Phase IIIb & IV clinical trials, non-interventional research programs, patient registries, expanded access programs, market access and commercialization consulting, and post marketing pharmacovigilance services. Leveraging PAREXEL’s extensive global infrastructure and our proprietary web-based technology platform, we provide specialist expertise to drive efficient, intelligently designed, global late phase programs that facilitate better stakeholder decision making. Late phase trials in Turkey and the Middle East offer excellent opportunities for rapid data acquisition, and help to meet urgent medical needs. PAREXEL’s Peri/Post-Approval Services has the regional experience and the global systems to design and conduct high quality clinical trials in this strategic region.

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WHEREVER YOUR JOURNEY TAKES YOU, WE’RE CLOSE BY.

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