WHITE PAPER

3 STEPS TO MIDDLE EAST SUCCESS

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.

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THE MIDDLE EAST

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, cardio-vascular 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.

ACRONYMS USED IN THIS PAPER

EDC	Electronic Data Center
CMA	Clinical Monitoring Associate
CRA	Clinical Research Associate
CRO	Contract Research Organization
CTA	Clinical Trial Agreement
EC	Ethics Committee
EGP	Egyptian Pound
EHR	Electronic Health Records
EUR	Euro
GCP	Good Clinical Practice
IATA	International Air Transport Association
ICF	Informed Consent Form
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
JFDA	Jordan FDA
MoH	Ministry of Health
PASS	Post-Authorization Safety Studies
PI	Principal Investigator
PMS	Post-Market Surveillance
PMS	Post-Marketing Surveillance
QV	Quality Verification (Pharmacology)
REMS	Risk Evaluation and Mitigation Strategy
SIV	Site Initiation Visit
USD	US Dollar

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.

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.

CASE STUDY 1

Primary Objective

Among the population at risk of atherothrombatic events, the study sought to evaluate the long-term risk (yearly event rate) of atherothrombatic 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 atherothrombatic 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

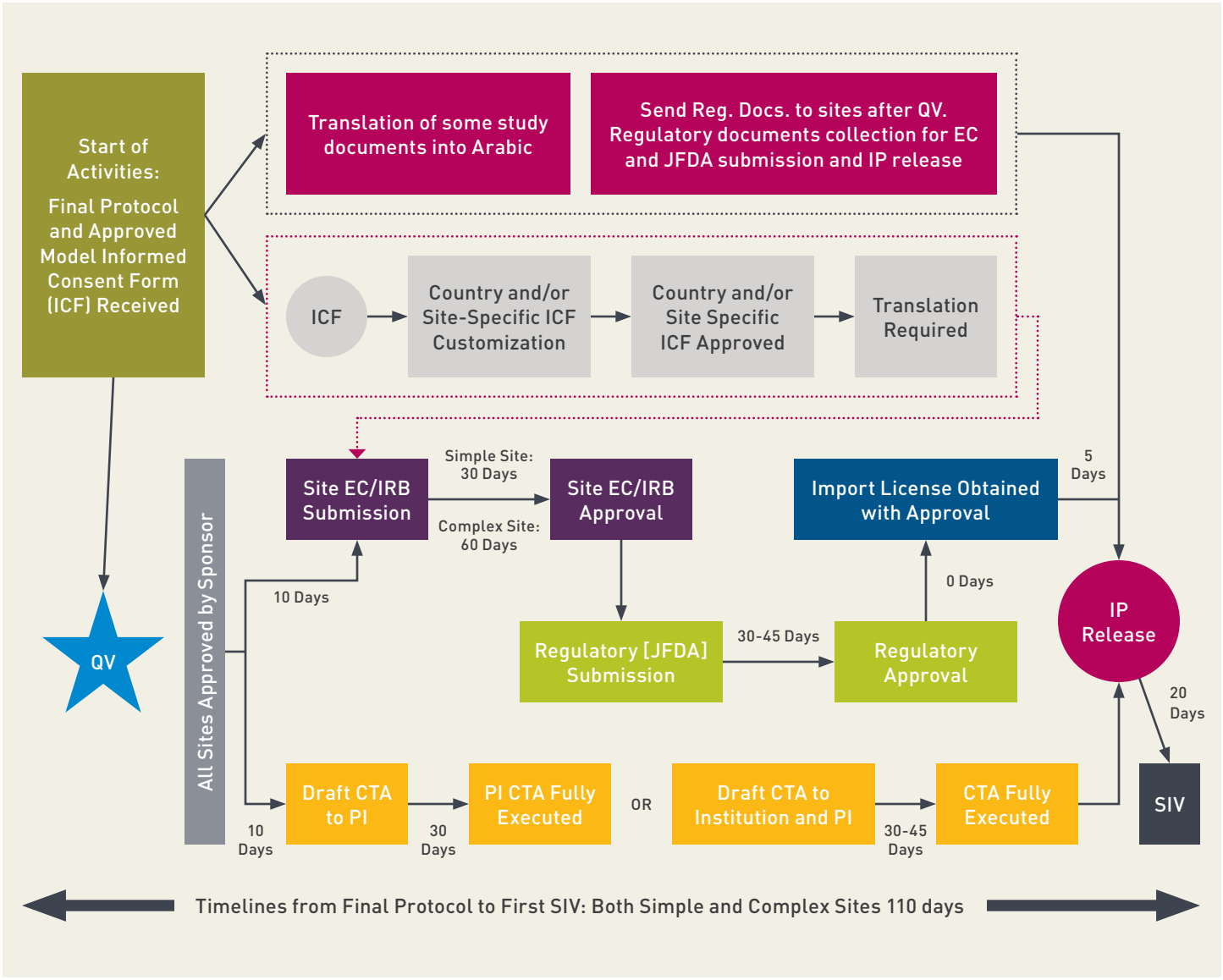
Advantages of using the Middle East region

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)

Final protocol to first site initiation visit (SIV) overview: sequential process



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.

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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.

PAREXEL Innovation

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- Electronic Health Records (EHR)

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.

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.

KEY SERVICE AREAS DETAIL

Phase IIIb/IV Trials	Observational Research	Expanded Access Programs	Post-Marketing Safety	Epidemiology	HEOR
• Phase IIIb • New indications • New formulations • Medical outcomes • Direct comparison • Phase IV trials • Large simple	• Product safety & outcome registry • Cohort studies • Non-interventional studies • Cross-sectional studies • Prospective & Retrospective research • Post-Authorization Safety Studies (PASS)	• Treatment IND • Emergency use protocols • Compassionate use • Named patient basis programs • Post-marketing safety • New standard risk-management plans • Post-marketing pharmacovigilance • Case processing • Case reporting • Active pharmacovigilance programs • Japan Post-Marketing Surveillance (PMS)	• New standard risk management plans • Post-marketing pharmacovigilance • Case processing • Case reporting • Active pharmacovigilance programs • Japan Post-Marketing Surveillance (PMS)	• Fully integrated epidemiology services • Epidemiology consulting • Design, conduct, analyses and communication of real world studies • Risk-management effectiveness evaluations • Regulatory strategies for REMS and PMS	• Burden of disease • Cost minimization assessments • Cost benefit evaluations • Patient-reported outcome studies • Clinical outcome studies

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WP-PERIMIDEAST-FEB14