PRA Health Sciences

WHITE PAPER

Local Representation: What Clinical Trial Sponsors Need to Know

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Introduction

Clinical Trial Sponsors are required to establish a "Local Representative" in certain countries in order to meet Regulatory obligations. A Local Representative assumes selected responsibilities for a trial, and as a result are held legally liable for those responsibilities. During an inspection, a Local Representative must demonstrate the following:

- A sufficient level of control and oversight for the conduct of a Clinical Trial in the respective country
- Authority (written and in practice) to fulfill all Local Representative responsibilities
- Sufficient time and resources to fulfill all Local Representative responsibilities

In this white paper, best practices are described as well as required Sponsor/Local Representative agreement areas. It is important that major subject areas are agreed in order to ensure that the conduct of the clinical trial does not cause issues when the new drug application is assessed by the competent authorities. Although Local Representation applies to multiple areas of Pharmaceutical Development (Regulatory, Legal, etc.), this Whitepaper is limited to the area of Pharmacovigilance.

The decisions related to Local Representation are complex and must be discussed in detail between Sponsors and Local Representatives. A Clinical Service Provider can assume Local Representation based upon two key factors:

- The scope of Drug Safety services provided for the countries in question
- A Sponsors ability/willingness to provide the 3rd party with sufficient information and authority to effectively oversee Drug Safety activities for the countries in question

Terminology

The following key terms are used within this Whitepaper:

- A **Sponsor** is a person or entity who takes responsibility for and initiates a clinical trial. Key responsibilities of Sponsors include:
  - Selecting qualified investigators
  - Ensuring proper monitoring of the investigation
  - Maintaining a clinical trial or IND application approval in accordance with applicable local legislation
  - Ongoing safety evaluation of the investigational product
  - Ensuring that global regulators, IRBs/IECS and investigators are promptly informed of significant new adverse effects or risks with respect to the drug as required by local legislation
- A **Local Representative** is an individual or entity that is viewed by local regulators as the Sponsor of a clinical study being performed within a particular nation. The term "Local Representative" is synonymous with "Legal Representative"or "Local Sponsor". The Local Representative typically is responsible for:
  - Interfacing with regulatory authorities, ethics committees, and study sites including safety reporting
  - Signing agreements that are governed by the applicable nation's laws, including clinical trial agreements with investigators or institutions
  - Processing official communications, including service of process for lawsuits
  - Determining or maintaining appropriate clinical study insurance for the study being performed in the nation
- According to existing EU regulations (and similar to other Worldwide regulations), a Legal Representative:
  - Must be established, if the Sponsor does not have a legal entity in the European Economic Area (EEA)
  - Must reside in the EEA

- One Legal Representative must act on behalf of a Sponsor in a single Clinical Trial for such activities as:
  - Interfacing with regulatory authorities, ethics committees, and study sites
  - Signing agreements that are governed by the applicable nation's laws, including clinical trial agreements
  - Official communications, including processes for lawsuits
- According to the Clinical Trial Regulation (EU) No 536/2014, which is expected to become effective in 2020, a Legal Representative is:
  - Responsible for ensuring compliance with a Sponsor's Clinical Trial obligations, which implies that the legal representative has the same responsibilities and liabilities as the sponsor and should act on behalf of the sponsor based on a contractual agreement (see CLINICAL TRIALS REGULATION (EU) NO 536/2014, DRAFT, QUESTIONS &ANSWERS, VERSION 2, June 2019.)
  - The addressee for regulatory communication with the Sponsor

Case Study – The Importance of Local Representation Decisions

In December 2016, PRA became involved in a Sponsor inspection related to a marketing authorization application in South Korea. This application was submitted by a Sponsor several years after the study was conducted. PRA was not involved in any submission activities.

Both PRA and the Sponsor were taken by surprise by the perspective of the South Korean regulatory inspectors. These regulators maintained that PRA was the de facto "Sponsor" of the IND as the Local Representative of record and therefore responsible for the conduct of the study within their country.

As a result, the Sponsor submission was inspected through PRA. The global Sponsor's involvement and oversight in the study was not of concern to the regulatory inspectors.

The regulatory authorities further required PRA personnel (both Drug Safety and Quality Assurance) to reside in South Korea, demonstrating their intense interest in these areas as they pertain to the quality of Clinical Trials and Drug Safety.

This experience has given PRA good reason to clarify their specific position on Local Representation on behalf of Sponsors, not only in South Korea but also in other countries. The below considerations are the results of discussions with authorities in various countries about Local Representation.

The Decision Process – Drug Safety Scope

The contracted scope of services has a significant effect on a vendor's authority over the conduct of the clinical trial in the country in which Local Representation is assumed. The diagram below is highly simplified, but it illustrates the key factors related to Local Representation as it relates to Drug Safety scope of services.

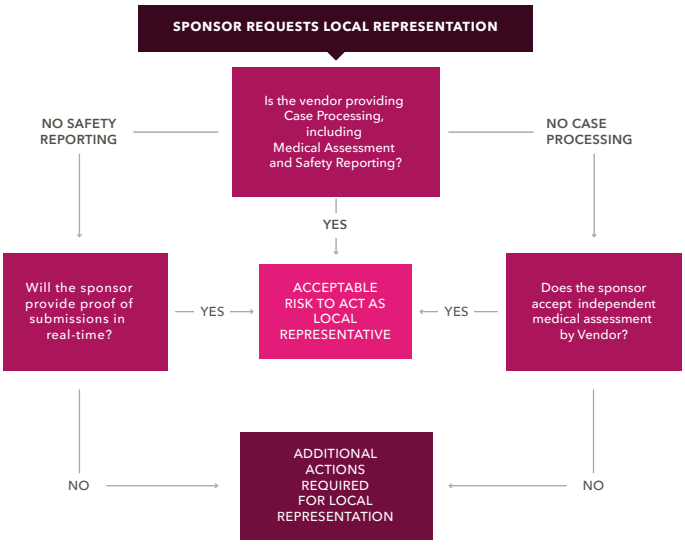

Figure 1: Local Representative – High-Level Decision Process on Scope

If the vendor is contracted for full Safety Services, (e.g. collecting Serious Adverse Events (SAEs) from investigators, processing and medically reviewing SAEs, evaluating SAEs for expedited reporting to authorities, IRBs/IECs and investigators) and is responsible for cumulative safety review as well as generation of annual safety reports (i.e. Development Safety

Update Report), the vendor has control and oversight of the study from a drug safety perspective as required for a Local Representative.

However, when some of these drug safety services are not contracted to the Local Representative, the Sponsor and Vendor must reach agreement on how to address the information and authority gap.

Best Practices for Local Representation

In cases where the Local Representative is not responsible for Case Processing and/or Expedited Safety Reporting services, the following best practices, although not comprehensive, may provide the Local Representative with oversight about the safety aspects of the trial to meet its obligations. In practice, each situation must be independently examined to ensure sufficient oversight.

The Sponsor will immediately provide the Local Representative with the following:

- Any observations that might materially influence the risk-benefit analysis of the Study drug
- Any identified significant safety issues that have arisen from safety analysis that may threaten the safety of study subject or may have influence on the conduct of clinical trial
- Any actions taken by another country's regulatory authority due to safety issues

The Sponsor will provide the following at the beginning of an agreement and at the time of document revisions:

- Sponsor Case Management SOPs and associated Control Documents for verification of compliance with applicable legislation

The Sponsor will regularly share the following in near-real-time:

- Monthly SAE listings (including a process for discussion of the rationale for individual SAE reportability)
- Listings and/or copies of Cases submitted to regulatory authorities (including Event terms and submission dates and other minimal information)
- Monthly Compliance Metrics, including root cause and information on all corrective and preventive actions for late reports
- Audit rights for Sponsor 3rd Parties, if the Sponsor contracted drug safety responsibilities to another vendor
- Latest Drug Safety audit/inspection certificates with confirmation that all critical and major findings, if any, have been resolved to the auditor's/inspector's satisfaction

In scenarios where the Local Representative is not contracted for Medical Review of safety data, an independent medical assessment of all cases or at least a random sampling of cases may close the gap of oversight for some regulators.

Summary

Although it is clear that Local Representation is required in some countries, the process and information-sharing requirements necessary to appoint a vendor as a Local Representative can be complex.

By implementing the concepts and best practices in this whitepaper, a Sponsor can:

- Reduce the risk of misunderstanding or misinterpreting country specific Regulations related to Local Representation
- Minimize time spent discussing remedies for Local Representative oversight responsibilities
- Understand the data and process needs for typical situations resulting from Local Representation

Appendix – Selected Country and Area Specific Information

Local Representation is currently required in the following countries:

Area	Countries
Europe	European Economic Area (EEA) – Each member nation of the Europe Union + Norway, Liechtenstein and Iceland require a local representative within one member nation of the European Union
Europe	Switzerland
Asia Pacific	Australia
Asia Pacific	New Zealand
Asia Pacific	Taiwan
Asia Pacific	India
Asia Pacific	Indonesia
Asia Pacific	Japan
Asia Pacific	Singapore
Asia Pacific	Vietnam
Asia Pacific	South Korea
Asia Pacific	China
Asia Pacific	Hong Kong
Latin America	Argentina
Latin America	Peru
Latin America	Mexico

Note: The list above is correct at the time of this writing, but it may not be inclusive for the future.

Selected country-specific guidance as it pertains to Local Representation (as of December 2017):

- Australia: Under the Therapeutic Goods Act of 1989, the TGA can request any of the following: metrics, reports, pharmacovigilance audits, etc. that would give information on whether the reporting within Australia has occurred to the appropriate standards; any information from cases that have occurred within Australia; any Safety related action taken by another countries regulatory body (this is part of the Australian expedited safety reporting to Ministry of Health (MoH) guidance); any information related to the release, quality, safety of the drug that has been supplied to Australia. TGA clearly holds the local Sponsor liable.
- Hong Kong: A vendor must receive the cases submitted in order to act as the Local Representative. This is supported by the Department of Health notice on local drug safety reporting for all the certificate holders.
- Singapore: Local Sponsor assumes overall responsibility for ensuring that safety reporting submissions are performed in accordance with local regulatory requirements. According to section 4(5) of the Health Products (Clinical Trials) Regulations, "the Sponsor may delegate all or any of the Sponsor's functions under these Regulations to any person, but any such arrangement does not affect the responsibility of the Sponsor." The Singapore Ministry of Health recommends that Local Sponsors have access to all important safety information to be able to assume the overall responsibility for the clinical trial and act in a timely manner should a safety event warrant action.
- South Korea: As IND Holder, a vendor is regarded by SK regulators as the de facto Sponsor of the Clinical Trial. Any inspections would be through the Local Representative. South Korea regulators will only accept safety reports from the Local Representative, i.e. submission of safety reports may not be delegated by the Local Representative, and would also hold the vendor assigned as Local Representative liable for any noncompliance.

Contact Information

For further information or to discuss PRA's legal representation services, please contact your PRA account director or the PRA employee below:

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