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I. GENERAL OVERVIEW

Often overlooked in the early planning of a human clinical trial, insurance requirements specific to foreign jurisdictions may have a significant impact on a company's clinical program and a material impact on its bottom line. The clinical impact may include delay in enrollment as well as a decision not to enroll at all in a particular country from a cost/benefit perspective. Historically, the costs to secure insurance that meets local requirements were insignificant, and therefore typically not strategic to the clinical trials planning process. An evolution has taken place in recent years outside of the United States whereby a more uniform approach to protecting patients in human clinical trials has prevailed and continues to gain momentum in just about every country today. This movement towards uniform protection has created a complexity of risk management and insurance issues for both insurance companies and life science companies alike. The key aspects of coverage are described in this overview to help become familiar with terminology to be encountered, and as a guide to set expectations as a company prepares for enrollment of patients in human clinical trials outside of the United States.

Form of Insurance

The form of insurance to be encountered will be stated either as "admitted" or "non-admitted." The simple distinction between each is that insurance required to be issued on an "admitted" form refers to a policy of insurance that will be written and issued in the specific locale by an insurer authorized to transact

business under the confines of the local insurance laws. "Admitted" policies are written in the local language and currency. "Admitted" policies may be written for an annual renewable period or for a period that reflects the full anticipated length of the trial. Some countries may not allow multi-year policies, but when available they allow the company to budget the full expense of the insurance up-front instead of having to pay multiple premiums as policies renew. Coverage that is written on a "non-admitted" basis does not subject the insurer to the same statutory insurance requirements, but may allow the insurer greater flexibility in the design of the policy and the coverage. Generally speaking, "admitted" coverage is required in a majority of popular countries wherein human clinical trials are conducted.

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The most commonly accepted form of insurance available for most types of products in human clinical trials is that which is written on a “claims made” basis, as opposed to being written on an “occurrence”

basis. With a “claims made” policy, a claim is covered under the policy in effect at the time the claim is made (with some deviations permissible), regardless of when the injury occurred as long as the period of injury is encompassed within the policy retroactive date. “Occurrence” policies allow claims to be covered under the policy period in effect at the time of injury. While “occurrence” policies are advantageous to the insured, most insurers do not write drug exposures or other perceived long tail liability exposures on any form but “claims made.” It should be noted however, that several countries have enacted statutory insurance requirements mandating sunset clauses to “claims made” policies that subject the insurer to liability for periods up to 10 years for each protocol conducted.

Global Territory & Restricted Jurisdiction.

There is a distinction between the terms found in master policies written on an “excess & DIC (Difference in Conditions)” basis and those written on a “primary” basis (these terms are discussed in section II below). Common forms of insurance extend coverage to products sold or used around the world. However, only a global form with global jurisdiction will respond to claims/suits brought in any jurisdiction (except those precluded by US sanction), as opposed to claims brought only within the United States, as is the case with policies noted with a “world-wide” territory definition.

Extended Reporting Periods, Tail Period or Sunset Clauses.

As a feature of all “claims made” policies, these provisions exist to permit coverage for claims that may be made after the policy has expired or has been cancelled. An example would be where a trial has ended and there are no additional trials planned for a particular country, yet continued protection for prior liability is required by contract and also for prudent business purposes. These provisions are generally priced in addition to the policy premium; however, insurers subjected to the requirements of several countries enacting sunset clauses price the coverage into the annual policy premium. In general, these periods range from 5 to 10 years, but unlimited durations are sometimes available or required.

II. STRUCTURING HUMAN CLINICAL TRIALS INSURANCE

The terms and structure of a human clinical trials insurance program should be reflective of the sponsor company’s risk tolerance, product/patient profile, enrollment territory, contractual requirements with clinical sites, CRO’s, investigators and corporate partners, among other potential business relationships. Focusing on the enrollment territory, the following scenarios exist.

Scenario 1: US Trials Only

A US company conducting human clinical trials wherein patients are only enrolled at sites in the United States has a degree of flexibility in the design of its insurance program to manage its clinical trials risk. A single primary insurance policy is issued with a 12-month term designed to cover anticipated trial activity of the sponsor during the same period. Generally, both primary “admitted” and primary “non-admitted” insurance policies are an available and acceptable form of insurance. There are no laws in the United States requiring human clinical trials coverage, let alone to be placed on an “admitted” basis. Any such

requirement would generally be promulgated contractually between the sponsor and related party to the conduct of the clinical trial. Typically, a “non-admitted” insurance policy is an acceptable form of coverage.

The territory of coverage would be properly placed as “global” coverage, although consideration should be given to writing coverage with an unrestricted jurisdiction should the sponsor expect to begin trials outside of the United States at any point during the next 12-month policy period. This will provide a coverage trigger for claims brought inside or outside of the United States. Absent the possibility of any expected foreign exposure, the underwriting of coverage and the mechanics of issuance are fairly simple. The required evidence of insurance may be generated upon binding coverage.

Scenario 2: Foreign Trials Only

A US company conducting human clinical trials wherein patients are only enrolled at sites outside of the United States may present additional underwriting issues, mechanics of issuance and costs in placing the insurance program. The parameters will be determined based upon the existence of statutory insurance requirements that may be required in a particular country and/or by

a particular IRB. Issuing coverage for countries that do not mandate “admitted” coverage, onerous policy language, or excessive policy limits, is fairly simple. In this case, a primary insurance policy may be underwritten domestically on a

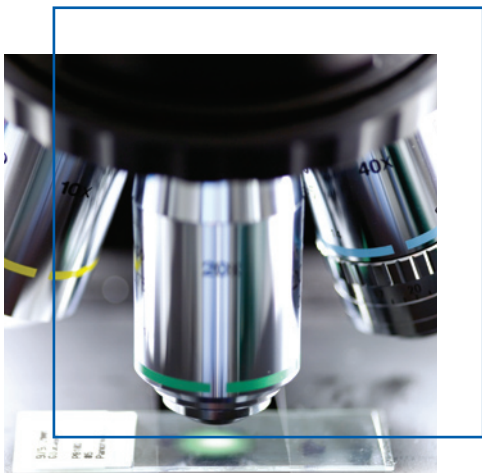
“global” “non-admitted” or “admitted” basis with an unrestricted policy jurisdiction. The required evidence of insurance may also be issued domestically for delivery to the foreign site, CRO, IRB or investigator. Issuing coverage in a country requiring “admitted” paper, specific statutory language, and/or limit requirements adds an additional level of complexity and additional time to secure. In this scenario, a single master global policy is issued as either “non-admitted” or “admitted” and local underlying “admitted” policies will be issued in the specific locale that meet compliance with statutory requirements. The master global policy would exist as “excess and DIC” over the locally issued “admitted” policy, but is in no way a substitute or is it primary to that of the policy covering the statutory requirement. This master policy, while not required or recognized by local jurisdictions is needed to protect the sponsor from claims brought back in the United States, since the local policy will only cover claims made locally.

Scenario 3: US and Foreign Trials

A US company conducting human clinical trials wherein patients are enrolled at a site inside and outside of the United States may present a combination of issues between scenario number 1 and 2 above. A master global insurance policy will be issued on either an “admitted” or “non-admitted” basis, with local underlying policies being issued on an “admitted” basis and subject to statutory language and limit requirements as needed. While the master global will be a 12-month policy term, the local underlying policy may likely be issued to run for the life of the covered trial(s).

Scenario 4: Investigator Initiated Trials

Sponsors providing products to clinical investigators or other physicians create a liability exposure which may not be automatically covered under a clinical trials liability



insurance program. For this exposure, coverage often needs to be specifically negotiated with the insurance company. In scenarios where the provision of the product by the sponsor is governed and regulated by a clinical protocol, the protocol must be reviewed and underwritten in accordance with how each particular insurer grants coverage for all clinical trials under the policy they have issued. Coverage can be provided under a local “admitted” policy, a global master policy or both as may be prudent.

When product is provided by a sponsor outside of a clinical protocol, a product liability risk is created since the exposure is no longer controlled within the protective regulatory framework afforded by the clinical trial process. For insurance to apply, coverage must be specifically negotiated to the policy. Typically, a “non-admitted” global master policy can be arranged or endorsed to cover the risk. Since there are no statutory requirements in the world to maintain products liability insurance, a global master policy written on a “non-admitted” basis is universally accepted in support of non-statutory requirements such as those existing within contractual relationships with business partners.

III. CHALLENGES

The challenge to securing insurance requirements for foreign trials is time and cost. Recognizing at the same time that the universe of insurance companies with the ability to offer coverage for certain liability exposures is fairly small (i.e. pediatric populations, vaccine products, plasma exposures), the number able to secure coverage around the world is even smaller.

A multitude of issues may arise country by country at any point in the process of underwriting coverage for a specific trial. For example, certain insurance companies have restrictions on how much insurance they can underwrite on any single indication. Hence, when entering multiple

countries inclusive of those that require high limits of coverage per patient and per protocol, the capacity that the insurer has to offer may be exhausted, leaving the sponsor to seek alternative insurers when entering the next country. Additionally, most insurers cannot issue policies in certain countries at all, and either rely upon affiliated insurance companies to secure coverage under joint agreement, or require the sponsor to seek alternative insurers in the particular locale. Once coverage is underwritten on the specific product and a premium is developed for the risk presented by the trial, the mechanics of issuing the required evidence of coverage may also present complexities. It is common for local IRB’s to receive evidence of coverage and require amendments in order to move forward with enrollment. Depending upon the nature of changes required, additional underwriting consideration and time may be required to promulgate the changes. The main issues typically encountered include:



- Limited insurance marketplace
- Time and cost
- Difficult product class from an underwriting standpoint
- Missing information in the submission to underwriters, such as translated protocol or consent forms, updated clinical site information, IRB approved consent form
- Entering a country where the insurer cannot offer coverage
- Entering countries with strict statutory requirements which “tap” the insurers capacity

IV. INFORMATION REQUIRED TO AVOID DELAYS

- Application - General Products/Clinical Trials
Application along with any specific application required by a specific locale, such as Germany
- Clinical Trials Worksheet (Includes Phase, and # of participants per site)
- Protocol and Informed Consent in English, as well as translated versions to the specific country being entered, as may be specifically requested
- Best estimate of expected enrollment in each country, and at each site, including duration of trial
- Copy of applicable contractual requirements with Sites, CRO's SMO's, Investigators, etc. Specifically indemnity, Insurance, and Hold Harmless sections.
- Contact information for those individuals ultimately in need of evidence of insurance.

V. CONNER STRONG INSURANCE SOLUTIONS

As an insurance brokerage firm working exclusively within the Life Science industry, Conner Strong is at the forefront of providing solutions to global clinical trial exposures. As a result of our specialty focus, we have helped insurers bring about the necessary expertise required by our clients as they expand on their global programs. Resulting from over a decade of "hands on" experiences involving environmental changes effecting insurance for human clinical trials, Conner Strong leads the industry with solutions including:

- Direct access to leading domestic insurers in the life sciences industry, all having global capabilities and knowledge specific to human clinical trial.
- Direct access to global insurers domiciled outside of the United States, with specific knowledge of the conduct of human clinical trials and access across all European insurance markets.

- Vast experience negotiating insurance provisions on behalf of clients with major organizations including CRO's, SMO's university sites, investigators, contract manufacturers, contract packagers, animal facilities and laboratories.
- Consulting and insurance brokerage services for all aspects of the clinical process
- Supply chain risk management
- Enterprise risk management
- Expert negotiation of technical science issues involving the underwriting of products insured.

For more information, please visit the Conner Strong web site at connerstrong.com, or contact Daniel Brettler directly at 1-877-861-3220.

