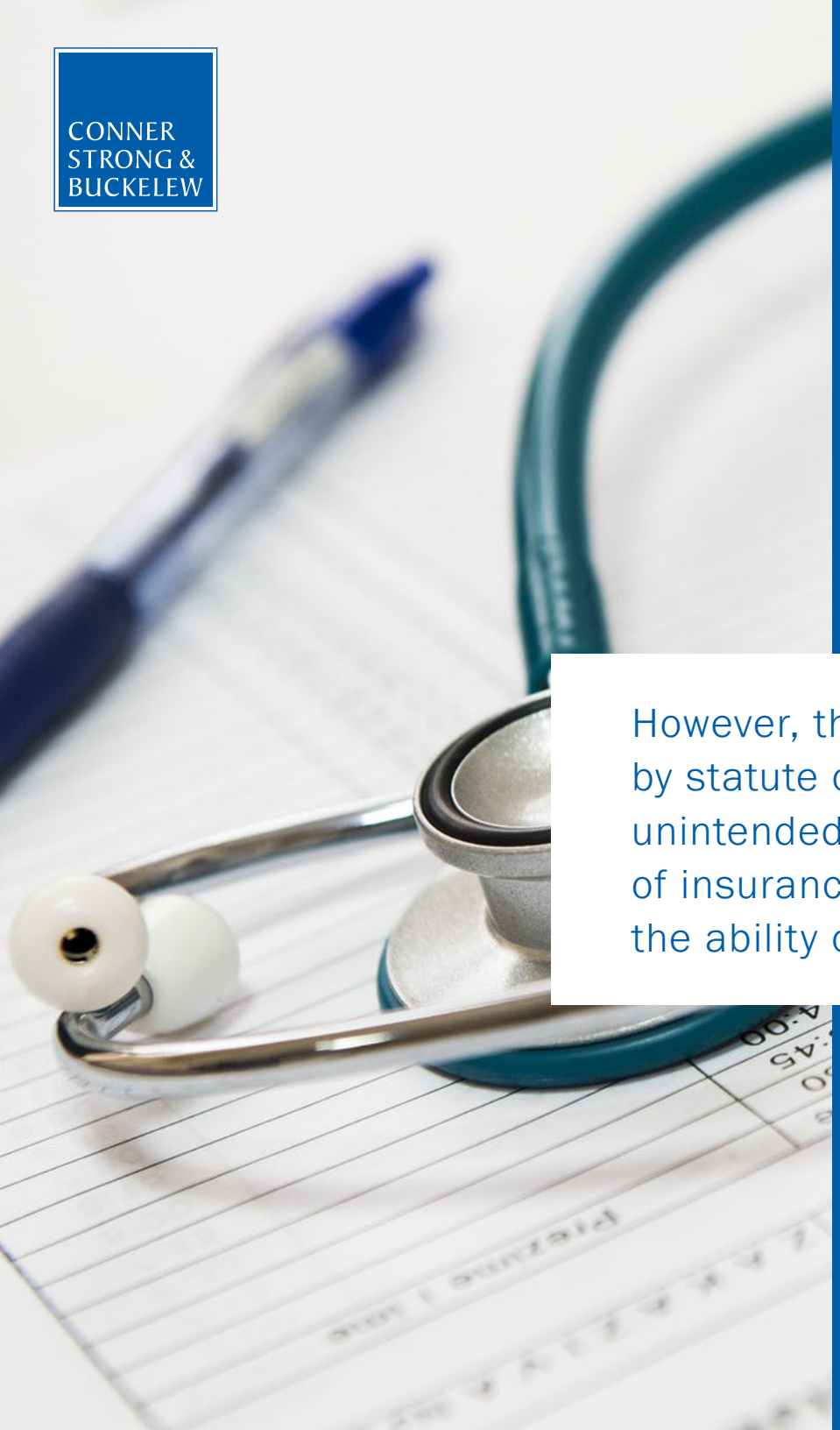
CONNER STRONG & BUCKELEW

# JUGGLING RECRUITMENT RISKS IN CLINICAL TRIALS

*Outlining the impact of risks and obligations related to clinical trial participant travel*

CONNER STRONG & BUCKELEW



Successfully executing a clinical trial requires juggling the complexities associated with the clinical process along with developing sufficient incentives to promote enrollment. For many sponsors, removing barriers to participation is essential not only to improve the chances of reaching enrollment targets but to assure that both the science behind the protocol and patient safety are balanced to achieve the sponsor's goals. Often balancing science with a successful recruiting effort while ensuring that the balance sheet is protected from exposures which might not be otherwise protected under traditional negligence-based clinical trials insurance policies factor into the success or failure of the recruiting effort. Further, governmental reforms may make insurance an important piece of the regulatory process in some countries.

However, these requirements, whether mandated by statute or ethics committees, may have the unintended consequence of limiting the availability of insurance (and affordability), thus compromising the ability of sponsors to conduct trials.

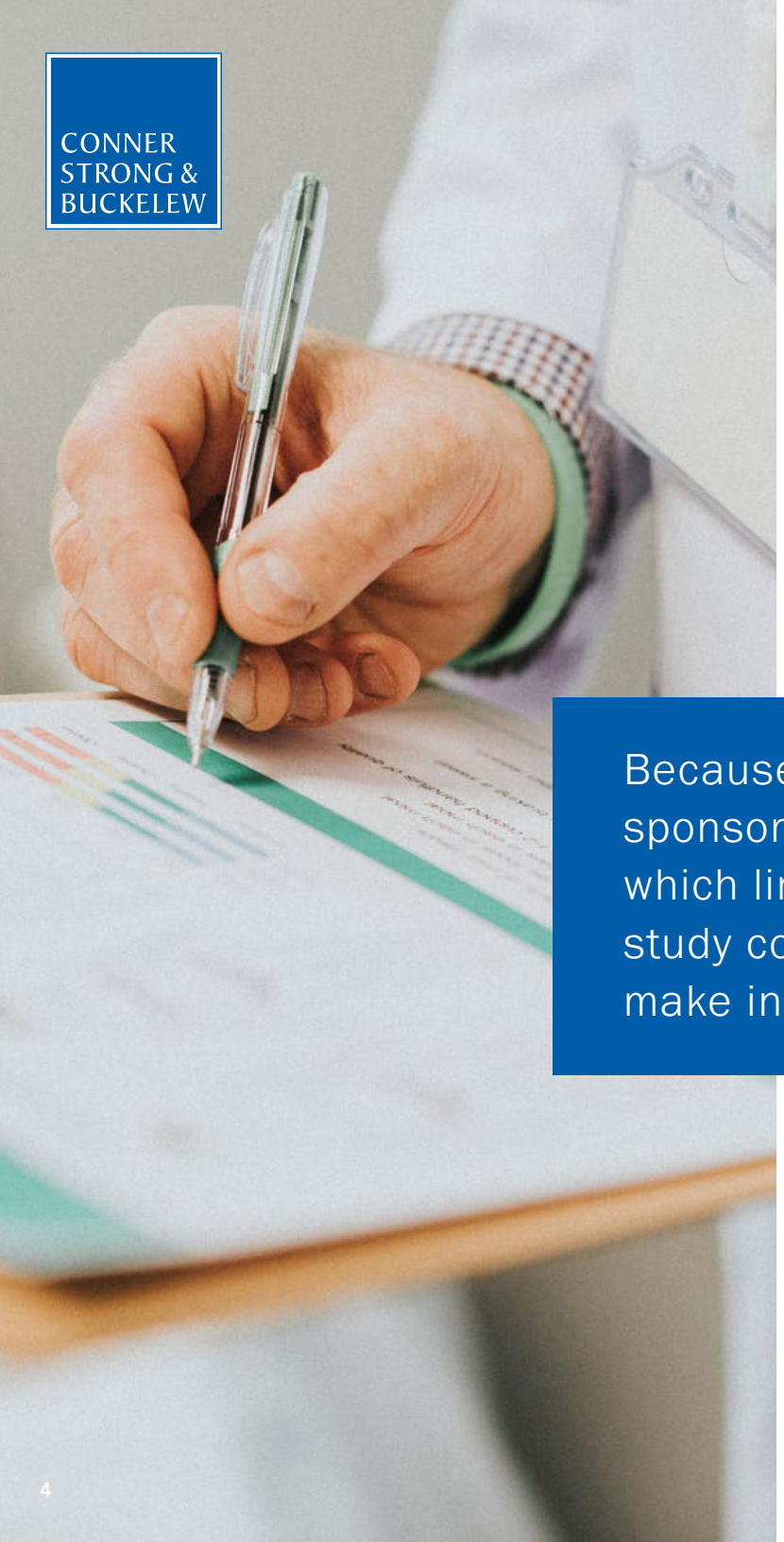
Regulators are trying to balance participant safety with the desire to avoid putting bureaucratic obstructions in the path of life-saving innovations. Still, regulatory variations from country to country and differing legal frameworks on such issues as advertising, recruiting, reimbursements, data privacy and human subject protections are making it more challenging to recruit subjects and balance inducements with safety as sponsors draft clinical trial agreements and informed consent documents.

While sponsors must balance a multitude of issues in order to organize an investigation, address requirements for subjects and investigators and ultimately create a comprehensive protocol and consent process, finding suitable participants often means going far and wide since the pool of or subjects may be limited and/or affected by numerous variables such as use of existing medications, other health conditions, involvement in other studies and even geography.

Jurisdictional requirements may vary with regulations, laws and even ethics committee preferences involving requirements to begin and perform the investigation. While legal liability is the standard for the safety of subjects, including treatment and exposure to investigational products in the U.S., other jurisdictions operate based on local laws or regulations with some requiring no-fault payments, necessitating different insurance solutions. In addition, contractual requirements present yet another area in which a sponsor may unnecessarily assume liabilities that they aren't well suited to control.

## ROLE OF REGULATION

Regulation plays a role with respect to the standards required of a sponsor, an investigator and/or a trial site. While paying subjects for participation in clinical research may raise difficult questions that should be addressed by an institutional review board (IRB) or ethics committee, reimbursements for travel expenses to and from trial sites are not considered to raise issues regarding undue influence, according to the FDA's Office of Good Clinical Practice. On Jan. 25, 2018, the FDA updated its guidance to institutional review boards (IRBs) and clinical investigators to clearly allow reimbursements to patients in clinical trials for lodging and travel. According to the guidance, ethics reviews should continue to look at the amount of compensation given to participants, including for reasons like time, inconvenience and discomfort. The FDA's guidance is directed to the IRB/Ethics Committee to execute and oversee. The guidance suggests that IRBs should receive the amounts and schedule of all payments, including end-of-study bonuses, during the initial review to ensure that they are not coercive according to federal regulations, including 21 CFR 50.20[1]. An important component of this guidance is the direction that all information concerning payment should be spelled out in the informed consent document. By doing so, the sponsor can define the scope of compensation including obligations they may elect[2] to assume for subject travel.



CONNER STRONG & BUCKELEW

## CLINICAL TRIALS INSURANCE

While the protocol sets forth the rules of engagement, including recruiting qualified subjects and performing clinical activities necessary to the study, the consent process determines the patients' understanding of benefits and risks associated with the study. Patient consent should not only spell out the study goals, risks and rewards, but any obligations the sponsor may offer to influence participation. In addition, a well written patient consent may provide a framework for the insurance company to structure insurance coverage to protect the sponsor, investigators and others the sponsor may engage contractually to help manage the investigation or oversee/report results to regulatory authorities.

Because insurance policies typically respond to the sponsor's legal liability, a well drafted consent form which limits liability can improve the clarity around the study commitments sponsors make, reduce risk and make insurance more affordable.

Typically, such insurance is limited to a trial site and the clinical activities that the subject may be exposed to. In some cases, medical payments insurance may be included to assure that treatment is prompt and addresses immediate injuries or adverse reactions by the patient.

# CLINICAL TRIAL SUBJECT TRAVEL RISKS: A GROWING CONCERN

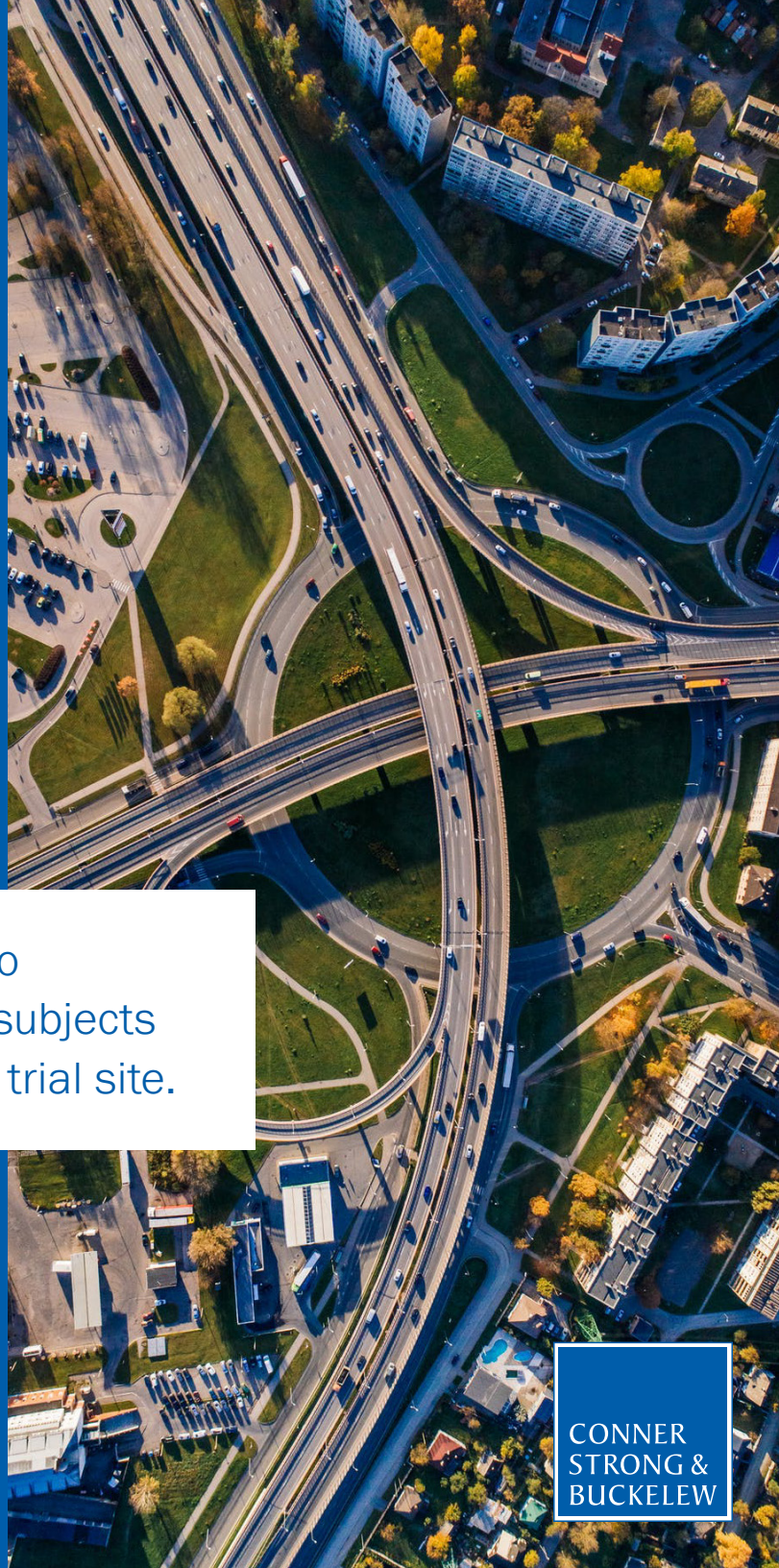
The terms and structure of a human clinical trial insurance program should reflect the sponsoring company's risk tolerance, product and patient profile, enrollment, geographic factors and contractual requirements with clinical sites, CROs, investigators and corporate partners. Increasingly, the sponsor is pressured to fill out the patient census for the trial especially in instances where they are studying a rare disease. What is often overlooked are the exposures faced by subjects who may need to travel, sometimes between countries, to participate in a study. While compensation is increasingly used to recruit subjects, it has only been until recently that the consent form has addressed travel risks and expenses. Increasingly, sponsors are including provisions in their consent documents that obligate them to address injuries or illnesses for subjects and companions/caregivers that might arise during the journey to or from the trial site.

Unfortunately, typical clinical trial insurance may not respond to that obligation, creating potentially significant financial consequences for the sponsor in the event that an accident or illness arises during the trip.

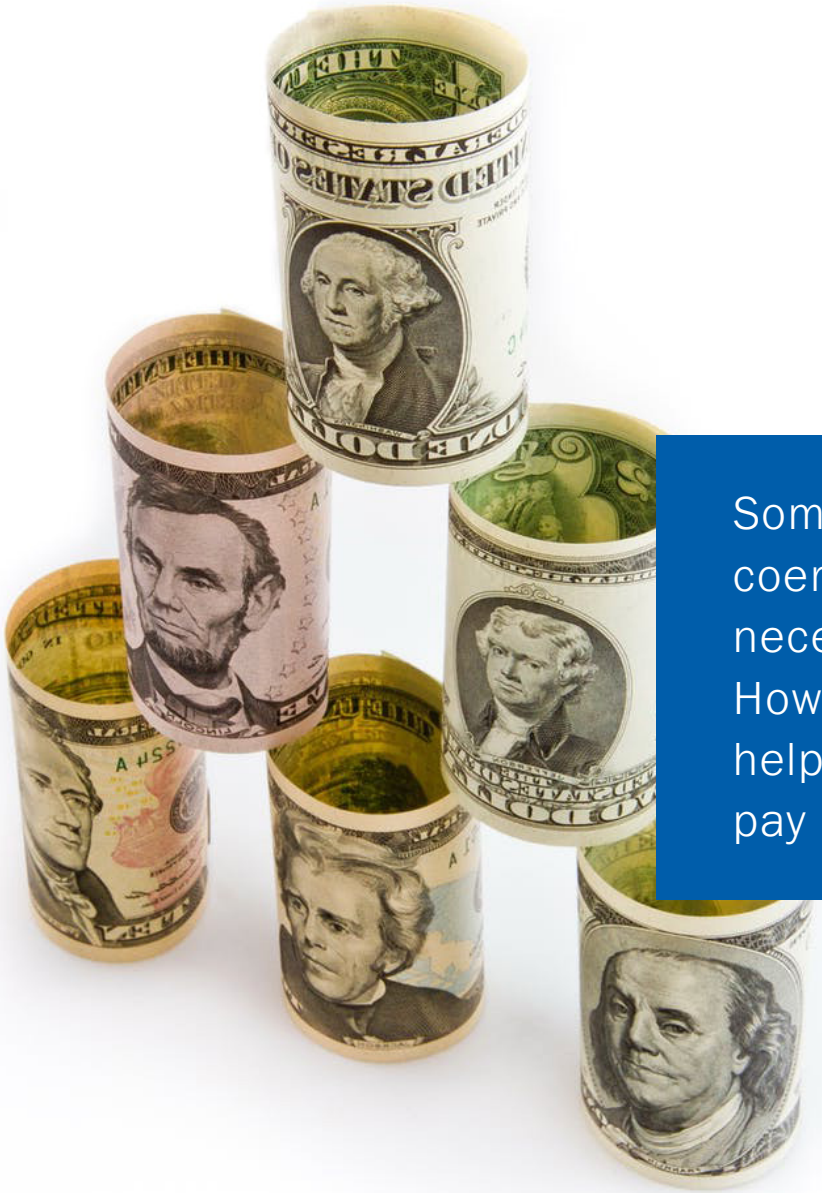
> Careful review of clinical trial provisions is imperative to establish whether medical payments might indemnify subjects who are injured in the process of traveling to or from a trial site.

Such insurance may only indemnify for an event arising out of a sponsor's negligence, as a result of contractual obligations or may only apply geographically to limit the scope and substance of any coverage available in the clinical trial policy.

Perhaps a better option is to seek a travel and accident policy tailored to afford benefits to a subject who has an injury, sustains disability or illness that necessitates medical treatment, hospitalization, or affords repatriation expenses in the event of death while traveling outside of the home to/from the trial site.



CONNER STRONG & BUCKELEW



## TYPICAL REQUIREMENTS

Compensation is not always offered, but in some cases participants in a clinical trial may receive some form of compensation in exchange for their participation. Compensation is most common in Phase I trials involving healthy volunteers and is paid in recognition of their decision and contribution to the advancement of the science. CROs often utilize compensation as part of the recruitment process for clinical studies with verbiage that may offer limited opportunities to earn money in exchange for participation. In some cases it may be monetary, in others the protocol may specify reimbursement for certain expenses associated with the subject's participation, including travel expenses to and from the site, accommodations, meals, lost wages, and perhaps certain specified services (i.e., medical expenses) considered essential to subjects recruited to participate in a particular study.

In the U.S., the practice of paying subjects for research participation is widespread, though a polarizing topic.

> Some believe paying research subjects may be coercive, while others believe payments are a necessary part of recruitment for clinical research. However, there is only a small amount of guidance that helps investigators determine whether or how much to pay participants in a given study.

In fact, the U.S. Code of Federal Regulations governing clinical research does not specifically address the issue of payment of research subjects, rather it leaves the decision to IRBs that operate as ethics committees used by institutions to review, approve and oversee clinical research involving human subjects. While operating with minimal guidance, IRBs may therefore be responsible for determining the acceptability and amount of payments to research participants. Consequently, according to a 2005 study on the topic published in PubMed, payment practices vary widely in the U.S.[3]

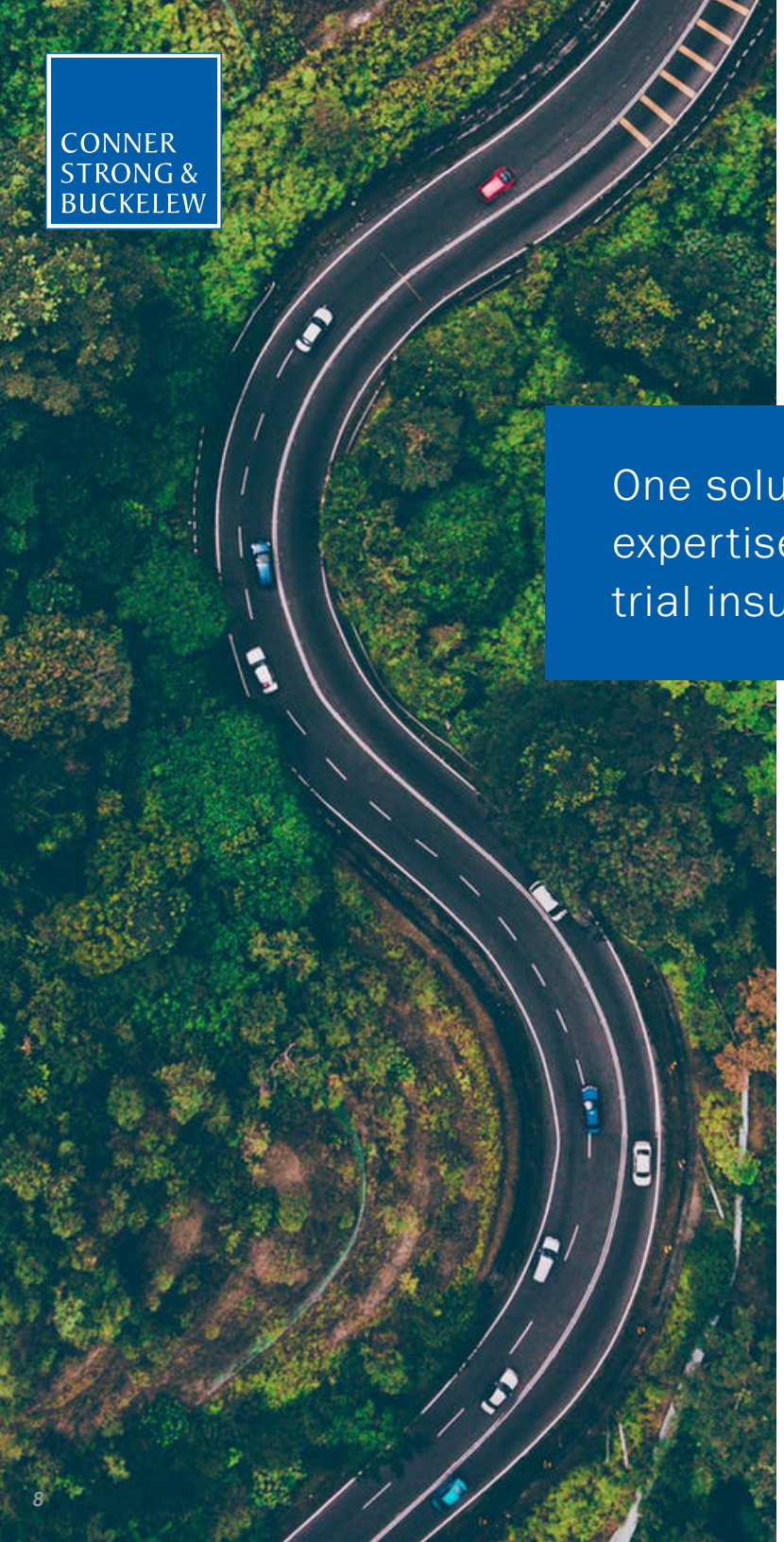
In Europe, the practice varies depending on the country. Some exclude compensation entirely while many allow compensation only in conjunction with review and approval by the appropriate Ethics Committee[4]. In the EU Clinical Trial Regulation (536/2014)[5], it directs that no incentives or financial inducements are given to vulnerable populations such as incapacitated participants or minors (or their legal representatives), including individuals with mental disabilities, or pregnant women, except for compensation for expenses and lost earnings directly related to clinical trial participation. In other words, this regulation dictates that no undue influence be exerted on subjects involved as participants in a clinical trial. The EU regulations also address whether insurance is necessary to indemnify subjects who are exposed to risk during treatment considered more than incidental. In such cases, sponsors are obligated to ensure that adequate insurance coverage is in place.

According to the European Patients Academy (EUPATI), the EU also requires sponsors and CROs to be completely transparent about financial transactions made with participants or with the trial site itself[6]. The ICF (informed consent form) must contain reference to any compensation offered and the insurance coverage offered should a participant be injured during the clinical trial[7]. There are various models available to sponsors to set the amount of compensation for subjects electing to participate in a clinical trial. EUPATI offers guidance through the publication of compensation models such as one included in their whitepaper on compensation in clinical trials.[8]

## COVERAGE PROVISIONS FOR SPONSOR OR CONTRACTOR OBLIGATIONS ON THE SPONSOR'S BEHALF

Indemnity (or in certain countries no-fault obligations) for injuries or harm to subjects of a clinical trial is primarily addressed through the purchase of clinical trial insurance protection, which indemnifies subjects for injuries arising directly from the investigational product or treatments associated with the trial. For injury or harm outside of the trial or trial site, including reimbursement for medical expenses or other costs, clinical trial insurance often fails to address this risk.






In the event it does, it is limited to indemnification of certain medical expenses. Coverage may be further limited by deductibles or co-participation clauses. In Europe, Germany is one of the few countries in which insurance provisions beyond the trial site are customarily required by an ethics committee, but only for travel within the country. Of course, depending on the nature of the investigation, it may be necessary to recruit subjects across Europe or beyond. This is something German regulations fail to recognize.

One solution offered by certain underwriters with expertise in the life sciences industry is to pair clinical trial insurance with travel and accident products.

Travel and accident insurance often includes coverage for specified amounts due to loss of life, physical disability, including certain illnesses, or impairments. Coverage for subjects of a clinical trial may include both subjects and thosev accompanying them as a parent, guardian or caregiver. Coverage may specify a limit of insurance for accidental death and dismemberment, for accident medical expense and for medical evacuation or repatriation expense. Typically, the policy will specify a principal sum for each section subject to a maximum benefit amount for that section. In many cases, insurers will automatically aggregate maximum benefits between two and 10 times. Depending on the principal sum insured, it is important to assure that aggregate limits are provided in multiples sufficient to address the total participants involved in the study.

Coverage often specifies that it will apply specifically to a class of insured persons, so it is important to assure that the description includes “all clinical trial participants and any accompanying parent, guardian or caregiver.” The policy may also include a provision for covered activities or covered activities hazards. If so, it is important to work with your agent or broker to assure that the underwriter specifies language that affords protection while the specific class of insured persons is traveling to clinical trials scheduled and sponsored by the insured policyholder including coverage while traveling directly to or from such clinical trials.

Such language should specify words such as “supervised by,” as it is important to assure that it is defined to include the sponsoring insured along with any contractors, such as CROs, investigators or site operators that may be involved in the clinical trial. It is also important to note effective dates and end dates of coverage and to note that covered activities often includes language that expressly limits coverage so that it ends immediately when the insured participant (subject) returns from a trial site to their primary residence.

In addition to the coverages noted, some insurers offer a variety of travel assistance services to help the subject with pre-travel information, emergency travel arrangements, transportation, dependent care, legal or translation services, replacement of lost or stolen travel documents, security information services, referral to medical or dental professionals, coordination of medical records and arrangements for accommodations.

## JURISDICTIONAL LIMITATIONS FOR TRAVEL ACCIDENT

In some jurisdictions, including the U.S., travel and accident insurance may not be allowed for patients in clinical trials as an eligible group. Examples include New York and New Jersey in the U.S. In such cases, even though the policy may address participants with principal residence in permissible states, any participants enrolled from states with restrictions may not be insured.

In such case, if you have made a commitment to offer participants reimbursement for injuries or harm during travel associated with the study, it may be possible to work with the clinical trial insurer to modify medical payments provisions for additional consideration to allow for indemnification for injuries or harm associated with travel to and from the clinical site. Of course, for any participants that fall under this protection, it is important to note that indemnity provisions are an extra hurdle for a participant to receive protection. Furthermore, it is essential that the ICF specify the obligation, including an amount of compensation permitted to assure that the indemnity arrangement is triggered.

When recruiting participants from across state lines, it is absolutely imperative that clinical trial sponsors, investigators, CROs and all other involved parties check the specific laws within the states participants are traveling to and from in order to close any potential gaps in travel and accident coverage.


# A BROKER'S VALUE

It is important to retain an insurance broker knowledgeable of your industry and with deep expertise on the exposures, including the impact of your commitments or those of your contractors to compensate those subjects recruited to participate in a sponsored clinical trial. Significant relationships with specializing life science underwriters is essential to protect your balance sheet. Such insurance professionals can assure that coverage is in place in compulsory jurisdictions worldwide and that you have adequate limits of insurance and coverage across the globe. They can also identify underwriters with the bandwidth to address travel and accident obligations you may offer to recruit the necessary subjects. Their ability to find underwriters able to do so will make your coverage more seamless. Combined with a strong claims-handling pedigree, working with such professionals may save you heartache and protect your firm's reputation, your directors and officers and the critical assets that help you stand out with peers, suppliers and customers.

To learn more about Conner Strong's life science practice

**Visit Our Life Sciences Insurance Consulting Page**

1 USFD & C CFR section 50.20. https://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm
2 USFD & C CFR section 50.20. https://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm
3 Grady C, Dickert N, Jawetz T, Gensler G, Emanuel E. An analysis of U.S. practices of paying research participants. Contemp. Clinical Trials. 2005; 26:365–375. PubMed https://www.ncbi.nlm.nih.gov/pubmed/15911470
4 Perspectives in Clinical Research. Compensation in clinical research: the debate continues. Mansi Pandya and Chetna Desai. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3601710/
5 European Parliament (2014. Regulation (EU) No 536/2014 on clinical trials involving medicinal products for human use. See: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1558539734912&uri=CELEX:32014R0536
6 European Patients' Academy (EUPATI), Compensation in clinical trials. See: https://www.eupati.eu/clinical-development-and-trials/compensation-clinical-trials/
7 European Patients' Academy (EUPATI), Compensation in clinical trials. See: https://www.eupati.eu/clinical-development-and-trials/compensation-clinical-trials/
8 European Patients' Academy (EUPATI), Compensation in clinical trials. See: https://www.eupati.eu/clinical-development-and-trials/compensation-clinical-trials/

CONNER STRONG & BUCKELEW

INSURANCE | RISK MANAGEMENT | EMPLOYEE BENEFITS


**DAN BRETTLER**

Managing Director, Life Science and Technology Co-Practice Leader

973.659.6456

dbrettler@connerstrong.com