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PRO TE: SOLUTIO™

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OBTAINING VALID INFORMED CONSENT IN CLINICAL RESEARCH

DEAR CLIENT

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Football season may be over for another year, but this edition of "Pro Te Solutio" takes a look at clinical trials from a few different positions, both on the field and off.

Questions tackled in this issue include the threshold issue of master agreements for a clinical trial. A master agreement is the linchpin for the clinical trial: it is where the key players are identified, positions are assigned, and strategies are put into action. In "Balancing the Needs of Sponsors and Research Sites to Effectively and Efficiently Negotiate Clinical Trial Agreements", we explore the challenges of making sure you get what you want in your master agreement—and also offer a perspective from the other side.

Another article addresses the "must have" in any playbook: understanding what is adequate to secure informed consent. In "Obtaining Valid Informed Consent in Clinical Research", our authors describe the ever-changing regulations and requirements for adequate informed consent.

Even after the clinical trial is finished and results published, that is not the end of the game—for the researchers, the company, or the data. Our final article, "How Clinical Trial Data Impact Issues in Litigation," is an exercise in identifying the points in litigation where clinical trial data may come into play.

We also share a thumbnail sketch, in our "New and Noteworthy" section, of an FDA draft guidance on naming biosimilars. This may be a player to watch in the months and years ahead.

As always, we hope that this information provides insight and information that is useful to you in your endeavors. Go team!

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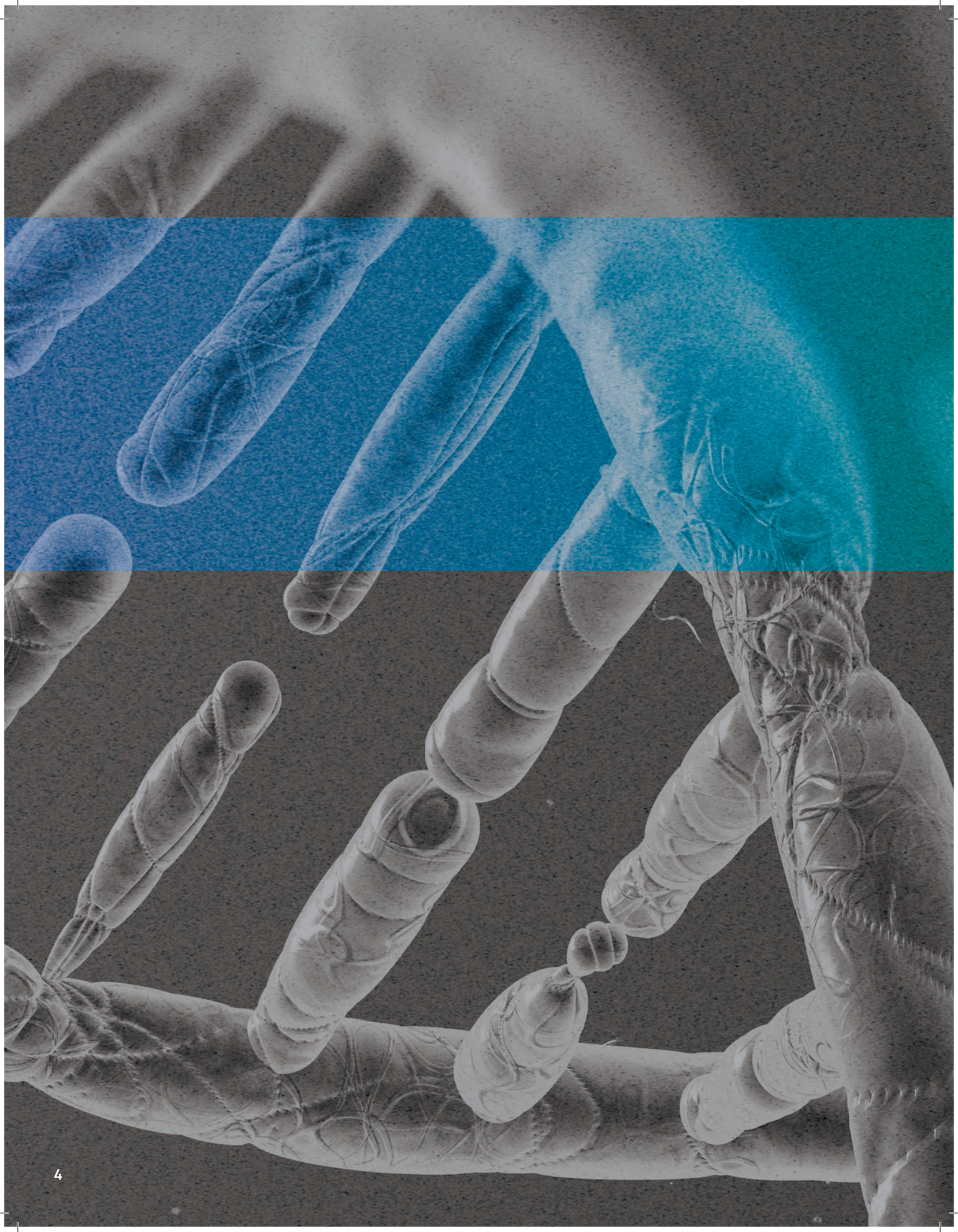


BALANCING THE NEEDS OF SPONSORS AND RESEARCH SITES TO

EFFECTIVELY AND EFFICIENTLY

NEGOTIATE CLINICAL TRIAL AGREEMENTS

Before a research site begins work on a sponsor-initiated clinical trial, the sponsor and the site should enter into a "clinical trial agreement" or "CTA," to establish the obligations of each party, to convey certain rights to each party, and to allocate risks between the parties. Typically, the sponsor provides its CTA template to the site for review, and the parties will proceed to negotiate the CTA – with each side looking to lock in terms favorable to it.

Each CTA negotiation presents its own unique set of challenges. However, virtually every one will devote significant time to the following issues: ownership and use of trial data, intellectual property, publications, and trial participant injury. Parties often dig in their heels on these provisions without fully understanding these issues or their importance within the context of clinical trial setting. The resulting delays can be detrimental to the parties as well as to the potential trial participants and are both unnecessary and avoidable.

Knowing your bottom-line position, understanding the rationale behind the other side's stance, recognizing the relative importance of the provision to each side, and making reasonable compromises under the circumstances can reduce stalemates, speed up the negotiation process, and get the trial site up and running much more quickly.

Not only that, but savvy sponsors and sites can capitalize on the momentum

built during a successful CTA negotiation by using the final negotiated terms as a foundation for drafting a master clinical trial agreement. A master clinical trial agreement, or master CTA, eliminates time consuming negotiations in future trials and gets them running with little to no delay.

RESOLVING COMMON STICKING POINTS IN CLINICAL TRIAL AGREEMENTS

1. OWNERSHIP AND USE OF TRIAL DATA

Ownership of trial data may be addressed in its own separate CTA provision or may be folded into another section, such as confidential information or intellectual property. Regardless of where it is located, ownership and use of trial data are sensitive topics for both sponsors and sites.

The Sponsor's Perspective: It is not uncommon for a sponsor to present the site with CTA language that gives the sponsor exclusive ownership of and unlimited right to use *all data related to the site's participation in the trial.* From the sponsor's viewpoint, its position is justified because it designed the trial protocol and paid the site for conducting the trial.

The Site's Perspective: The site will often respond that the sponsor is only entitled to own the data specifically contemplated by the protocol (e.g. case report forms (CRFs) and trial-specific test results) and that underlying original source documents, which document the existence of the participant and substantiate the integrity of the trial data collected (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participant diaries or evaluation checklists, pharmacy dispensing records, and microfilm or magnetic media, x-rays), are the property of the site. Additionally, the site will likely seek to limit the sponsor's use of the trial data. For instance, if the site is a non-profit entity, it may contend that it cannot conduct research on a work-for-hire basis and must be allowed to use trial data, including data that is owned by the sponsor for non-commercial research and education purposes and/or patient care.

The Compromise: Even the sponsor must acknowledge that a request to own all data related to the trial is too broad and reaches beyond what the sponsor actually needs to protect its interests and move the development of its product to the next stage. A properly drafted protocol will require that all necessary data end points be submitted to the sponsor on CRFs. The sponsor does not need the underlying source documents, a fact recognized by the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice (ICH GCP) §8.3.13. But it may need to audit the source documents at some point in the future, and will likely reserve its right to do so.

With respect to use of the trial data, the site should not object to the sponsor's use of it, provided such use is not prohibited by law and is authorized by the trial participants' informed consent and authorization documents. Similarly, the sponsor's interests are not infringed by granting the site the right to use trial data *generated and contributed by the site for internal and non-commercial research, education, and/or patient care.* Protection of all such rights is exemplified here:

> Any and all information, documents, reports, data, results, and other information generated by Research Site pursuant to the Protocol that are required by the Protocol to be delivered to Sponsor and all copies thereof (collectively, the "Trial Results"), will be the property of Sponsor.

> Subject to Trial Subjects' informed consent and authorization documents, Sponsor may use the Trial Results for any lawful purpose.
>
> Notwithstanding the foregoing, the parties acknowledge and agree that the source documents, as defined in the Good Clinical Practice: Consolidated Guidelines published by the Food and Drug Administration, generated by Research Site and the data contained therein shall not be deemed Trial Results and are the exclusive property of Research Site; provided, however, that Sponsor shall have the right to inspect, audit, and/or copy the source documents pursuant to this Agreement and subject to the informed consent and authorization documents.

Genetic Data: An Evolving Sub-set of Trial Data. As the field of personalized medicine continues to evolve, the ownership and use of biological specimens and the data derived therefrom pose new challenges to the negotiation of trial data ownership and use. Both sponsors and sites may seek to own and/or use specimens (e.g., blood or tissue samples) and the data derived from such specimens.

It is likely unnecessary for the sponsor to actually *own* the biological samples as long as the sponsor has the *right to use* the samples. The site should not object to the sponsor's use of the specimen provided such use does not violate applicable law and is authorized by the informed consent and authorization documents. If the sample is taken pursuant to the protocol, then it is reasonable for the sponsor to limit the site's use of the sample and any data derived therefrom to trial-related purposes. For example:

> Sponsor shall have the right to possess, control, retain, store, use and dispose of biologic specimens collected pursuant to the protocol ("Specimens") in accordance with applicable laws and regulations to the extent authorized by the informed consent and authorization documents. Sponsor will own all protocol required data derived from the Specimens ("Specimen Data"). Sponsor will use Specimens or

It is likely unnecessary for the sponsor to actually own the biological samples as long as the sponsor has the right to use the samples.

> Specimen Data only to the extent not prohibited by applicable law, in accordance with the protocol, and subject to the informed consent form and authorization documents. Research Site will use Specimens and Specimen Data only for purposes of this Trial.

2. INTELLECTUAL PROPERTY OWNERSHIP

Disputes over ownership of trial-related intellectual property are similar to issues regarding ownership of trial data, but focus directly on who owns *inventions or discoveries* related to the investigational product or the trial in general.

The Sponsor's Perspective: The Sponsors will want broad language through which it owns *all inventions, developments, discoveries, or improvements related to the trial or the investigational product.*

The Site's Perspective: In the face of such broad language, the site will – almost without fail – object to the sponsor's language for its breadth. Additionally, the site may be unable to give away its intellectual property rights due to its non-profit status.

The Compromise: One way to span the gap between the sponsor and the site is to draft language that provides for site ownership of inventions created solely by the site and for joint ownership of inventions created by both the site and the sponsor. It will also be necessary to include

language that gives the sponsor an option to negotiate a license for the site's interest in either or both. For example:

> Any inventions or discoveries made by the Research Site in the performance of the Trial that: (i) are improvements, enhancements, or modifications to the Sponsor's Investigational Product; (ii) are new uses specific to the Sponsor's Investigational Product; (iii) incorporate Sponsor Confidential Information; or (iv) are anticipated by the Sponsor's protocols will be the sole property of Sponsor ("Sponsor Invention") .
>
> All inventions developed solely by the Research Site that are not sponsor Inventions shall be owned by Research Site ("Research Site Inventions"). All inventions that are not Sponsor Inventions that are developed by one or more employees of both Sponsor and Research Site under this Agreement shall be owned jointly by Sponsor and Research Site ("Joint Inventions") .
>
> Sponsor shall have, without option fee, a time-limited, first option to negotiate an exclusive, worldwide, compensation-bearing license to any Research Site Invention and Research Site's rights in any Joint Invention. Sponsor shall advise Research Site in writing of its interest in obtaining an exclusive license to any Research Site Invention and/or Research Site's rights in any Joint Invention within sixty (60) days of Sponsor's receipt of notice of Research Site Invention and/or Joint Invention.

3. PUBLICATION RIGHTS

Publication issues most commonly arise between sponsors and academic institutions. Both sponsors and academic institutions want to publish trial results to share information about the clinical trial with the medical community and the public in a timely, accurate, and orderly manner; ensure the safety of the trial participants and the general public; advance science and medicine; meet regulatory obligations and industry guidelines; increase visibility; and promote their reputations within medical and scientific communities and with the general public. However, the independent publication goals of each party can result in a disagreement over CTA language.

The Sponsor's Perspective: The Sponsor prefers narrowly tailored language that ensures protection of its intellectual property and confidential information; facilitates multi-site coordination; safeguards the integrity of trial results, and furthers its competitive advantage.

The Site's Perspective: Sites are primarily focused on contributing to public knowledge; disclosing results for use in future research; and advancing its investigator's professional interests. The site will likely view the sponsor's language as an attempt to limit its academic freedom, interfere with its ability to publish data before other sites, and stymie its efforts to promote transparency and patient safety and education.

The Compromise: The key to resolving opposing interests can be resolved by making reasonable concessions on what information the site can publish, the timing of such publication, and the sponsor's ability to prevent publication of certain information. For example:

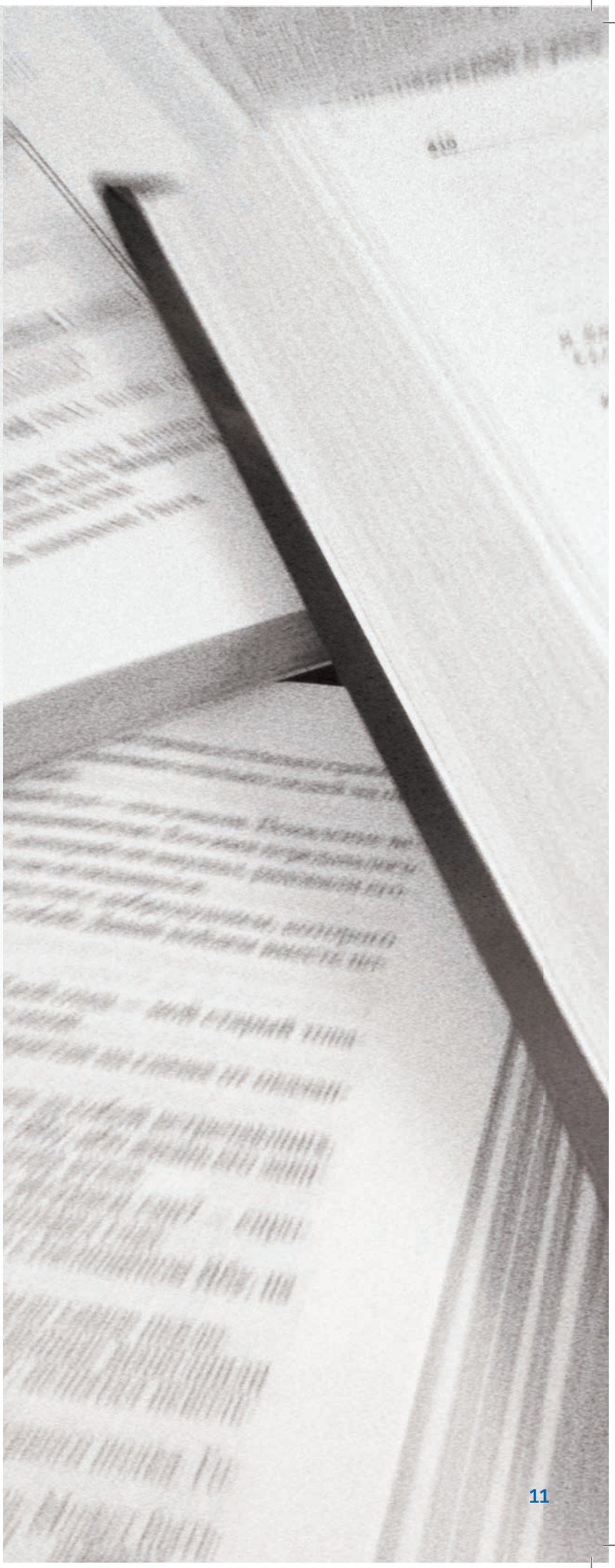
Publication issues most commonly arise between sponsors and academic institutions.

Research Site has the right to publish the results that it contributes and generates as a result of its Trial participation with due regard to the protection of Sponsor's Confidential Information provided that any such publication shall be delayed until the earlier of (i) the publication of the multi-center publication; (ii) notice from Sponsor that no multi-center publication will be forthcoming; or (iii) Twelve (12) months after the conclusion of the Trial all sites.

Research Site shall submit any proposed publication to Sponsor at least sixty (60) days before submission for publication. Sponsor will have the right to review and comment upon the publication in order to protect Sponsor Confidential Information and/or Intellectual Property. Prior to releasing such publication, Research Site will delete Sponsor Confidential Information and Sponsor Intellectual Property. Upon Sponsor's request, publication will be delayed up to ninety (90) additional days to enable Sponsor to secure adequate intellectual property protection. Notwithstanding the foregoing, Sponsor cannot (i) require deletion of result generated and contributed by Research Site; (ii) require deletion of information needed to explain results and their scientific significance; or (iii) require deletions that make the publication incomplete, inaccurate, or misleading.

4. TRIAL PARTICIPANT INJURY

Trial participant injury is generally one of the most heavily negotiated provisions in a CTA. A sponsor is not legally required to cover medical expenses incurred in the treatment of a participant's injuries; however, most sponsors voluntarily agree to some level of reimbursement for medical expenses. While the parties generally agree that the reimbursement should be limited to medical expenses



(*i.e.,* not lost wages, pain and suffering, etc.), the sponsor's initial reimbursement offer usually falls short of what the site feels is adequate.

The Sponsor's Perspective: The sponsor's proposed injury reimbursement language usually requires that injury be directly caused by participation in the trial, provides that solely the sponsor will make the determination on causation, excludes certain intervening causes, and establishes a reasonable rate of reimbursement that is consistent with what would be paid outside of the context of the trial. Additionally, in an effort to reduce its financial risk, the sponsor may require that the site seek reimbursement of expenses from private insurers before seeking reimbursement from the sponsor.

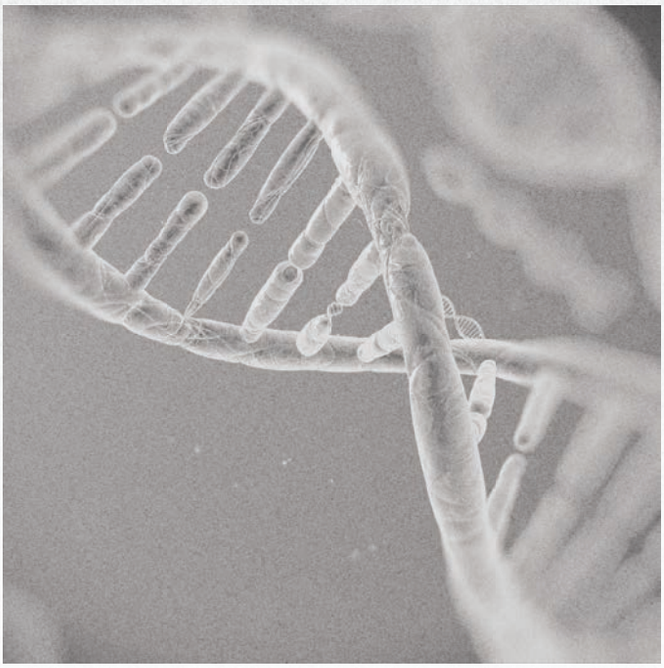
The Site's Perspective: The site will likely remind the sponsor that since the sponsor is the ultimate beneficiary of the research, the sponsor's coverage of medical expenses should be as broad as possible. Consequently, the site will balk at narrowly tailored language, at attempts to exclude reimbursement – especially when predicated on the participant's behavior – and at disparate treatment based on the participant's insured status. Additionally, the site may have an issue with the determination of causation being solely the sponsor's call.

The Compromise: Once each side recognizes that the other party has valid and reasonable reasons driving its position on trial participant injury, compromises that serve the needs of both sponsor and site can easily be made. While some provisions will likely require a more thorough benefit/risk analysis by the sponsor before concessions can be made, *e.g.,* removing the requirement to file insurance and deleting the exclusion related to the trial participant's negligence or failure to follow instructions, the parties should be able to agree to:

- tie the injury to the trial but make allowances for aggravation of pre-existing injuries;
- mutual determination on causation or simply remain silent;

- exclude reimbursement caused by the site's negligence (which is consistent with common law principles of liability); and
- establish a rate of reimbursement equivalent to what an insurer would pay or negotiate a set flat rate acceptable to both parties.

Notwithstanding the foregoing, it is critical to note that, due to kick-back concerns, the terms agreed upon by the parties in the CTA cannot offer reimbursement beyond what the informed consent document promises to the trial participant.



USE OF AGREED UPON CTA TERMS IN MASTER CLINICAL TRIAL AGREEMENTS

To further reduce CTA negotiation time for future CTAs, sponsors and sites can capitalize on the momentum built during a successful CTA negotiation by using the final negotiated terms as a foundation for drafting a master clinical trial agreement.

A master clinical trial agreement, or MCTA, is an umbrella agreement between the sponsor and site where both parties agree upon a set of contractual terms and conditions for future clinical trials. Establishing a MCTA alleviates the need to re-negotiate the CTA's terms each time a new clinical trial is contemplated. Instead, a short and simple individual trial agreement is executed for each new trial. The individual trial agreement will incorporate the terms of the MCTA and set forth conditions specific to the particular study, such as protocol title, principal investigator name and budget.

While the MCTA will have some unique provisions, such as language describing the use of individual trial agreements and the term of the master agreement, the majority of the provisions should be comparable to the recently completed CTA. The parties may need to renegotiate if the MCTA will apply to a wider range of trial phases/investigational products or if additional levels of institutional review and comment may be required for master agreement. However, the vast majority of the prior language should be able to carry over into the MCTA, keeping negotiation time to an absolute minimum. As a result, trials can get up and running without delay.

CONCLUSION

Sponsors and clinical trial sites have a common interest in quickly negotiating clinical trials. By simply understanding the needs of the other party, recognizing where compromises can be made, and leveraging prior agreed upon language, the parties can effectively and efficiently eliminate CTA sticking points and quickly begin research activities. ■

By Kim Coggin

OBTAINING VALID INFORMED CONSENT IN CLINICAL RESEARCH

Over the last seven decades, federal lawmakers and regulators have developed an expansive set of informed consent requirements designed to protect individuals participating in clinical trials and to ensure that such trials meet ethical standards. Failure to satisfy all of these legal requirements can expose research sponsors, investigators, and even clinical trial sites to significant risk. Far beyond a one-action item on the to-do list, legally effective and compliant informed consent is an ongoing, dynamic process requiring that information about the clinical research be provided to the participant[1] so that each individual can make an informed decision about his or her involvement in the trial.[2] Because this is an ever-changing area of law – just this past spring the FDA released draft guidance on obtaining informed consent through text messaging and other electronic means – research sponsors, investigators, and clinical trial sites should periodically review their informed consent templates and processes to ensure continued compliance.

BACKGROUND

The Nuremberg Code of 1947 set forth basic ethical principles and standards for medical experimentation on human beings. The Code arose from the revulsion over war crimes committed by Nazi doctors using humans as test subjects

in concentration camps.[3] The Code requires obtaining voluntary consent from people in order to use them as test subjects.[4] In the mid-1960s, the World Medical Association Declaration of Helsinki expanded this concept by requiring that such consent also be *informed*.[5] The ethics principles developed under the Nuremberg Code and the Declaration of Helsinki serve as the basis for U.S. law currently governing informed consent in clinical research as well as many other state and local laws regarding the extent of information to be provided to participants in order for their consent to be legally effective.[6]

REQUIREMENTS OF INFORMED CONSENT

Obtaining a patient's informed consent is usually a multi-step process, including an initial meeting with the participant to review the consent form, giving him or her time to consider the form, confirming an understanding of the terms in a follow-up meeting, and updating the terms of the consent form throughout the trial as needed. Generally, the requirements for obtaining informed consent in clinical research are as follows:

(1) The investigator is responsible for obtaining the informed consent prior to the person's participation;[7]

(2) The consent must be legally effective;

(3) The investigator must provide the prospective participant sufficient opportunity to consider whether to participate in the trial and minimize the possibility of coercion or undue influence;

(4) The information given to the participant must be written in language understandable to him or her;[8]

...an institutional review board ("IRB") or independent ethics committee ultimately has final approval of what the consent form will look like...

(5) The consent may not include exculpatory language through which the participant waives or appears to waive any legal rights or releases or appears to release the investigator, the sponsor, site or its agents from liability for negligence.[9]

While the trial sponsor and trial site typically negotiate the terms of the informed consent form for a clinical trial, an institutional review board ("IRB") or independent ethics committee ultimately has final approval of what the consent form will look like, including its contents and allocations of risk.[10] An IRB ensures that the information provided to participants in the informed consent contains all federally mandated elements, which include:

(1) A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the person's participation, a description of the procedures to be followed, and identification of any experimental procedures;

(2) A description of any reasonably foreseeable risks or discomforts to the participant;
(3) A description of any benefits to the participant or to others which may reasonably be expected from the research;
(4) Disclosure of appropriate alternative procedures or treatment, if any, that might be advantageous to the participant;[11]
(5) A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained and noting the possibility that the FDA may inspect the records;[12]
(6) For research involving more than minimal risk, an explanation of any compensation or medical treatment for injury and, if offered, an explanation of treatment or where further information may be obtained;[13]
(7) Contact information for (i) who can answer pertinent questions about the research and the participant's rights, and (ii) who to contact in the event of a research-related injury;
(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits earned, and that the participant may withdraw from the program at any time without penalty or loss of benefits earned;[14] and
(9) A specific database statement that clinical trial information has been or will be submitted to a clinical trial registry databank.[15]

An IRB may require that additional information be provided when, in the IRB's judgment, the information would meaningfully add to the protection of the rights and welfare of participants.[16]

Informed consent must be documented by a written form approved by the IRB and signed and dated by the participant at the time of consent.[17] A copy of the form must also be given to the participant.[18] The consent can either be (i) a written document that embodies all requisite elements (which may be read to the subject, but there must be adequate opportunity for the participant to read the form before signing), or (ii) a short form document stating that the required elements were presented orally to the participant in the presence of a witness, which is signed by the participant.[19]

As a trial site, sponsor, or investigator, it is imperative to analyze other special considerations specific to the trial for purposes of obtaining consent.

As a trial site, sponsor, or investigator, it is imperative to analyze other special considerations specific to the trial for purposes of obtaining consent. Trials involving children or patients with mental disorders, diverse populations, non-English speaking participants, illiterate participants, or an intention to use data or samples for genetic testing present unique challenges for consent and additional legal requirements come into play.[20]

CURRENT ISSUES TO CONSIDER IN NEGOTIATING CLINICAL RESEARCH INFORMED CONSENT

One major issue to be carefully considered is whether the participant will be entitled to compensation for injuries

and/or reimbursement for treatment costs associated with injuries incurred during the trial. If so, the consent should provide clear direction on who is responsible for such compensation or reimbursement, including whether the patient will be required to seek insurance reimbursement first.

Additionally, trial sites and sponsors should consider whether a local or central IRB will be used to review and approve the consent form and, when using a local IRB, identify the form selected. Determining the exact form to use can lead to a "battle of the templates" between the sponsor and site.

A third serious consideration is the inclusion of language to comply with (i) accreditation boards, such as the Association of Accreditation of Human Research Protection Programs, (ii) HIPAA, which has major implications as to how the participant's protected health information may be used in the study, and (iii) the Medicare Secondary Payor Act, which affects the ability of the sponsor to receive protected health information it normally would not obtain and obligations to report to the Centers for Medicare and Medicaid.

CONTINUING OBLIGATIONS DURING THE TRIAL

Even after the trial has begun and research is well underway, it may be necessary to obtain informed consent on a continuous basis. A researcher is obligated to update participants on new information that may:

(1) Be relevant to the participant's willingness to continue in the trial;

(2) Affect adversely the rights, safety, or well-being of participants;

(3) Impact the trial's methodology, procedures, or outcomes; and/or

(4) Alter IRB approval for the study conduct.[21]

This gives the participant the opportunity to ask questions or to raise concerns and even to withdraw the consent that was previously given.[22] Subsequent informed consent may also be necessary if there is an error creating

a possible adverse effect on any of the requisite elements of a valid consent (*e.g.,* a researcher learns at a later date that the language used in the form was not understandable to the participant).[23]

An IRB will review the research at intervals appropriate to the degree of risk, but not less than once per year.[24] Further, an IRB has authority to observe or have a third party observe the consent process and the research.[25]

LOOKING AHEAD: THE USE OF ELECTRONIC INFORMED CONSENT IN CLINICAL TRIALS

In March 2015, the FDA released a draft guidance covering the use of electronic media and processes to obtain informed consent for FDA-regulated clinical investigations of medical products, including drugs and biological products, medical devices, and combinations of such products for human use.[26] This would enable investigators, sponsors, and IRBs to use electronic means, such as texts, podcasts, and interactive Web sites, to convey information related to the study and to obtain and document informed consent. [27] Many believe the use of electronic informed consent allows for easier and faster communication with participants and better facilitates the participant's ability to comprehend the information via interactive interfaces.[28]

The FDA's guidance provides that electronic informed consent must still comply with all of the current federal regulations governing informed consent. In addition, it recommends four major considerations to implement an electronic informed consent process for sites and sponsors:

(1) Protecting human participants;

(2) Facilitating and improving people's understanding of the information conveyed during the consent process to ensure an informed decision to enroll;

(3) Ensuring appropriate documentation of the electronic consent; and

(4) Ensuring data quality and integrity when consent is obtained electronically.[29]

The FDA has not yet published its final guidelines; however, all those involved in the realm of U.S. clinical trials should expect major advancements and new challenges in their interactions with participants during clinical investigations and the informed consent process if electronic informed consent is approved.

CONCLUSION

The complexities of the informed consent process in clinical investigations should not be discounted. Failure to comply with relevant requirements can result in administrative actions, civil or criminal penalties, and even affect the outcome of subsequent litigation involving the studied product. Although the FDA's guidance may offer some relief in the future to ease and facilitate the process of obtaining informed consent, the number of requirements and elements necessary for that consent to be legally effective will not be changing any time soon. ■

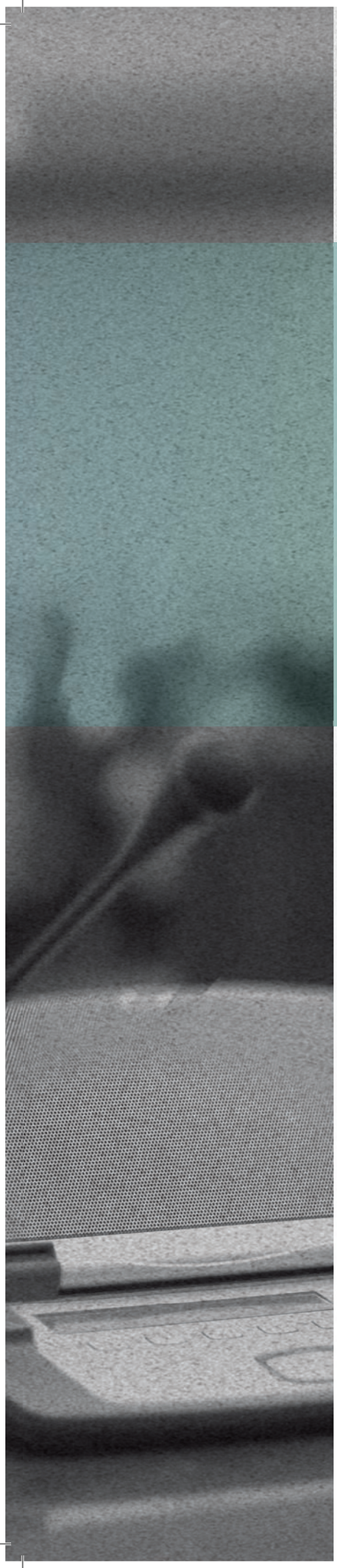
1. For purposes of this article, any reference to "participant," with regard to disclosures and consents means the participant or the participant's legally authorized representative, as applicable.
2. 21 CFR 50.20 et seq.
3. *Trials of War Criminals Before the Nuremberg Military Tribunals under Control Council Law*, U.S. Government Printing Office, No. 10, Vol. 2, pp. 181-182 (1949), *available at* http://www.hhs.gov/ohrp/archive/nurcode.html.
4. *Id.*
5. *The Declaration of Helsinki (Document 17.C),* World Medical Association (1964), as revised 1975, 1983, 1989, 2000, and 2002, *available at* http://www.fda.gov/ohrms/dockets/dockets/06d0331/06D-0331-EC20-Attach-1.pdf.
6. 21 CFR 50.25(d).
7. The investigator does not have to conduct a consent interview but is ultimately responsible for obtaining the consent.
8. *Understandable* means that the information is presented in a language and at a reading level comprehensible to the person, including the explanation of scientific and medical terms. The investigator should avoid terms such as "fully explained" or "fully understand," as the participant cannot genuinely claim to fully understand the clinical investigation.
9. 21 CFR 50.20. This does not mean a sponsor, investigator, or site has to compensate for injuries to the participant if the participant is negligent. Exceptions to these requirements are available upon certain investigator and physician certifications as to the existence of specific facts which make obtaining informed consent infeasible, where the U.S. President has waived consent for the administration of a new drug to an armed forces member, for emergency research, or where the IRB waives the consent requirements because it finds that the research presents no more than a minimal risk of harm to participants and involves no procedures for which written consent is normally required outside the research context. *See* 21 CFR 50.23, 50.24, 56.110.
10. 21 CFR 56.109. An IRB is a committee charged with performing an ethical review of proposed research involving humans and is given its authority by the FDA and U.S. Department of Health and Human Services, Office for Human Research

Protections. *IRBs and Assurances,* U.S. Department of Health & Human Services, http://www.hhs.gov/ohrp/assurances/index.html (last visited Oct. 12, 2015).

11. This should amount to "sufficient information" and include pertinent alternatives such as, supporting care with no additional disease directed therapy; this should be more than a list but a full risk/benefit explanation may not be required.
12. Note that absolute confidentiality should not be promised or implied.
13. This does not mean the sponsor must pay for injuries; if the sponsor will not pay, the consent must include a statement to the effect of: "no funds have been set aside for medical treatment for injury; the cost will be billed to you or your insurance." These do not *waive* a participant's legal right to seek redress.
14. 21 CFR 50.25(a). Additionally, federal regulations also require that the consent disclose certain points and include other information based on the particular details of the study, for example any additional costs the subject could incur from participation in the research. 21 CFR 50.25(b).
15. 21 CFR 50.25(c). The database statement must read: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."
16. 21 CFR 56.109.
17. 21 CFR 50.27.
18. *Id.* Although not required, providing the *signed* version of the copy provided to the participant helps to protect investigators and sites.
19. 21 CFR 50.27. Where a short form consent is used, a copy of the consent, along with a written summary of the oral presentation, must be provided to the participant. The witness must sign both the short form consent and a copy of the summary. Furthermore, the person obtaining the consent must also sign a copy of the summary.
20. 21 CFR 50.50 et seq.
21. Umesh Chandra Gupta, *Informed consent in clinical research: Revisiting few concepts and areas.* NCBI Perspectives in Clinical Research (Jan-Mar 2013), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3601699/.
22. *Id.*
23. *Id.*
24. 21 CFR 56.109.
25. *Id.*
26. *Use of Electronic Informed Consent in Clinical Investigations – Questions and Answers Guidance for Industry – Draft Guidance,* Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) and the Office of Good Clinical Practice (OGCP) in the Office of Medical Products and Tobacco (15 Mar. 2015), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436811.pdf.
27. *Id.*
28. *Id.*
29. *Id.*

By Caroline Eley

By Julie Watson Lampley



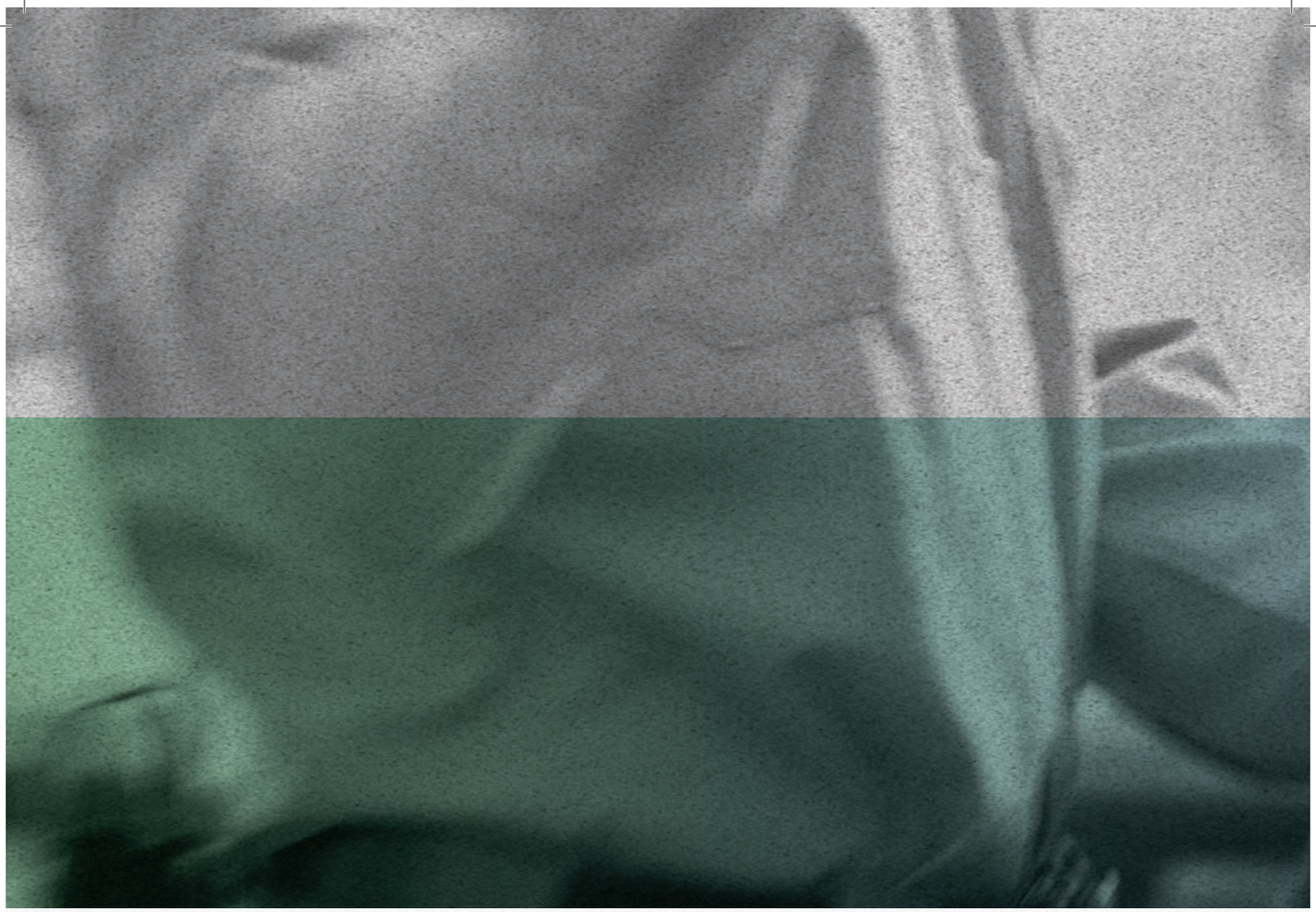
HOW CLINICAL TRIAL DATA

IMPACT ISSUES IN LITIGATION

Clinical trials can provide the most robust and comprehensive evidence that a drug or medical device is safe and effective. The Department of Health and Human Services recognizes that "clinical trials produce the best data available for healthcare decision making" and "are important because they advance medical knowledge and help improve patient care."[1] *It is therefore not surprising that the data from clinical trials and a drug manufacturer's interpretation of such data often take center stage in product liability cases.*

A well-designed and conducted clinical study has many benefits: it may be the most powerful evidence to dismantle the opinions of a plaintiff's expert (e.g., one who selectively relies upon negative aspects of the study and disregards data that do not support the expert's opinions), thus disproving allegations of design defect or inadequate warnings. A well-designed study can also be effective proof of a company's good faith in developing and appropriately marketing a product based on sound study results.

On the other hand, any clinical trial is always subject to retrospective criticism. Such criticisms may include that the study was under-powered and therefore cannot provide a statistically supported conclusion, or that the trial was plagued with poor patient selection, lacked sufficient follow-up, or failed for lack of blinding. Beyond these structural problems, plaintiffs often fault the study's



ultimate conclusions that the product is safe and effective due to the improper use of liberal success standards and large confidence intervals to inflate results.

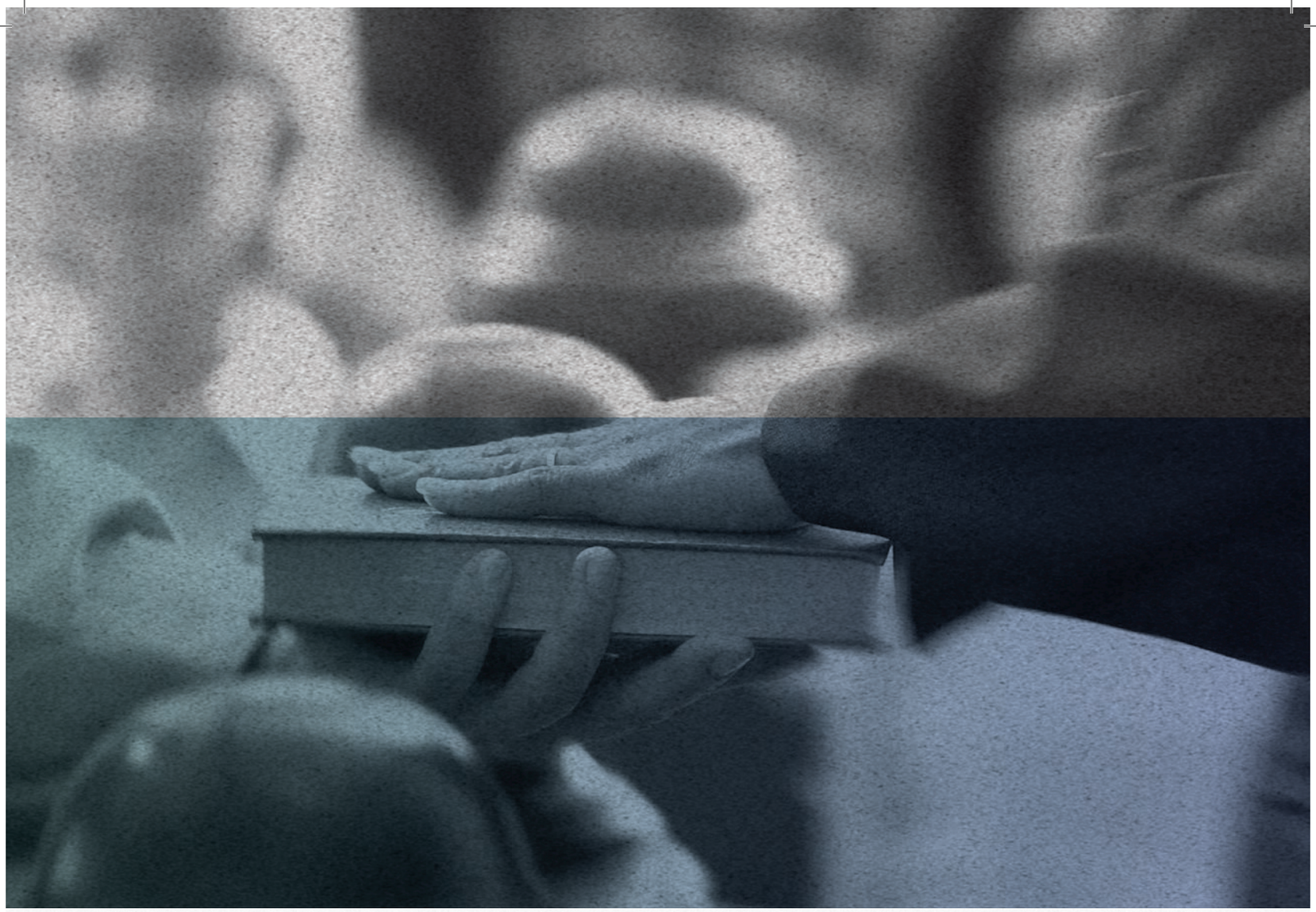
Given the current state of the mass tort market, clinical trial data are—and will be—the focus of important litigation issues. A few major topics, including discovery, witness selection and evidentiary issues, are discussed below.

A. CLINICAL TRIAL DATA AND DISCOVERY.

Clinical trial data may be held by a trial investigator, an institution or a university. Such information may be subject to subpoena, which risks confidentiality of the data as well as presenting a time-consuming obligation to respond for the investigator. This is particularly true if release of the information could impact the sponsor's ultimate goal of product approval by leaking useful information to competitors. In such a situation, the sponsor may seek a protective order or otherwise intervene to quash the subpoena.

In addition, such data may be considered a business record of the trial sponsor: a compilation of events near the time of experience that the sponsor would maintain in the regular course of business. This designation not only makes the data discoverable from the sponsor, but paves the way for wholesale admission of the information at trial.

The clinical trial data may even be considered an admission of the sponsor, particularly where the information was provided to the FDA as part of an approval process. Of course, one can presume that if the information was submitted to the FDA as part of the approval process, then it would support the sponsor's position as to the safety and



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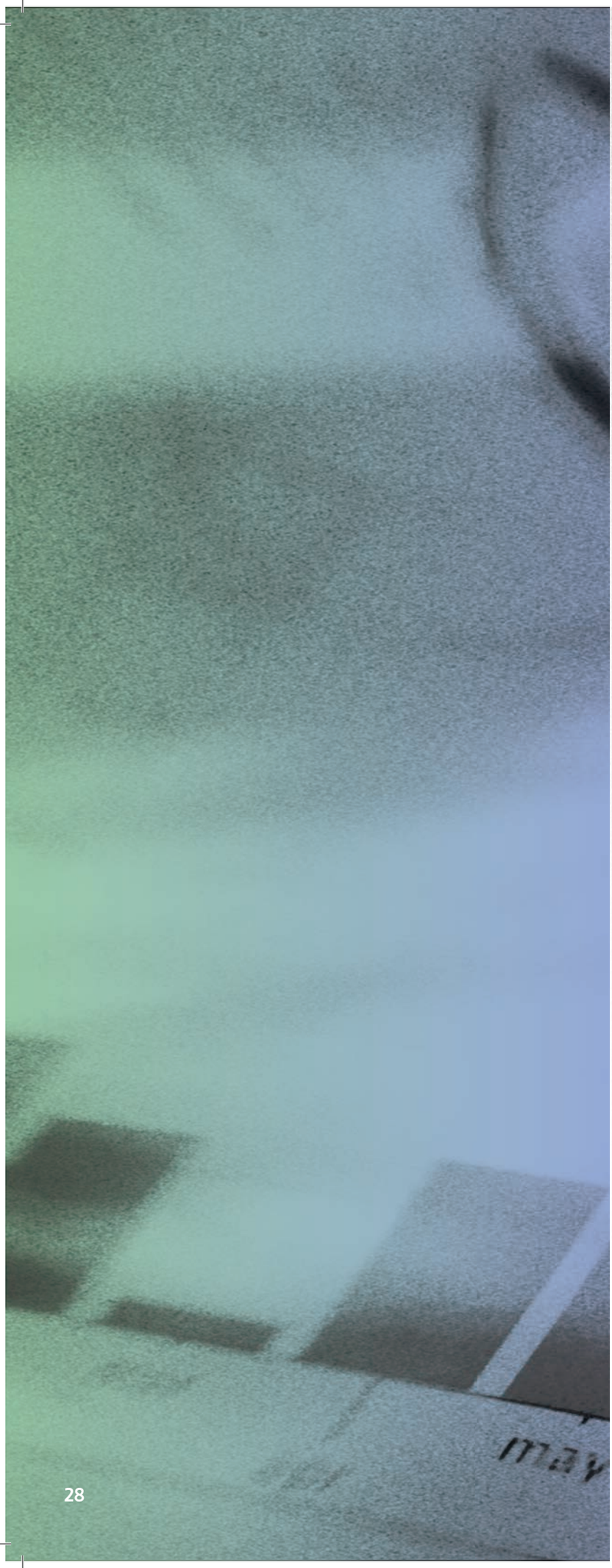
efficacy of the drug or device. This is more likely to become an issue if later studies refute the originally submitted information or otherwise undercut the propriety of the sponsor's reliance on it. Thus, even where clinical trial data are not within the control of the product manufacturer, any completed protocol forms or data compilations provided to the manufacturer from the study can be cast as business documents or potentially as admissions.

B. WHO IS THE BEST WITNESS AT TRIAL?

Clinical trial data and the patterns discerned from such studies will be a likely focus in any products liability trial. Clinical studies are often sponsored to some degree by a manufacturer, especially when a company is looking to validate a drug or device's safety and efficacy before that product reaches the market. Plaintiffs will undoubtedly seek to develop a narrative to cast doubt on the results—such as



strongly suggesting (if not saying outright) that any positive results from the study are tainted and cannot be trusted because the results are bought and paid for. Knowing this tactic is in plaintiffs' playbook, manufacturers must develop a more accurate narrative, such as explaining how clinical trial data demonstrate the manufacturer's careful study of the product and development of adequate warnings.

No matter the vantage point, one thing is clear: clinical trial data are complicated and highly technical material. Despite their utility in showing product safety and labeling adequacy, clinical data are often rife with dense statistical analyses of complicated information that

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may confuse jurors—or perhaps even worse, lull them to sleep. Judges, particularly those undertaking a new docket of pharmaceutical product liability cases, may have never been exposed to the complex science behind clinical trials, and as a result may be completely unfamiliar with the methodology supporting the interpretation of clinical trial data. Biostatistics (statistics related to biological data) must be broken down into manageable information to establish either the safety of the product or to show that any reported adverse events are not statistically significant related to product safety.

Given that a lay jury (or judges without scientific expertise) may be called upon to scrutinize clinical trial data, a critical issue is identifying the best witness for introduction of this proof. A biostatistician can delve deeply into the

minutiae of the data, but unless such a deep dive into the particulars is critical, such information may be of limited value due to its complexity.

Often the best witness would be the clinical trial investigator who can explain the details of the study by reason of first-hand participation. An investigator knows exactly how the trial was conducted, how data were compiled and interpreted and how such information was reported to the sponsor. But this witness may also be subject to impeachment on the basis of bias, either by virtue of being directly compensated by the sponsor or by virtue of working at the university or institution that is paid by the sponsor.

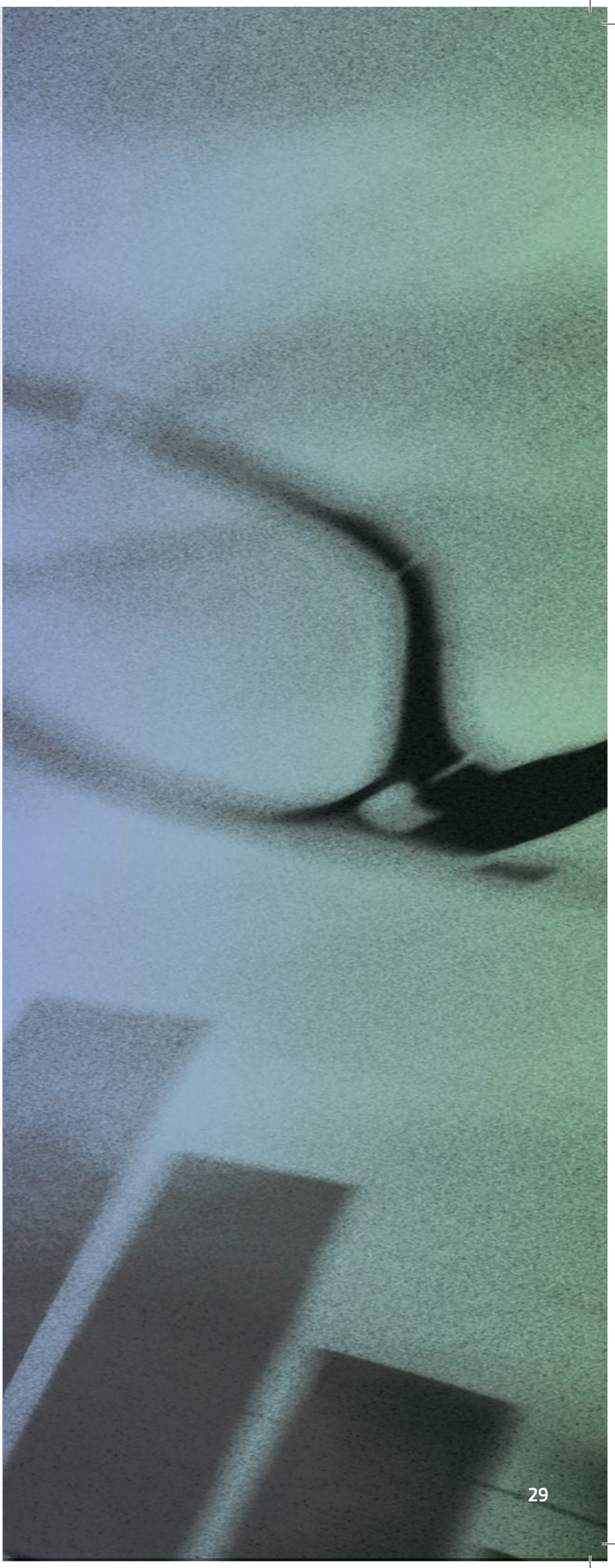
And a thorough company-sponsored clinical trial can itself be used to undercut such claims of bias. This is particularly true where the study identifies:

- Shortcomings or limitations of a drug or device
- New complications associated with a drug or device
- Scientific or medical controversies surrounding a drug, device, or surgical procedure
- Adverse events, including statistically supported percentages and durations
- Recurrence rates and/or the need for surgical re-intervention
- Definitions of surgical or treatment success
- Ideas to make future studies more robust
- Identification of areas in which a drug or device can be improved as medical science evolves.

Openly discussing the complications that arise in a clinical trial illustrates that the sponsor carefully considered and was transparent about complications. This can undercut a common plaintiff theme: that the manufacturer was motivated to downplay negative results in a rush to get the product to market.

C. REIGNING IN PLAINTIFF'S EXPERT.

Not to be overlooked is the usefulness of clinical trial data in exposing the bias of a plaintiff's expert. If the expert failed to consider all of the data or dismissed the entire trial



as company-sponsored, this provides a basis to challenge the plaintiff's expert's methodology because of cherry-picking data and focusing only on information helpful to the plaintiff's case. Such cherry-picking renders these opinions unreliable.

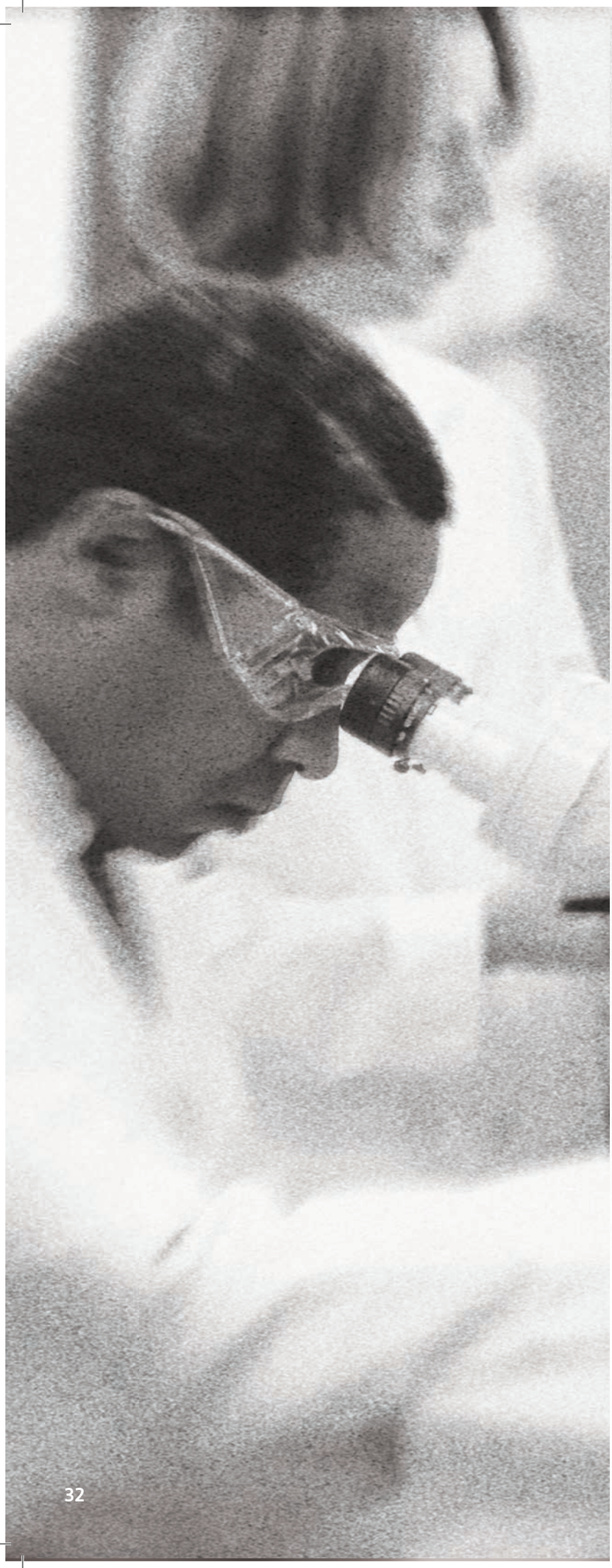
In addition, plaintiff's experts who testify on clinical trial data may be tempted to go beyond "just the facts" and offer opinions that venture into corporate ethics, conduct or state of mind. Experts may attempt to use any negative data from the clinical trial to opine that the product manufacturer "knew better" or put profit over public safety. Courts have routinely excluded such testimony as speculative and misleading.

D. STRENGTHS AND LIMITATIONS OF CLINICAL TRIALS.

There are important determinants to evaluate the strength or weakness of a clinical trial when evaluating the data in a litigation setting.[2] Such factors should be thoroughly vetted with the product manufacturer's witnesses related to clinical trials. These factors should also be evaluated in preparing to examine plaintiff's experts and to discount any study that undercuts the safety and efficacy of the subject product.

One key factor concerns the population of patients in the study. Whether the selected participants are proper ones to test the ultimate hypothesis is a central question. It is also critical to determine if the participants were told of the potential effects of treatment, both positive and negative. Planting the "seed" of the ultimate conclusion may introduce bias into the trial by stimulating the placebo effect.

In addition, the sample size must be sufficient to yield the statistical power necessary to identify and define clinically meaningful differences. This may require a power analysis to determine an appropriate sample size that will permit the investigator to identify the meaningful differences between treatments. Any such power analysis should be conducted in advance of the study. So, too, the participants must be sufficiently diverse to mirror the age, gender and race distribution of the target population so that the results can be generalized to additional treatment settings. Finally, the site(s) of the clinical trial can impact the eventual



success/failure rates of the trial. For example, if the trial is conducted at a single site with exceptionally skilled physicians, the results may be subject to additional scrutiny due to the inability to recreate the results in the general population.

The outcome of any clinical trial should be scrutinized to determine if it was clinically supported. This may include evaluation of both objective and subjective outcomes and an analysis of the clinical relevance of the supporting data. Part of the examination of the outcome will include whether there was an open-phase of the trial where patients were no longer blinded to treatment. This again may create an issue of bias/placebo effect and compromise the conclusions because of the lack of a control group. So, too, whether clinical trial follow-up has been conducted may be paramount. The follow-up period should be sufficient for the outcomes being evaluated to manifest, and a failure to follow-up may compromise the reliability of the study.

While clinical trial data, their interpretation and their analysis may be complex and are likely something never encountered by the ordinary juror, dissection of the information plays a key role in both bolstering a product manufacturer's claims of product safety and efficacy and in challenging a plaintiff's expert's opinions to the contrary. Presentation of such important data at trial requires a deft hand and a knowledgeable witness. ■

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1. http://www.nhlbi.nih.gov/studies/clinicaltrials
2. Hannan EL. *Randomized Clinical Trials and Observational Studies: Guidelines for Assessing the Respective Strengths and Limitations*, J. Am Coll. Cardiol. Intv., 2008;1:211-217.

NEW AND NOTEWORTHY

WHAT'S IN A NAME? FDA PROPOSES NEW GUIDANCE ON NAMING FOR LICENSED BIOSIMILARS

On August 27, 2015, FDA published its first draft guidance for the industry on "Nonproprietary Naming of Biological Products." Biological products, or "biologics," are medical products that generally come from living organisms (e.g., humans, animals, yeast, bacteria) and are ordinarily used to prevent, diagnose, or treat diseases. Examples of biologics include vaccines, blood transfusion products and gene therapies. A "biosimilar" is a biologic that gains FDA-approval based on a showing that it is "highly similar" to another already-FDA-approved biologic (a "reference product") and there are no clinically meaningful differences between the two products in terms of safety and effectiveness.

Biologics can be expensive. Biosimilars undergo an abbreviated, less-costly licensure process and therefore may create significant cost-savings for consumers. Unlike generic versions of drugs, a biosimilar is not an exact duplicate of its reference product; rather, it is only a close replica.

FDA's draft guidance states that each previously licensed and newly licensed biosimilar must bear a unique four-letter suffix in addition to the nonproprietary name it will share with its reference product. In requiring different

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FDA requested comments on and is still considering whether interchangeables should share the same name as their reference products, or whether a distinguishing suffix should also be required for such products.

suffixes for biosimilars and their reference products, FDA seeks to help physicians and pharmacists distinguish between the products to "minimize inadvertent substitution" and, more generally, to "facilitate pharmacovigilance for all biological products."

PROS VS. CONS

Proponents of FDA's approach argue that distinguishing between biosimilars and their reference products will help avoid industry confusion and prevent adverse reactions in patients who could otherwise be unknowingly switched from a reference product to a biosimilar. Some biotech drugmakers have stressed the safety risks of inadvertently switching patients to alternate versions of biologics, emphasizing that biosimilars are not perfect copies of their reference products.

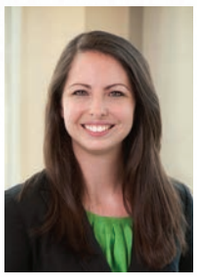
Critics of the approach, however, contend that biosimilars should carry a name identical to their brand-name counterparts in order to lessen confusion about the safety and efficacy of biosimilars and to facilitate increased use of and access to cost-saving biosimilars in the marketplace.

THE REMAINING QUESTION FOR INTERCHANGEABLES

FDA's proposed rule also contemplates naming for interchangeables. An interchangeable is a type of biologic that has been shown to meet certain Public Health Service Act standards enabling it to be substituted for its reference product without requiring intervention from the prescribing healthcare provider, meaning that pharmacists may freely substitute interchangeables with their reference products. To be interchangeable, a product must demonstrate biosimilarity *and* produce the same result as the reference product in any given patient without any increased risk in terms of safety or diminished efficiency. FDA requested comments on and is still considering whether interchangeables should share the same name as their reference products, or whether a distinguishing suffix should also be required for such products.[3] ■

1. 42 U.S.C. § 262 (i)(2)(A); Public Health Service Act § 351(i)(2).
2. FDA, Nonproprietary Naming of Biological Products; Draft Guidance for Industry; Availability, 80 FR 52296, 52297 (Aug. 28, 2015).
3. Id. at 52296; see also PHS Act at § 351(i)(3).

By Kate Mara Dowd



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