No. 18-

IN THE

Supreme Court of the United States

MARION LIU,

Petitioner,

v.

JANSSEN RESEARCH & DEVELOPMENT, LLC,

Respondent.

ON PETITION FOR A WRIT OF CERTIORARI TO THE CALIFORNIA COURT OF APPEAL, SECOND APPELLATE DISTRICT, DIVISION FIVE

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

According to the National Institutes of Health, there are currently over 3,000 on-going clinical drug trials in the United States which are either currently active or currently recruiting test subjects.[1] It is also estimated that 19 million Americans participate as test subjects in clinical research trials every year.[2]

Numerous ethical codes, including the Nuremberg Code, developed after the human experimentation atrocities in World War II, the Belmont Report, issued by the United States National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the Declaration of Helsinki, developed by an international consortium of researchers, and federal regulations, including 21 C.F.R. § 312.50 and 21 C.F.R. § 312.56, all emphasize the importance of protecting the health and safety of clinical trial test subjects as a paramount consideration in every research endeavor.

The question presented is: Whether a drug company which is medically monitoring the participants of its drug study has a duty under federal regulations to exercise

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1. See, https:// clinicaltrials.gov/ct2/results?term=number +subjects&cntry =US&Search=Apply&recrs=b&recrs=a&re crs=f&recrs=d&age_v=&gndr=&type=&rslt=, most recently accessed on July 5, 2018.

2. Scutti, *Clinical Trials Do Go Wrong: How Many Human Subjects Are Injured By Scientific Research Each Year?*, Innovation, 2/5/16 (available at http://www.medicaldaily.com/x-files-clinical-trials-human-experimental-subjects-372422, accessed on July 5, 2018.

its independent power to stop a clinical study and refer a participant to medical care when it is aware that the participant is suffering from a life-threatening medical condition making him or her unsuitable to participate in the study or whether, as the California Court of Appeal, Second Appellate District, Division Five held, the study sponsor has no obligation to intervene even when it is aware that the clinical investigator it hired to conduct the clinical trial has failed to exercise reasonable care in making decisions about the enrollment of the test subject and has maintained the test subject in the study despite clear evidence of the test subject's failing health.

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PETITION FOR A WRIT OF CERTIORARI

Marion Liu, the mother of decedent Augustine Liu, II, and the plaintiff in the trial court, respectfully petitions for a writ of certiorari to review the judgment of the California Court of Appeal, Second Appellate District, Division Five.

OPINIONS BELOW

The decision of the California Court of Appeal, Second Appellate District, Division Five, App., *infra*, 1a-34a, is available at 2018 WL 272219. The California Supreme Court denied the plaintiff's petition for review of that decision. The California Supreme Court's denial is at App., *infra*, 59a. The Los Angeles Superior Court's order on the issues is contained in the relevant portions of the transcript at App., *infra*, 35a-58a.

JURISDICTION

The judgment of the California Court of Appeal, Second Appellate District, Division Five was entered on January 3, 2018. App., *infra*, 2a. On April 11, 2018, the California Supreme Court denied Marion Liu's Petition for Review of that judgment. App., *infra*, 59a. The jurisdiction of this Court is invoked under 28 U.S.C. § 1257(a).

CONSTITUTIONAL, STATUTORY, AND REGULATORY PROVISIONS INVOLVED

Pertinent constitutional, statutory, and regulatory provisions are set forth in the appendix to this petition. App., i*nfra*, 60a-62a.

STATEMENT

A. Legal Background

Drug companies seeking approval for the marketing and sale of drugs to be administered to human beings in the United States must comply with extensive regulatory requirements established under the Food, Drug and Cosmetic Act, 21 U.S.C. §§ 301, et seq. ("the FDCA"). Among the requirements for approval, a drug company must conduct test studies on human subjects in order to assure that the drugs are safe and effective. 21 U.S.C. § 355(i), 21 C.F.R. § 312.1. Pursuant to the FDCA, the Food and Drug Administration ("the FDA") has promulgated specific regulations delineating the responsibilities of those involved in that human research, including the drug company itself ("the sponsor") and the clinical investigators hired by the drug company to actually conduct the research studies. (21 C.F.R. §§ 312, et seq.)

In 21 C.F.R. § 312.50, the FDA identified the "General responsibilities of sponsors," establishing that: "Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), *ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols* contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug." (Emphasis added.)

Next, the FDA also specified in 21 C.F.R. § 312.56(a) that "[t]he sponsor shall monitor the progress of all clinical investigations."] Most critically, subdivision (b) of that regulation requires that a "sponsor who discovers that an investigator *is not* complying with the signed agreement . . ., the general investigation plan, or the requirements of this part or other applicable parts *shall promptly either secure compliance or . . . end the investigator's participation in the investigation*." (Emphasis added.) The power and duty to intervene under § 312.56(a) is critically important. Indeed, what would be the point of imposing a monitoring duty if the sponsor were not required to intervene when things go awry and the clinical investigator's lack of action threatens the health and safety of a study subject?

In its decision below, while acknowledging that "FDA regulations impose on study sponsors a general duty to monitor the progress of their studies to ensure compliance with study protocols and the health and safety of participants," the Court of Appeal concluded that the drug company's duty under those federal regulations is limited and "is intended to protect participants generally from foreseeable harm caused by the drug studies themselves, including participants' adverse reactions to study medications." App., *infra*, 19a. But, the Court of Appeal concluded, drug companies owe *no* duty to intervene in any aspect of the medical supervision rendered during a clinical trial conducted in an inpatient setting because "it is not foreseeable to a study sponsor that study physicians with the primary responsibility for participants' health and safety will fail to recognize, diagnose, and properly treat preexisting, life-threatening conditions that first manifest during drug studies . . . ." App., *infra*, 19a.

B. Facts and Procedural Background

Augustine Liu, II ("Augustine"), the son of plaintiff and petitioner Marion Liu, began treatment for mental illness in 2000,when he was 17 years old. App., *infra*, 4a. He was diagnosed with schizophrenia in 2004 and was prescribed the antipsychotic drug, Seroquel. App., *infra*, 4a. Dr. Madeleine Valencerina ("Valencerina") became Augustine's treating psychiatrist in 2008, and she continued her patient on that medication. App., *infra*, 4a.

In late 2008, defendant Janssen Research & Development ("Janssen") obtained FDA approval for a proposed drug study to analyze the safety and efficacy of a long-acting injectable formulation of its antipsychotic drug, Risperidone (study drug). App., *infra*, 4a. Defendant selected Valencerina as the study's principal physician/investigator for the trial. App., *infra*, 4a. Valencerina conducted clinical trials through Clinical Pharmacological Studies, Inc. (CPS), an entity in which she held an ownership interest. App., *infra*, 4a. The FDA and an institutional review board approved Valencerina as the principal physician/investigator and also approved defendant's proposed study protocol and plan for monitoring the progress of the study. App., *infra*, 4a.

Valencerina recruited Augustine to participate in defendant's drug study. App., *infra*, 4a. Augustine completed the informed consent and related paperwork in Valencerina's office and enrolled in the study on February 19, 2009. App., *infra*, 4a.

Augustine underwent a screening electrocardiogram (EKG) and blood test that day. App., *infra*, 5a. Valencerina

reviewed the screening EKG on February 20, 2009 and blood test results on February 21, 2009. App., *infra*, 5a. The EKG was "abnormal," with the report indicating "sinus tachycardia; old myocardial infarction" and "non-specific T wave abnormalities possibly secondary to heart disease." The blood test revealed slightly elevated liver enzymes. App., *infra*, 5a. Valencerina concluded the results were not clinically significant and, based on Augustine's otherwise normal physical examination and denial of a family history of cardiac disease, admitted him to the study. App., *infra*, 5a.

On February 22, 2009, Augustine entered College Hospital, a psychiatric facility, for the first phase of the study. App., *infra*, 5a. A second blood test followed on February 23, 2009. App., *infra*, 5a. One-half hour after that test, Augustine was injected with a non-therapeutic one milligram dose of the study drug to test for adverse reactions to any of its ingredients. App., *infra*, 5a.

Within two hours of receiving the test dose, Augustine underwent a second EKG. App., *infra*, 5a. The EKG report issued the same evening, and it indicated Augustine's cardiac condition had worsened. App., *infra*, 5a. Valencerina reviewed the February 23, 2009 blood test report on February 24, 2009. App., *infra*, 5a. Augustine's liver enzyme levels were much higher than they had been on February 19, 2009. App., *infra*, 5a. To rule out laboratory error, Valencerina ordered a retest on February 24, 2009. App., *infra*, 5a.

On February 25, 2009, after the retest confirmed Augustine's liver enzymes had risen alarmingly, Valencerina transferred him from College Hospital to

Coast Plaza Doctors Hospital, an acute-care facility. App., *infra*, 6a. There, Augustine was diagnosed with cardiomyopathy, pneumonia, failing liver function, and altered mental state. App., *infra*, 6a. Augustine died on the afternoon of February 26, 2009. App., *infra*, 6a. The cause of death was dilated cardiomyopathy in conjunction with other factors, including multiple organ failures and pneumonia. App., *infra*, 6a.

Petitioner Marion Liu sued Janssen for the wrongful death of her son, Augustine. App., *infra*, 1a.

At the trial of the action, Marion Liu presented evidence, including several expert opinions, to demonstrate Augustine was not competent to enroll in the drug study; Janssen, who also received Augustine's EKG and blood test results, did nothing to intervene in his care; defendant failed to intervene in the decision to administer the one-milligram test dose; and that dose was a substantial factor in Augustine's death. App., *infra*, 10a.

The trial court ruled during the trial that the principal investigator in a drug study "is making judgments which are independent of the sponsor's interests and are intended to be in the interest of the patient or the subject for the purpose of protecting the subject from adverse consequences of the trial. I think that the physician in her or his unfettered discretion recommends inclusion of the subject in the trial and I think that the physician's responsibility during the trial to monitor the reaction of the subject to the environment and to the test drug is evidence that the physician is making decisions which are independent of the program or the structure imposed by the sponsor." App., *infra*, 12a. Thus, the trial court ruled,

and the appellate court confirmed, that a clinical trial sponsor has no independent responsibility for intervening to protect the health and safety of a human clinical trial subject when its monitoring discloses that the clinical investigator has not followed the protocol with respect to which candidates should be enrolled.

In granting a partial directed verdict at the close of evidence, the trial court identified two negligence theories that Marion Liu could pursue against defendant: "I do think that a sponsor has independent responsibilities to the patient, and Janssen in this particular structure has seen to it that it would obtain information about the reaction of the subject to the test drug and to the physical condition of the subject such that it had reasonably assumed responsibilities to make its own judgment separately from the physician as to whether or not this subject should stay in the program [or] should be - - if the circumstances warranted taken out of the program and provided medical care for the subject's benefit." App., *infra*, 54a-55a.

Thus, one issue was couched in terms of Janssen's independent duty to intervene in Augustine's medical care, even if the medical issues preexisted, or were unrelated to, the study itself. Another was based on Janssen's duty to monitor the administration of the study drug itself and the resulting effects it had on Augustine.

Accordingly, based on the trial court's decision, the jury was permitted to consider whether the drug company had an independent duty to intervene and timely refer Augustine to a cardiologist or hepatologist or transfer him to an acute care facility for treatment of his preexisting heart disease. App., *infra*, 13a-14a.

The jury was presented with a special verdict form that asked whether Janssen and Valencerina were negligent and, if so, whether the negligence of either was "a substantial factor in causing the death of Augustine Liu II." App., *infra*, 14a. The jury answered these four questions in the affirmative. App., *infra*, 14a. The jury awarded Liu $3 million in general damages and $5 million in future damages. App., *infra*, at 14a. It assessed the percentages of fault at 70 percent for Janssen and 30 percent for Valencerina. App., *infra*, 14a. Based on the verdict, the trial court entered a judgment against Janssen in the amount of $5.6 million. App., *infra*, 14a.

On Janssen's appeal, the California Court of Appeal reversed the jury's verdict, holding that, as a matter of law, Janssen only "undertook a general duty not to harm Augustine as part of the clinical study. That duty encompassed administration of the test dose." App., *infra*, 15a. And, the appellate court further stated,"[a]s a matter of law, we also conclude the scope of that duty did not extend to diagnosing or treating Augustine's preexisting heart disease or intervening in his medical care and the medical decisions related to that condition." App., *infra*, 15a-16a. Thus, the Court of Appeal held that the sponsor of a drug study had no duty to intervene to protect the health and safety of a clinical trial subject, even when its monitoring disclosed that the principal investigator was committing malpractice and thereby causing injury to the health and safety of that person.

REASONS FOR GRANTING THE PETITION

A. The Health And Safety Of Clinical Trial Subjects Is Of Critical Importance.

The modern rules relating to medical experimentation on human subjects began with the Nuremburg Code.[3] As described in a Special Article in the New England Journal of Medicine, "[t]he Nuremberg Code is the most important document in the history of the ethics of medical research. The Code was formulated 50 years ago, in August 1947, in Nuremberg, Germany, by American judges sitting in judgment of Nazi doctors accused of conducting murderous and torturous human experiments in the concentration camps (the so-called Doctors' Trial). It served as a blueprint for today's principles that ensure the rights of subjects in medical research." (Shuster, *Fifty Years Later: The Significance of the Nuremberg Code*, N Engl J Med, 337:1434-1440 (November 1997).)[4]

In 1964, the World Medical Association developed the Declaration of Helsinki to address the obligations owed by researchers to the subjects of human experimentation.[5] And in 1979, the FDA itself adopted the principles articulated in the Belmont Report, issued by the National Commission for the Protection of Human Subjects of

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3. Available from the website of the National Institutes of Health, history.nih.gov/research/downloads/nuremberg.pdf

4. Available at https://www.nejm.org/doi/full/10.1056/NEJM199711133372006, accessed July 7, 2018

5. Available at https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/, accessed July 7, 2018

Biomedical and Behavioral Research.[6] Finally, in 1997, the FDA also adopted the International Conference on Harmonisation; Good Clinical Practice: Consolidated Guideline ("GCP Guidelines"). (62 FR 25692-01.)

Collectively, these principles and guidelines emphasize the importance of obtaining meaningful informed consent, especially from populations that could be subjected to coercion or duress, such as prisoners, or those who are physically or mentally vulnerable. GCP Guidelines, 62 FR 25692-01, § 1.61. Those principles and guidelines also put the onus on researchers to protect the subjects of their human experimentation for the simple reason that the researchers are much more likely to know or have the information relevant to the risk and hazards associated with the experiment and the ability to monitor and assess the subject's physical health during it. *Grimes v. Kennedy Krieger Institute, Inc.,* 366 Md. 29, 101-102, 782 A.2d 807, 850-851 (Md. 2001).

Indeed, as the Maryland Court of Appeals discussed extensively in *Grimes v. Kennedy Krieger Institute, Inc.,* 366 Md. 29, 782 A.2d 807 (Md. 2001), the nature of human experimentation, even when conducted by pharmaceutical companies for the development of new drug therapies, creates the potential for extreme danger to study participants and requires an extremely high degree of caution. For example, under the Nuremburg Code, "[n]o experiment should be conducted where there is a prior reason to believe that death or disabling injury will

6. Available at https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html, accessed July 7, 2018

occur." *Grimes*, *supra,* 366 Md. 29, at 76, 782 A.2d 807, at 835, fn. 31; Belmont Report, Rule 5. Similarly, the "degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment." *Grimes, supra,* 366 Md. 29, at 76, 782 A.2d 807, at 835, fn. 31. And "[p]roper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death." *Grimes, supra,* 366 Md. 29, at 76, 782 A.2d 807, at 835, fn. 31*;* Belmont Report, Rule 7. Significantly, the "*highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment*." *Grimes, supra,* 366 Md. 29, at 76, 782 A.2d 807, at 835, fn. 31; Belmont Report, Rule 8. emphasis added.

Even more specifically, the GCP Guidelines adopted by the FDA (and expressly mandated in Janssen's clinical trial protocol in this case) requires that the sponsor of a clinical trial (i.e., Janssen here) must take responsibility for the safety and well-being of human subjects in its studies: "The sponsor should designate appropriately qualified medical personnel *who will be readily available to advise on trial-related medical questions or problems*." GCP, 62 FR 25692-01, § 5.3, "Medical Expertise," emphasis added.

Further, the GCP Guidelines confirm that "The purposes of trial monitoring are to verify that: . . . (a) The rights and well-being of human subjects *are protected*." GCP, 62 FR 25692-01, § 5.18.1, "Purpose," emphasis added.

B. The Relevant Federal Regulations Cannot Protect The Health And Safety Of Clinical Trial Subjects Unless They Are Broadly Construed To Require Clinical Trial Sponsors To Intervene In Every Phase Of The Trial And Take Action When The Health And Well-Being Of A Subject is Compromised.

The ethical principles discussed above are intended to assure that the health and well-being of the subjects of human experimentation are protected; indeed, they require that the subjects' health and well-being be accorded the highest level of consideration in conducting a clinical trial – over and above considerations regarding the importance of the purpose of the study itself. *Grimes*, *supra*, 366 Md. 29, at 101-102, 782 A.2d 807, at 850-851.

Those codes and principles – and the duties imposed on the sponsor of such human experiments – are embodied in the federal regulations at issue here. 21 C.F.R. section 312.50 expressly places responsibility on the clinical trial's sponsor for "ensuring proper monitoring of the investigation [and] *ensuring that the investigation is conducted in accordance with the general investigational plan and protocols*." (Emphasis added.)

Significantly, mere monitoring is not the limit of the sponsor's obligations. Rather, 21 C.F.R. 312.56, subdivision (b) expressly imposes on the sponsor the obligation to intervene when the clinical investigator is failing to act appropriately in protecting the subjects' health and safety: A "sponsor who discovers that an investigator is not complying with the signed agreement . . ., the general investigation plan, or the requirements of this part or other applicable parts *shall promptly either secure*

compliance or . . . end the investigator's participation in the investigation." (Emphasis added.)

Thus, not only do clinical drug trial sponsors have the responsibility and the power to assure that the clinical investigators are performing the clinical trial properly and are doing everything necessary to protect the health and safety of the trial subjects, but the failure to do so can have terrible consequences beyond just this case. Indeed, requiring sponsors to fulfill those duties can have a significant impact on the health and safety of millions of Americans because deaths and injuries in the course of clinical trials occur with frightening frequency.

As discussed in Scutti, *Clinical Trials Do Go Wrong: How Many Human Subjects Are Injured By Scientific Research Each Year?*, Innovation, February 2016, it is estimated that 19 *million* Americans participate in clinical research trials *each year*.[7] But, as also recognized in that article, there is no comprehensive tracking of injuries or deaths occurring during those trials and Scutti further notes that even though drug companies are required to submit "adverse event reports" to the FDA, injuries and deaths are significantly underreported.

Similarly, New Yorker magazine published an article in 2008 by Carl Elliot, a professor of bioethics and philosophy and the University of Minnesota, entitled *Guinea-pigging: Healthy human subjects for drug-safety trials are in demand. But is it a living?*[8] In that article,

7. Available at http://www.medicaldaily.com/x-files-clinical-trials-human-experimental-subjects-372422, accessed July 5, 2018

8. Available at https://www.newyorker.com/magazine/2008/01/07/guinea-pigging, accessed July 6, 2018

Professor Elliot discussed several incidents of deaths and serious injury occurring in clinical trials and the financial incentives for cutting corners in assuring the health and safety of trial subjects.

In 2006, the New England Journal of Medicine published an article, *Injury to Research Volunteers – the Clinical-Research Nightmare*[9], which concluded that "[a]lthough it is important to emphasize that most phase 1 studies have been safe, it is equally important to ensure that lessons are learned" and that "[a]cademia, the pharmaceutical and biotechnology industries, and regulators must work together to prevent such clinical-research nightmares from happening in the future."

A study regarding Japanese clinical trials reported that during a three-year period from April 2007 to March 2010, there were 84 injuries requiring hospitalization and nine death cases. Kurihara, et al., *High Rate of Awarding Compensation for Claims or Injuries Related to Clinical Trials by Pharmaceutical Companies in Japan*, PLOS, 1/8/14[10].

In addition to those reports, other articles, lawsuits and news reports provide some indication of the extent of the problem. See, e.g., *University of Texas M.D. Anderson Cancer Center v. Jones,* 485 S.W.3d 145 (Tx 2016); *Grimes v. Kennedy Kreiger Institute, Inc.* 366 Md. 29, 782 A.2d 807 (Md. 2001); *Salva v. Blum*, 277 A.D.2d 985 (N.Y. 2000); Matharu, *The troubled history of clinical drug trials*,

9. Available at http://www.nejm.org/doi/full/10.1056/NEJMp068082, accessed July 6, 2018

10. Available at http://journals.plos.org/plosone/article?id=10.1371/journal. pone.0084998, accessed July 7, 2018

The Independent (January 15, 2016);[11] Butler & Callaway, *Scientists In The Dark After Clinical Trial Proves Fatal*, Nature (January 18, 2016)[12]; Young, *French study's death recalls 2006 U.K. clinical trial disaster*, Relias, IRB advisor (April 1, 2016)[13]; Elliott, *University of Minnesota Blasted for Deadly Clinical Trial*, Mother Jones (April 3, 2015)[14]; Gervais, *One Death, Three Serious Brain Injuries in Phase I Trial*, Medscape (January 15, 2016)[15]; Vinluan, *Liver Damage, Patient Deaths Lead FDA to Halt SeaGen Leukemia Trials*, Exome (December 27, 2016)[16]; Bowen, *Case Studies: Compensation for family after cancer patient dies in drug trial overdose*, Field Fisher[17].

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11. Available at https://www.independent.co.uk/life-style/health-and-families/health-news/the-drug-trials-that-went-wrong-a6814696.html, accessed July 9, 2018

12. Available at https://www.nature.com/news/ scientists-in-the-dark-after-french-clinical-trial-proves-fatal-1.19189, accessed July 7, 2018

13. Available at https://www.ahcmedia.com/articles/137519-french-studys-death-recalls-2006-uk-clinical-trial-disaster, accessed July 7, 2018

14. Available at https://www.motherjones.com/politics/2015/04/dan-markingson-university-minnesota-clinical-trials-astrazeneca/, accessed July 7, 2018

15. Available at https://www.medscape.com/viewarticle/857379, accessed July 7, 2018

16. Available at https://www.xconomy.com/seattle/2016/12/27/liver-damage-patient-deaths-lead-fda-to-halt-seagen-leukemia-trials/, accessed July 7, 2018

17. Available at http://www.fieldfisher.com/personalinjury/case-studies/medical-negligence/cancer-claim/testicular-cancer/compensation-for-family-after-cancer-patient-dies-in-drug-trial-overdose, accessed July 7, 2018

These, and other, articles illustrate that clinical trial injuries and deaths are not so rare that this Court should not involve itself in the issue. Indeed, this Court's intervention on this issue can assure that, going forward, clinical trials will be conducted with greater protection for the health and safety of the subjects.

To that end, it is critical that the *scope* of the federal regulations be examined. Sections 312.50 and 312.56 can, of course, arguably be construed to allow drug study sponsors to simply sit back and take a "hands-off" approach to the operation of the study and the actions of the clinical investigators, as determined by the Court of Appeal in this case. Such a construction, however, begs the question of why there would even *be* a monitoring duty in that context. In other words, if a sponsor could simply sit back and watch the show as it unfolds, but take no action, why bother with a monitoring duty at all?

Alternatively, those sections can be construed, in light of the relevant ethical codes and the underlying purposes of the Good Clinical Practice Guidelines intended to protect the health and safety of study subjects, to require drug company sponsors to take an active role in reviewing, in real time, the information provided to them during the course of the study (including test results), and thereby assure that the clinical investigators are fulfilling their own responsibility to make medical decisions that are in the best interest of the study's subjects. If they do not, the sponsor can – and should – take action to protect the study subjects.

And the responsibilities of the sponsor should be comprehensive, in two differing respects: (1) In monitoring

every phase of the study; and (2) In protecting the health and safety of the subject, even if the danger arises from a pre-existing condition rather than a condition caused directly by the study drug.

As to the first aspect, the duty of the sponsor to assure that the health and safety of the trial subjects are protected, should encompass every procedural step in the study process. Thus, for example, even though a clinical investigator has primary responsibility to assure that only eligible candidates are admitted to the study, the scope of the sponsor's independent monitoring duty should extend to verifying that the screening test results confirm that the candidate is properly eligible under the protocol's mandates and, if the candidate is not, to direct the clinical investigator to exclude that candidate from the study. And, obviously, that same scope of the monitoring duty should continue throughout the conduct of the study, with real-time review and assessment of the on-going test results and intervention when an alarming medical condition develops.

As to the second aspect, the Court of Appeal's decision in this case outlined a very narrow interventional duty, despite the federal regulations, by limiting the sponsor's consideration only to medical issues related to the use of the drug itself. App., *infra*., 15a-16a. That decision declined, therefore, to impose on the sponsor any obligation to take action where the injuries result solely from the malpractice of the clinical investigator. App., *infra*., 20a-21a.

There are two problems with that approach. First, it is only through hindsight that it can be determined

whether an injury arising during the course of the study is the result of the investigational drug or something else. Allowing a study sponsor to make such a determination "on the fly," as it were, will only encourage sponsors to simply ignore the problem until it is too late. Indeed, one major purpose of clinical drug trials is to discover what the potential side effects of the investigational drugs are, in order to assess whether their risk/reward balance favors approval of the drug. See U.S. Drug Administration, For Patients, Learn About Drug and Device Approvals, The Drug Development Process.[18] If a sponsor can unilaterally decide during the course of the study that the deterioration of a subject's health is not related to the use of the test drug and that the sponsor therefore need not take action to assure that the issue is timely and properly addressed by the clinical investigator, that will only encourage such decisions and will result in detriment to the study subjects.

And second, the Court of Appeal's assessment simply makes no sense, legally or logically, because the decision grants drug manufacturers a broad swath of immunity for their own negligence if a physician or other healthcare provider is involved in the drug trial, which will virtually always be the case. Indeed, it is difficult to imagine a drug trial that does not involve a healthcare provider. Oddly, though, in this context, the cornerstone of the Court of Appeal's decision is that a physician's negligence, i.e., medical malpractice, is unforeseeable in a healthcare context. If that premise has any logic, it is not apparent. It calls to mind Captain Renault's feigned discovery in Rick's Casino that "I am shocked—shocked—to find

18. Available at https://www.fda.gov/ForPatients/Approvals/Drugs/ ucm405622.htm, accessed July 7, 2018

that gambling is going in here!" (Casablanca (Warner Bros. 1942).) The Court of Appeal feigns equal shock that malpractice can occur in drug trials.

The Court of Appeal acknowledged that a drug manufacturer has "a general duty not to harm the study participants as part of the clinical protocols." App., *infra*, 17a. But in the very next paragraph, the Court of Appeal largely eviscerated such a duty by holding that a drug manufacturer has no duty to treat a patient's preexisting disease or to intervene in "the medical care and decisions precipitated by Augustine's [the patient's] test result." *Ibid.* The threshold problem is that the Court of Appeal misframed the issue in order to support its desired result.

Context matters. As the jury necessarily found, Janssen knew, before subjecting Augustine to the drug trial, that he suffered from heart and liver conditions that made him unsuitable for the trial. But Janssen's clinical investigator failed to act promptly, and Augustine died. The key point is that Augustine's death was not unrelated to the study drug, because that was the drug that was being tested and why Augustine was in the study.

Equally or more troubling is the Court of Appeal's cornerstone conclusion that medical malpractice is unforeseeable in a medical setting, more specifically, a drug trial. One must wonder why a physician cannot be negligent in the course of a drug trial. Does a physician wave the Rod of Asclepius in a drug trial and somehow metamorphize into a deity incapable of error? Of course, not. Medical malpractice in a drug trial is both factually and legally foreseeable.

And that foreseeability imposes a duty on the drug study sponsor to fulfill its monitoring duty by taking reasonable steps to assure that, should such malpractice occur, the sponsor can intervene and protect the subject from the consequences of such malpractice.

Nor does such a rule place unwarranted burdens on the sponsor. Sponsors already have elaborate monitoring duties and systems in place. All that is required in order to fulfill the obligations imposed under the federal regulations is to require a sponsor to actually *perform* its monitoring duties reasonably and to use its power to intervene to protect the study subjects' safety. Doing so will assure the health and well-being of study subjects – which, is, after all the expressed goal of the applicable ethical standards, codes and guidelines.

One last point. Because of worries regarding the validity of the data derived from clinical trials, it is critically important that sponsors not be permitted to intervene in the management of a clinical trial study in a way that will invalidate or misrepresent the data produced from the study. A broad application of sections 312.50 and 312.56 may raise the concern that the monitoring duty could be used to manipulate or undermine the validity and effectiveness of the study. To the contrary, however, such a broad monitoring and intervention duty will actually enhance the validity and reliability of the data derived from the study. The strictures of a drug study protocol are designed to assure that accurate and valid data is derived from the study. If a study subject with a pre-existing condition is admitted to the study, that may well skew the data derived from the study in unknown or unanticipated ways. Further, if a subject's health deteriorates during

the course of the study – whether related to the use of the study drug or not – that will, again, skew the data derived from that subject's experience. Intervention by a sponsor to assure that drug study subjects are provided with referral to medical care outside the study parameters will not only assure that the health and safety of study subjects are paramount, but will also serve to clarify and provide more certainty with respect to the ultimate data generated.

C. This Case Provides An Ideal Vehicle For Establishing The Effective Parameters Of The Federal Regulations

The circumstances in this case present two different contexts in which to measure the scope of the federal regulations at issue. First, because the Court of Appeal determined that the injuries did not arise from the administration of the test drug itself, this case permits assessment of whether the monitoring and intervention requirements of the federal regulations require action on the part of a sponsor irrespective of whether the danger to the health and safety of a study subject is the result of the test drug or the malpractice of the clinical investigators hired by the sponsor. Second, because the claims in this case, at least in part, arise from the failure of the sponsor to adequately monitor and intervene in Augustine's enrollment into the study itself, this case offers an opportunity to examine the chronological scope of the monitoring and intervention duties, i.e., when do they start?

This case illustrates the critical importance of how these federal regulations should be interpreted and applied.

Because approximately 19 million Americans every year are put at risk during the course of clinical trials, it is essential that the nature and scope of a sponsor's duties to those clinical trial subjects is delineated and clarified. This case provides a proper vehicle for examining the issue presented and will, in fact, directly assist clinical trial sponsors in understanding and fulfilling their obligations.

CONCLUSION

For all the reasons stated, it is respectfully requested that this petition for writ of certiorari be granted.

Respectfully submitted,

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July 2018

APPENDIX

APPENDIX A — DECISION OF THE COURT OF APPEAL OF CALIFORNIA, SECOND APPELLATE DISTRICT, DIVISION FIVE, FILED JANUARY 3, 2018

IN THE COURT OF APPEAL OF CALIFORNIA
SECOND APPELLATE DISTRICT
DIVISION FIVE

B269318
(Los Angeles County Super. Ct. No. BC432264)

MARION LIU, AS SUCCESSOR IN INTEREST TO AUGUSTINE LIU, DECEASED,

Plaintiff and Appellant,

v.

JANSSEN RESEARCH & DEVELOPMENT, LLC,

Defendant and Respondent.

B270332
(Los Angeles County Super. Ct. No. BC432264)

MARION LIU, INDIVIDUALLY,

Plaintiff and Respondent,

v.

Appendix A

JANSSEN RESEARCH & DEVELOPMENT, LLC,

Defendant and Appellant.

January 3, 2018, Opinion Filed

Consolidated appeals from judgments of the Superior Court of the County of Los Angeles, Richard Fruin, Judge. Judgment in case number B270332 reversed. Judgment in case number B269318 affirmed.

INTRODUCTION

Plaintiff Marion Liu (Liu) and her husband, Augustine Liu, sued defendant Janssen Research & Development, LLC (JRD, defendant) for the wrongful death of their son, Augustine Liu II (Augustine).[1] At the time of his death, Augustine was participating in a drug trial for a new medication, Risperidone, and had received a one-milligram test dose.

Liu's husband died before trial, but Liu was permitted to proceed on his behalf as his successor in interest. Before the matter was submitted to the jury, however, the trial court determined the claims by Liu's husband for noneconomic damages did not survive his passing and entered judgment in defendant's favor against Liu in her successor capacity. Liu timely appealed (B269318).

1. To avoid confusion and with respect, we will refer to plaintiff's son as Augustine.

Appendix A

On Liu's individual wrongful death claim, a jury determined defendant was negligent and the negligence was a substantial factor in Augustine's death. Finding defendant 70 percent at fault, the net jury award to Liu for noneconomic damages was $5.6 million. Defendant timely appealed (B270332).

We consolidated the appeals from the two judgments. We conclude defendant did not owe Liu a duty of care to intervene in her son's medical care related to his preexisting heart disease. Defendant did owe a duty of care not to harm plaintiff's son insofar as administration of the drug itself, but the finding that the one-milligram test dose was a substantial factor in causing Augustine's death was not supported by sufficient evidence. Accordingly, we reverse the judgment on the jury verdict in Liu's favor against defendant.

It is unnecessary to discuss the merits of Liu's appeal from the adverse judgment in her successor capacity. Even if Liu's husband's wrongful death action for noneconomic damages survived his passing—and we agree with the trial court it did not—our duty and causation determinations foreclose any recovery by Liu in her successor capacity. We affirm the judgment in defendant's favor against Liu as her deceased husband's successor in interest.

Appendix A

FACTUAL BACKGROUND[2]

Augustine began treatment for mental illness in 2000, when he was 17 years old. He was diagnosed with schizophrenia in 2004 and was prescribed the antipsychotic drug, Seroquel. Dr. Madeleine Valencerina (Valencerina) became Augustine's treating psychiatrist in 2008, and she continued her patient on that medication.

In late 2008, defendant obtained FDA approval for a proposed drug study to analyze the safety and efficacy of a long-acting injectable formulation of its antipsychotic drug, Risperidone (study drug). Defendant selected Valencerina as the study's principal physician/investigator for the trial. Valencerina conducted clinical trials through Clinical Pharmacological Studies, Inc. (CPS), an entity in which she held an ownership interest. The FDA and an institutional review board approved Valencerina as the principal physician/investigator and also approved defendant's proposed study protocol and plan for monitoring the progress of the study.

Valencerina invited Augustine to participate in defendant's drug study. Augustine completed the informed consent and related paperwork in Valencerina's office and enrolled in the study on February 19, 2009.

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2. We include an abbreviated fact discussion at this point for context. A detailed recitation of the trial evidence is not required for us to analyze the dispositive issues on defendant's appeal.

Appendix A

Augustine underwent a screening electrocardiogram (EKG)[3] and blood test that day. Valencerina reviewed the screening EKG on February 20, 2009 and blood test results on February 21, 2009. The EKG was "abnormal," with the report indicating "sinus tachycardia; old myocardial infarction" and "non-specific T wave abnormalities possibly secondary to heart disease." The blood test revealed slightly elevated liver enzymes. Valencerina concluded the results were not clinically significant and, based on Augustine's otherwise normal physical examination and denial of a family history of cardiac disease, admitted him to the study.

On February 22, 2009, Augustine entered College Hospital, a psychiatric facility, for the first phase of the study. A second blood test followed on February 23, 2009. One-half hour after that test, Augustine was injected with a non-therapeutic one-milligram dose of the study drug to test for adverse reactions to any of its ingredients.

Within two hours of receiving the test dose, Augustine underwent a second EKG. The EKG report issued the same evening, and it indicated Augustine's cardiac condition had worsened. Valencerina reviewed the February 23, 2009 blood test report on February 24, 2009. Augustine's liver enzyme levels were much higher than they had been on February 19, 2009. To rule out laboratory error, Valencerina ordered a retest on February 24, 2009.

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3. "EKG" reflects the German spelling, Elektrokardiogramm. The record includes references to ECG, the English equivalent.

On February 25, 2009, after the retest confirmed Augustine's liver enzymes had risen alarmingly, Valencerina transferred him from College Hospital to Coast Plaza Doctors Hospital, an acute-care facility. There, Augustine was diagnosed with cardiomyopathy, pneumonia, failing liver function, and altered mental state. Augustine died on the afternoon of February 26, 2009. The cause of death was dilated cardiomyopathy in conjunction with other factors, including multiple organ failures and pneumonia.[4]

PROCEDURAL BACKGROUND

I. Summary Judgment for Defendant Partially Reversed

The fourth amended complaint (revised) alleged three causes of action against defendant (negligence, products liability, and negligent failure to warn). Also named with JRD in the negligence cause of action were Coast Plaza Hospital and the rest of the study defendants—Valencerina, Lau, CPS, College Hospital, and Collen. All study defendants except College Hospital and Collen successfully moved for summary judgment.[5]

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4. Dilated cardiomyopathy is a progressive condition that can take years to develop. Persons with the condition may be asymptomatic until it reaches a critical point, at which time the heart rapidly decompensates, causing reduced blood flow to the organs which begin to fail as a result.

5. The trial court denied the motion for summary judgment by study defendants College Hospital and Collen.

In response, Liu petitioned for writ of mandate.[6] The majority of a different panel in this Division granted in part Liu's request for extraordinary relief, reviving the second cause of action for negligence as to JRD, Valencerina, Lau, and CPS. (*Liu v. Superior Court* (Apr. 19, 2013, B246461) [nonpub. opn.] (*Liu I*).)[7] In that opinion, the majority specifically did not reach issues of agency or vicarious liability vis-à-vis JRD. (*Liu I*, 2013 Cal. App. Unpub. LEXIS 2766 at *8.)

Turning to the declarations of plaintiff's experts in opposition to the summary judgment motions, the majority in *Liu I* agreed "'[t]he rule that a trial court must liberally construe the evidence submitted in opposition to a summary judgment motion applies in ruling on both the admissibility of expert testimony and its sufficiency to create a triable issue of fact.'" (*Liu I*, 2013 Cal. App. Unpub. LEXIS 2766, at *22.) The majority then determined the declarations by plaintiff's experts—a pharmacologist and a cardiologist—were sufficient to defeat summary judgment on the negligence theory: "Even if the evidence

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6. She also appealed from the ensuing judgments in favor of these defendants, but voluntarily dismissed that appeal (B248529). Liu filed a second appeal in 2015 as successor in interest to her son's estate. This court dismissed that appeal on jurisdictional grounds in an unpublished opinion, *Liu v. Janssen Research & Development, LLC* (Mar. 23, 2017, B266368).

7. The petition was not granted as to the cause of action against Valencerina for dependent adult abuse and the causes of action against defendant for strict products liability for failure to warn and negligent failure to warn. (*Liu I*, 2013 Cal. App. Unpub. LEXIS 2766, at *27.)

regarding [the one milligram test dose of] Risperidone should have been excluded as to causation, drawing the necessary inference in the light most favorable to the opposing party [citation] the improper care afforded [Augustine] was sufficient to support the causation conclusion, if such support is necessary. The expert's opinion on causation should not have been omitted or deemed insufficient at this stage." (*Liu I*, 2013 Cal. App. Unpub. LEXIS 2766, at *26.) In the footnote appended to the last sentence of the foregoing excerpt, the majority also advised, "We render no opinion on the merits or on evidentiary issues that might arise at trial." (*Liu I*, 2013 Cal. App. Unpub. LEXIS 2766, at *26, fn. 9.)

II. New Summary Adjudication Motion in the Trial Court

Plaintiff returned to the trial court and proceeded on a solitary cause of action for negligence. The negligence allegations referenced Valencerina, Lau, CPS, College Hospital, and Collen and described various acts of medical malpractice, at least some of which were alleged to have violated defendant's drug study protocols. There were no allegations, however, specifically directed to any independent acts of misfeasance or nonfeasance by JRD.

Three study defendants—College Hospital and physicians Valencerina and Lau—filed a new motion for summary adjudication seeking a ruling that the second cause of action was for medical malpractice only and subject to the noneconomic damages limitation in Medical Injury Compensation Reform Act (MICRA). The trial

court granted the motion, thereby imposing the MICRA cap on any recovery by plaintiff as to those defendants.[8]

The trial court denied defendant's request for joinder in the summary adjudication motion, finding defendant sought to raise issues beyond the scope of the original motion. In so doing, however, the trial court made the following observation: "As a general proposition, . . . the Court would note its agreement with [defendant's] argument to the effect that, under [*Lathrop v. Healthcare Partners Medical Group* (2004) 114 Cal.App.4th 1412, 8 Cal. Rptr. 3d 668], MICRA's limitations on liability apply where [a] plaintiff seeks to hold a principal vicariously liable for the acts of its employees/agents."

III. Trial Against Defendant

Eventually, only JRD remained a defendant under the negligence theory. Defendant filed a number of motions in limine, including two to exclude trial testimony by plaintiff's cardiologist and pharmacologist as to general and specific causation, i.e., the administration of the one-milligram test dose contributed to decedent's demise. The trial court denied both motions, paving the way for cardiologist Jeffrey Goodman, M.D., and pharmacologist and toxicologist Laura Massey Plunkett, Ph.D., to testify.

The issues presented in defendant's appeal do not require us to summarize the 13 days of trial testimony.

8. Civil Code section 3333.2 limits noneconomic damages in medical malpractice actions to $250,000. Other than burial expenses, plaintiff sought only noneconomic damages.

Suffice it to say, plaintiff presented evidence, including several expert opinions, to demonstrate Augustine was not competent to enroll himself in the drug study;[9] defendant, who also received Augustine's EKG and blood test results, did nothing to intervene in his care; defendant failed to intervene in the decision to administer the one-milligram test dose; and that dose was a substantial factor in Augustine's death.

Before the close of evidence, defendant moved to strike Goodman's testimony and moved for nonsuit on the causation issue. The trial court denied both motions.

At the close of evidence, defendant orally moved for a partial directed verdict, arguing Valencerina, as the study physician/investigator, was not defendant's agent for purposes of finding defendant vicariously liable for any medical negligence by Valencerina:

> [Defense counsel]: [W]e think . . . agency is simply not something that can be found [on] the facts and circumstances of this case given . . . that the focus here is on the medical care provided by Dr. Valencerina, [and] that Dr. Valencerina had an obligation to exercise her independent medical judgment in making medical decisions on behalf of [decedent] in treating any conditions which arose during the course of the study. Dr. Valencerina had

9. These allegations formed the basis for the first cause of action against Valencerina, not defendant. But the trial court eliminated the first cause of action in granting Valencerina's motion for summary judgment, and this court did not revive it.

> a fiduciary relationship with [decedent] which is inconsistent with the type of control that's needed for a finding of agency. The structure of clinical research studies themselves, including the way they're required to be structured under the federal regulations, makes it important and clear that there needs to be some independence between principal investigator and sponsor of the study, and also makes it clear that medical care to be given to individual subjects during the course of the study is the responsibility of the principal investigator and is not the responsibility of the study sponsor. . . .
>
> And for those reasons and for the reasons we've stated earlier, we believe that [a verdict on] the issue of agency should be directed in favor of [defendant].

Plaintiff opposed the motion, arguing the trial court should submit the issue of agency to the jury. The trial judge disagreed with plaintiff and granted the motion in part[10]:

> The Court: . . . My view of the matter is that a physician/independent investigator is not an agent of the sponsor and there [are] a number of reasons for that.

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10. Plaintiff does not challenge any of the trial court's findings or conclusions in support of the order granting a partial directed verdict. She has consistently maintained the action against defendant is based on its own negligence, not any vicarious liability stemming from Valencerina's medical malpractice.

> To begin with, the FDA is trying to obtain unbiased information. I believe that's one of the reasons that it requires a protocol that has some independent oversight with respect to the way in which the study is conducted. I think that's one of the functions of the [institutional review board]. It's also one of the reasons that the protocol is approved by the FDA.
>
> Secondly, I think that a physician in a clinical trial, at least as described in this case, is making judgments which are independent of the sponsor's interests and are intended to be in the interest of the patient or the subject for the purpose of protecting the subject from adverse consequences of the trial. I think that the physician in her or his unfettered discretion recommends inclusion of the subject in the trial and I think that the physician's responsibility during the trial to monitor the reaction of the subject to the environment and to the test drug is evidence that the physician is making decisions which are independent of the program or the structure imposed by the sponsor.
>
> Consequently, . . . I am going to hold that the physician/independent investigator is not the agent of [defendant].

In granting a partial directed verdict at the close of evidence, the trial court identified two negligence theories that plaintiff could pursue against defendant: "I

do think that a sponsor has independent responsibilities to the patient, and [defendant] in this particular structure has seen to it that it would obtain information about the reaction of the subject to the test drug and to the physical condition of the subject such that it had reasonably assumed responsibilities to make its own judgment separately from the physician as to whether or not this subject should stay in the program [or] should be -- if the circumstances warranted taken out of the program and provided medical care for the subject's benefit."

Rephrasing the trial judge's words, one issue was couched in terms of defendant's independent duty to intervene in Augustine's medical care, even if the medical issues preexisted, or were unrelated to, the study itself. Another was based on defendant's duty to monitor the administration of the study drug, including whether the one-milligram test dose was a substantial factor in causing Augustine's death. This ruling meant all the evidence concerning Augustine's competency to decide to participate in the study ultimately was not relevant to the issue of whether defendant owed a duty to decedent.[11] However, based on the trial court's decision, the jury was permitted to consider whether defendant had an independent duty to intervene and timely refer Augustine

11. In *Liu I*, plaintiff "[did] not say the participation in the study per se caused or contributed to Liu's death; rather it was the decision to admit him to the study rather than to refer him immediately for a cardiac workup after the initial ECG and blood test results demonstrated the existence of serious cardiac problems and elevated liver enzymes; and why Liu's deteriorating condition was ignored." (*Liu I*, 2013 Cal. App. Unpub. LEXIS 2766, at *13.)

to a cardiologist or hepatologist or transfer him to an acute care facility for treatment of his preexisting heart disease.

The jury was presented with a special verdict form that asked whether defendant and Valencerina[12] were negligent and, if so, whether the negligence of either was "a substantial factor in causing the death of Augustine Liu II." The jury answered these four questions in the affirmative. The jury awarded Liu $3 million in general damages and $5 million in future damages. It assessed the percentages of fault at 70 percent for defendant and 30 percent for Valencerina. Based on the verdict, the trial court entered a judgment against defendant in the amount of $5.6 million.

DISCUSSION

I. Issues—Overview

Defendant raises a number of appellate issues. It first challenges the trial court's conclusion that it owed a duty to intervene in Augustine's medical treatment for his preexisting heart disease. Defendant next contends plaintiff's claims concerning Augustine's recruitment, consent, and enrollment in the study could not provide a basis for the jury's verdict. Defendant also challenges the sufficiency of the causation evidence, i.e., the one-milligram test dose was a substantial factor in Augustine's death. Finally, defendant contends misconduct by plaintiff's trial

12. As noted above, the basis for Valencerina's liability was necessarily medical malpractice.

counsel and evidentiary errors compel reversal or, at a minimum, remand for a new trial.

The issue based on recruitment, consent, and enrollment is easily resolved. Several years before trial, any potential for Valencerina to be liable based on the circumstances of Augustine's enrollment in the study (first cause of action against her for dependent adult abuse) was eliminated when the trial court granted her motion for summary judgment. Although evidence on these questions was received during trial, the trial court granted defendant's motion for a partial directed verdict and determined Valencerina was responsible for the enrollment decision, but did not act as defendant's agent in doing so.[13]

We conclude as a matter of law that defendant undertook a general duty not to harm Augustine as part of the clinical study. That duty encompassed administration of the test dose. As a matter of law, we also conclude the scope of that duty did not extend to diagnosing or treating Augustine's preexisting heart disease or intervening in

13. We repeat the relevant portion of the trial court's ruling: "[A] physician in a clinical trial, at least as described in this case, is making judgments which are independent of the sponsor's interests and are intended to be in the interest of the patient or the subject for the purpose of protecting the subject from adverse consequences of the trial. I think that the physician in her or his unfettered discretion recommends inclusion of the subject in the trial and I think that the physician's responsibility during the trial to monitor the reaction of the subject to the environment and to the test drug is evidence that the physician is making decisions which are independent of the program or the structure imposed by the sponsor."

his medical care and the medical decisions related to that condition.

We also conclude the trial court should have stricken the one-milligram test dose/causation testimony by expert Goodman. That testimony was insufficient to support a finding the test dose was a substantial factor in Augustine's death. Although defendant did not make a similar motion to strike Plunkett's testimony, her opinion was nonetheless insufficient to establish causation.

These conclusions compel reversal and we do not address defendant's other appellate issues.

II. Duty

A. Existence and Scope of Duty: Questions of Law Subject to *De Novo* Review

"The existence and scope of duty are legal questions for the court." (*Merrill v. Navegar, Inc.* (2001) 26 Cal.4th 465, 477, 110 Cal. Rptr. 2d 370, 28 P.3d 116.) As explained below, "foreseeability is a crucial factor in determining the existence of duty [citation], and . . . '[f]oreseeability, when analyzed to determine the existence and scope of a duty, is a question of law to be decided by the court.'" (*Delgado v. Trax Bar & Grill* (2005) 36 Cal.4th 224, 237, 30 Cal. Rptr. 3d 145, 113 P.3d 1159, quoting *Ann M. v. Pacific Plaza Shopping Center* (1993) 6 Cal.4th 666, 674, 25 Cal. Rptr. 2d 137, 863 P.2d 207.) We review the duty issue *de novo*. (*Coburn v. Sievert* (2005) 133 Cal.App.4th 1483, 1492, 35 Cal. Rptr. 3d 596.)

Preliminarily, we note that crafting a description of the duty issue in any negligence case is not a mere exercise in semantics. The description itself provides the framework for the appropriate duty analysis.

For example, plaintiff asserts defendant had "a general duty to assure that [Augustine's] health and safety were protected." She accordingly invokes Civil Code section 1714 and the duty analysis set forth in a long line of decisions spanning almost 50 years from *Rowland v. Christian* (1968) 69 Cal.2d 108, 70 Cal. Rptr. 97, 443 P.2d 561 to *Cabral v. Ralphs Grocery Co.* (2011) 51 Cal.4th 764, 122 Cal. Rptr. 3d 313, 248 P.3d 1170 (*Cabral*) and *Kesner v. Superior Court* (2016) 1 Cal.5th 1132, 210 Cal. Rptr. 3d 283, 384 P.3d 283 (*Kesner*). Under this analysis, the existence of a duty is the rule and courts will find an exception only "where 'clearly supported by public policy.'" (*Cabral, supra*, 51 Cal.4th at p. 771.)

We agree as a matter of law that defendant, as the drug manufacturer/sponsor of a clinical trial, undertook a general duty not to harm the study participants as part of the clinical trial protocols. Administration of the Risperidone test dose fell within the scope of this duty, and we will discuss the sufficiency of the evidence to support liability under this duty of care in part III, *infra.*

But the significant legal question that must be analyzed in this case is whether the general duty not to harm study participants encompassed a duty to diagnose or treat Augustine's preexisting, life-threatening heart disease and to intervene in the medical care and decisions precipitated by Augustine's abnormal test results. For the reasons that follow, we conclude it did not.

B. Analysis

Imposition of the more expansive duty advocated by plaintiff depends on whether it was foreseeable to defendant, as the study sponsor, that the study physicians would misdiagnose and fail to treat Augustine's life-threatening cardiac disease that also affected other organs.

Lack of foreseeability was pivotal in *Jackson v. AEG Live, LLC* (2015) 233 Cal.App.4th 1156, 183 Cal. Rptr. 3d 394 (*Jackson*). There, a concert tour promoter, at the request of the performer, agreed to pay for a physician to provide general medical services to the performer during the tour to ensure the performer's overall health. The performer died from a fatal overdose of medication administered by the physician during preparations for the tour, and his heirs sought to hold the promoter liable on, *inter alia*, a common law negligence theory. (*Id.* at pp. 1165-1171, 1173.)

On appeal from an order summarily adjudicating the negligence claim in favor of the promoter, this court affirmed the trial court's determination the promoter did not have a duty to protect the performer from the medical malpractice or criminal negligence of the physician. The physician's negligent medical decision to administer a dangerous sedative without proper oversight was not a foreseeable consequence of the promoter's general instructions to the physician to maintain the performer's overall health. (*Jackson, supra*, 233 Cal.App.4th at pp. 1174-1175.)

In this case, although FDA regulations impose on study sponsors a general duty to monitor the progress of their studies to ensure compliance with study protocols and the health and safety of participants, that duty is intended to protect participants generally from foreseeable harm caused by the drug studies themselves, including participants' adverse reactions to study medications. That is the duty defendant undertook.

The jury found negligence by both Valencerina and defendant contributed to Augustine's death. Based on the trial court's rulings, Valencerina's negligence was necessarily medical malpractice, e.g., the study physicians' negligent medical decisions in response to the abnormal medical tests, the first clinical signs of Augustine's preexisting, undiagnosed cardiac disease. As in *Jackson, supra*, 233 Cal.App.4th 1156, it is not foreseeable to a study sponsor that study physicians with the primary responsibility for participants' health and safety will fail to recognize, diagnose, and properly treat preexisting, life-threatening conditions that first manifest during drug studies, as Augustine's condition did here.[14]

Dekens v. Underwriters Laboratories Inc. (2003) 107 Cal.App.4th 1177, 132 Cal. Rptr. 2d 699 (*Dekens*) is also

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14. Plaintiff contends there was no physician-patient relationship between the study physicians and Augustine. But the trial court ruled the negligence cause of action against the medical professionals was based on medical malpractice only because a physician-patient relationship existed during the study. In granting the directed verdict on the agency issue, the trial court found Valencerina, as the study physician/investigator, had primary responsibility for Augustine's health and safety during the study.

instructive. The plaintiffs' decedent in *Dekens* repaired small appliances. He died of mesothelioma, contracted as a result of exposure to asbestos, which was then a not-uncommon component in small electrical appliances. His heirs sued Underwriters Laboratories (U.L.) on a negligent undertaking theory, contending the defendant undertook a certification process to safeguard the health of consumers, including those individuals who repaired U.L.-certified appliances. (*Id.* at p. 1179.)

U.L. successfully moved for summary judgment, and the Court of Appeal affirmed. The appellate panel posed two threshold questions: "Did U.L. undertake to provide services [to the decedent] and, if so, what was the scope of that undertaking?" (*Dekens, supra*, 107 Cal.App.4th at p. 1182.) The Court of Appeal agreed U.L. tested and certified appliances for safety based on electrical shock, heat, and fire, but found the undertaking did not include a "guarantee [of] safety from cancer-causing asbestos." (*Id.* at p. 1187.) The appellate panel explained, "U.L. met its burden on summary judgment by showing through admissible evidence that it never undertook to test small appliances for medical safety or to certify the appliances would not cause cancer. Plaintiffs failed to show a triable issue of material fact regarding the existence and scope of any such undertaking by U.L. The trial court properly granted summary judgment." (*Id.* at p. 1180.)

Here, defendant undertook the general duty to ensure study participants' health and safety during the study. That undertaking did not extend to protecting participants from unforeseeable medical malpractice

by study physicians in response to undiagnosed, life-threatening conditions. Like the defendant's undertaking in *Dekens*, JRD's undertaking as the drug study sponsor cannot reasonably be construed to include a "guarantee of safety" from any and all acts of medical malpractice by physicians who bear the primary responsibility for safeguarding the health of study participants.

The defendants in *Jackson* and *Dekens* prevailed in summary adjudication proceedings, while defendant here lost in a jury trial. Still, "[t]he existence of a duty of care is . . . decided on a case-by-case basis. [Citations.] '"While it is the province of the jury, as trier of fact, to determine whether an unreasonable risk of harm was foreseeable under the particular facts of a given case, the . . . court must still decide as a matter of law whether there was a duty in the first place, even if that determination includes a consideration of foreseeability."' (*M.W. v. Panama Buena Vista Union School District* (2003) 110 Cal.App.4th 508, 516, 1 Cal. Rptr. 3d 673 (*M.W.*).)

The verdict is a consideration in our analysis, however; and evidentiary conflicts concerning foreseeability would be resolved in plaintiff's favor. (*M.W., supra*, 110 Cal. App.4th at p. 516.) But the foreseeability evidence was not in conflict. Other than the abnormal EKG and elevated liver enzymes, Augustine did not present himself for participation in the study with any other symptoms. His advanced cardiomyopathy had not yet been diagnosed. The delay in diagnosing and treating Augustine's serious cardiac disease was not a foreseeable risk that would support an expanded scope of the general duty of care owed by defendant not to harm study participants.

In support of her duty analysis, plaintiff relies on *Kesner, supra*, 1 Cal.5th 1132 and *Coffee v. McDonnell-Douglas Corp.* (1972) 8 Cal.3d 551, 105 Cal. Rptr. 358, 503 P.2d 1366 (*Coffee*). However, neither decision provides authority for the broad scope of the duty plaintiff is advancing on appeal.

In *Kesner*, our Supreme Court determined employers and landowners owe a duty of care to prevent secondary exposure to asbestos that occurs when an individual carries the toxic fibers home on his or her person or clothing. (*Kesner, supra*, 1 Cal.5th at p. 1140.) The court in that case analyzed the duty issue under Civil Code section 1714 and the factors articulated in *Rowland, supra*, 69 Cal.2d 108. The foreseeability analysis was straightforward: An employer or landowner should reasonably foresee that individuals directly exposed to asbestos would, through their person, clothing, or other items, act as vectors and transfer asbestos to household members. (*Kesner, supra*, 1 Cal.5th at p. 1140.) The Supreme Court then determined no public policy considerations justified an exception to the general rule of duty in Civil Code section 1714. (*Id.* at p. 1156.)

The foreseeability factor in this case is significantly more tenuous: It is not reasonably foreseeable to a drug study sponsor that the response by study physicians—who, as the trial court found, are primarily responsible for the health and safety of participants while enrolled in drug studies—to a patient/participant's preexisting and undiagnosed disease, unrelated to the clinical trial, would fall below the standard of care for a medical practitioner.

Appendix A

In *Coffee, supra*, 8 Cal.3d 551, the defendant aircraft manufacturer required the plaintiff to undergo a pre-employment physical examination and blood test to determine his fitness to serve as a test pilot. (*Id.* at pp. 553-554.) The physicians who examined the plaintiff and cleared him for pilot duty were employees of the defendant. No medical practitioner reviewed the blood test results, however, because a secretary filed them away without first providing them to the physicians. (*Id.* at p. 555.) The blood test results indicated a likelihood the plaintiff was suffering from a disease serious enough that he would not have been hired. (*Id.* at pp. 555-556.)

Seven months later, the plaintiff was diagnosed with cancer. (*Coffee, supra*, 8 Cal.3d at p. 554.) He sued McDonnell-Douglas for failing to inform him of the results of his blood test and the three physician employees for failing to discover and disclose his preexisting disease. (*Id.* at pp. 554-555.) The jury returned a verdict in favor of the physicians, but against McDonnell-Douglas "on the negligence of other corporate employees [the secretary]" and the defendant appealed. (*Id.* at p.p. 555-556.)

The Supreme Court rejected the defendant's argument that it owed no duty to the plaintiff, as a prospective employee, to ascertain whether he was physically fit to be hired. (*Coffee, supra*, 8 Cal.3d at p. 557-558.) The court concluded a prospective employer generally owes no duty to a prospective employee to ascertain whether the latter is fit for employment. But an employer who assumes such a duty may be liable if the task is performed negligently. (*Id.* at p. 557.)

The principal distinguishing factor is that in *Coffee* the negligent actors were employees, i.e., agents, of the defendant, while that was not the case here. Also, *Coffee* presented no issue concerning the scope of the employer's undertaking, as it was undisputed the employer voluntarily undertook to ascertain the plaintiff's fitness to perform his job duties. In this case, the study physicians, not defendant, voluntarily assumed the primary responsibility for Augustine's health and safety during the study, including the responsibility to competently diagnose and treat any preexisting, life-threatening diseases.

III. Sufficiency of the Evidence That the One-Milligram Test Dose Was a Substantial Factor in Augustine's Death

As detailed above, the trial court ruled defendant had an independent duty to monitor Augustine's reaction to the single test dose and remove him from the study if the results warranted that action. We agree. Defendant asserts the evidence was insufficient to establish the single test dose was a substantial factor in Augustine's death. According to defendant, the testimony of plaintiff's causation experts that Risperidone can cause heart failure generally and that it did so specifically in this case, was speculative and otherwise unsupported by the necessary factual basis. Again, we agree.

A. Procedural Background—Causation

Defendant sought to exclude the causation testimony of plaintiff's experts Plunkett and Goodman, arguing their deposition testimony demonstrated they did not

have a factual basis for their conclusion that the one-milligram dose of Risperidone contributed to Augustine's death.[15] The trial court denied the motions.[16] Both experts then testified the test dose was a substantial factor in Augustine's death.

Defendant moved to strike Goodman's causation testimony as it related to the test dose and also moved for a partial nonsuit on the causation issue on the basis the experts' test-dose causation opinions were conclusory and lacked factual support. The trial court denied both motions and sent the causation issue to the jury. The causation testimony of Plunkett and Goodman was conclusory and based on speculation rather than facts. It lacked the requisite probative value to meet plaintiff's evidentiary burden on the causation issue and was insufficient to support plaintiff's verdict.

1. Plunkett, Ph.D.

When asked if it was her "opinion . . . in this case that [Augustine's] death may have been contributed by the 1-milligram [dose] of [Risperidone]?", Plunkett responded,

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15. Plaintiff called eight medical experts to testify at trial.

16. "Trial judges have substantial gatekeeping responsibility when it comes to expert testimony. . . .' [¶] Based on the provisions of Evidence Code sections 801 and 802, [footnote omitted] 'the trial court act[s] as a gatekeeper to exclude expert opinion testimony that is (1) based in matter of a type on which an expert may not reasonably rely, (2) based on reasons unsupported by the material on which the expert relies, or (3) speculative." (*Sargon Enterprises, Inc. v. University of Southern California* (2013) 215 Cal.App.4th 1495, 1504, 156 Cal. Rptr. 3d 372.)

"Well, I'm not here to talk about his cause of death. I'm not the physician in the case. But I do believe the [Risperidone] posed a risk to his health, and what I saw was consistent with [Risperidone] being a contributing factor of his death, yes." Defense counsel did not object.

Plaintiff's counsel persisted: "Q. So to be very clear, in this case you are telling this jury that this 1-milligram injection of Risperidone given to [Augustine] on Monday morning could have had some contribution to his death on Thursday, the 26th, is that correct? [¶] A. Yes, based on the existence of another cardiotoxic drug [Seroquel] already in his system and the fact he had an abnormal EKG before he took the drug." [¶] "Q. And then [defendant] picks [Augustine] up for this clinical trial, knows he's got a bad heart from the EKG, knows he's on Seroquel, which is not good for the heart, injects him with a drug that's got known cardiac risk problems, and he's dead two days later? [¶] A. Yes. That's what happened. [¶] Q. Does that all make sense in the context of this is something that's consistent when you inject a cardiotoxic drug into a man that's got a bad heart, and he's already on a drug that's got cardiac risks; is that what you mean by that? [¶] A. Yeah. Yes, exactly." Defense counsel did not object.

Plunkett added that Risperidone could cause abnormal heart rhythms in the general population, including arrhythmias: "[Risperidone] was known to affect heart function; specifically it could affect blood pressure; and it could also affect the conduction system, the way that the heart controls its beat. So when I was talking about arrhythmias, it's that idea . . . ."

Plunkett further testified patients with heart problems like Augustine who are administered Risperidone can experience abnormal heart rhythms that can lead to sudden death and Augustine's death was consistent with the known toxicities of Risperidone: "Q. And we went through the data earlier that people with problematic hearts who get Risperidone, they can have problems? [¶] A. Yes, that's correct. [¶] Q. They can die? [¶] A. Yes. [¶] Q. They can have arrhythmias which lead to sudden death? [¶] A. Yes. [¶] Q. And based upon what . . . you saw in your review of these records as to how [Augustine] ultimately passed, was it consistent with everything that we've seen in all [the] scientific information? [¶] . . . [¶] Yes. What happened [to Augustine] would be consistent with the known toxicities of the particular drug."

2. Goodman, M.D.

Goodman also concluded the single test dose of Risperidone was a substantial factor in Augustine's death. "Q. Dr. Goodman, . . . do you have an expert opinion as to whether or not the 1 milligram injected short-acting, immediate-release dose that he received on the 23rd of February 2009 was a substantial factor that contributed to [Augustine suffering] . . . congestive heart failure? [¶] . . . [¶] Yes, I do. [¶] Q. . . . And can you tell the jury what that opinion is? [¶] A. Yes, I think that in this gentleman with severe heart muscle dysfunction, liver failure, impending kidney failure, that the addition of a medication such as [Risperidone], which is metabolized by the liver and to some degree the kidney, I think that that medication actually pushed him over the edge and

contributed -- was a substantial contributing factor to his ultimate demise." [¶] . . . "A. So in his specific case with heart muscle dysfunction, with severe liver failure, with kidney dysfunction, this 1-milligram dose did contribute to his death." [¶] . . . [¶] Q. "So the question you were looking at is not whether he had dilated cardiomyopathy and the 1 milligram. It's having dilated cardiomyopathy, did getting this injection, was it a substantial factor in putting him over the edge and causing his death? [¶] A. Correct. [¶]

On cross-examination, Goodman denied Augustine experienced an arrhythmia as a result of the test dose. "Q. Your claim is that [Augustine] sustained some type of an arrhythmia due to the single 1-milligram dose; correct? [¶] A. No. My testimony is that [Risperidone] was a substantial contributing factor in this specific case, in this 25-year-old with severe heart failure, kidney failure, and liver failure, that the addition of this 1-milligram dose of [Risperidone] contributed to his demise. [¶] . . . A. [T]he medication is known to be cardiotoxic. It's contraindicated in patients with this type of condition and . . . it did contribute to [Augustine's] demise. He probably died an arrhythmic death. It was a combination of pump, plus arrhythmia. So in a way he did die from an irregular heart rhythm, but we all die from an irregular heart rhythm. Eventually your heart stops . . . ."

Goodman, however, admitted on cross-examination that he could not identify how the single test dose caused an injury to Augustine that contributed to his death. "Q. Are you able to identify for this jury the specific mechanism of injury that you claim the single 1-milligram

dose caused in [Augustine]? [¶] A. No, I'm not, and neither is [defendant]. In your publications, it says the mechanism of cardiac issues is unknown.

B. Experts' Causation Opinions re: Test Dose Did Not Constitute Substantial Evidence

Jennings v. Palomar Pomerado Health Systems, Inc. (2003) 114 Cal.App.4th 1108, 8 Cal. Rptr. 3d 363 (*Jennings*) and the authorities it cites provide the blueprint for our analysis of the sufficiency of the evidence to support expert testimony as to causation. "'The law is well settled that . . . causation must be proven within a reasonable medical probability based [on] competent expert testimony. Mere possibility alone is insufficient to establish a prima facie case.'" (*Id.* at p. 1118.) "[T]he plaintiff must offer an expert opinion that contains a reasoned explanation illuminating why the facts have convinced the expert, and therefore should convince the jury, that it is *more probable than not* the negligent act was a cause-in-fact of the plaintiff's injury." (*Ibid.*)

It is equally well-established an expert's opinions based on assumptions without evidentiary support or on speculative or conjectural factors have no evidentiary value and may be excluded. (*Jennings, supra*, 114 Cal. App.4th at p. 1117.) Similarly, when an expert's opinion lacks a reasoned explanation that connects the factual predicates to the ultimate conclusion, the opinion has no evidentiary value. In short, an "'expert opinion is worth no more than the reasons upon which it rests.'" (*Ibid.*) Likewise, an expert's conclusory opinion, without

an explanation of how the expert "employed his or her superior knowledge and training to connect the facts with the ultimate conclusion, does not assist the jury." (*Ibid.*)

Based on our review of the causation testimony of Plunkett and Goodman, we conclude there was insufficient evidence that administration of the single, one-milligram dose of the study drug was a substantial factor in causing Augustine's death. As defendant points out, although Plunkett testified Risperidone could cause electrical or heart rhythm problems in the general population, such as arrhythmias, there was no evidence Augustine died from heart issues associated with arrhythmias or heart rhythm problems.

Instead, the evidence showed Augustine died from a mechanical or pump failure due to severe cardiomyopathy, i.e., his heart reached a crucial point where it could no longer pump a sufficient volume of blood to supply his vital organs. Plunkett concluded the test dose played a role in contributing to Augustine's demise, but she failed to provide a factual basis to support that belief and freely admitted she was not qualified to render such an opinion.[17] Her conclusion did not rise to the level of substantial evidence under *Jennings, supra*, 114 Cal.App.4th 1108. (See also *People v. Wright* (2016) 4 Cal.App.5th 537, 545, 208 Cal. Rptr. 3d 686 ["'when an expert bases his or her conclusion on factors that are "speculative, remote or conjectural," or on "assumptions . . . not supported by the

17. "I'm not here to talk about [Augustine's] cause of death. I'm not the physician in the case."

record," the expert's opinion "cannot rise to the dignity of substantial evidence" and a judgment based solely on that opinion "must be reversed for lack of substantial evidence"""].)

Goodman also concluded the test dose was a substantial factor in Augustine's death. Like Plunkett, he provided no factual basis for the opinion. (*Jennings, supra*, 114 Cal. App.4th at p. 1117.) Distilled to its essence, Goodman's opinion acknowledged Augustine was still on his daily 800-milligram dose of Seroquel, another cardiotoxic drug, and had a severely diseased heart that compromised his liver and kidneys. Nevertheless, Goodman unequivocally concluded the administration of *any amount* of the test drug—including the one-milligram dose Augustine actually received—was sufficient to push Augustine "over the edge." Goodman, however, did not provide a reasoned explanation that illuminated for the jury how or why such a low dose of Risperidone could have had such a substantial effect on Augustine's life-threatening disease. Instead, as Goodman admitted on cross-examination, he could not specifically identify how or why the test dose likely was a substantial factor in the death of an individual with such advanced cardiomyopathy. Assumptions and conclusions not based on facts or based merely on conjecture and speculation are not evidence of the ultimate fact they are intended to prove.

As the court in *Bockrath v. Aldrich Chemical Co., Inc.* (1999) 21 Cal.4th 71, 79, 86 Cal. Rptr. 2d 846, 980 P.2d 398, observed, "In cases like the one before us, presenting complicated and possibly esoteric medical causation

issues, the standard of proof ordinarily required is "'a reasonable medical probability based upon competent expert testimony that the defendant's conduct contributed to [the] plaintiff's injury.'" [Citations.] [¶] 'The substantial factor standard is a relatively broad one, requiring only that the contribution of the individual cause be more than negligible or theoretical.' [Citation.] Thus, 'a force which plays only an "infinitesimal" or "theoretical" part in bringing about injury, damage, or loss is not a substantial factor' . . . ." Here, at best, plaintiff's causation experts opined as to a theory that might have contributed to Augustine's death, but did not provide the necessary factual basis to qualify that theory as substantial evidence.

IV. Appeal from Judgment Against Liu as Her Husband's Successor in Interest

The judgment against Liu in her capacity as her husband's successor in interest was based on the trial court's ruling that claims for noneconomic damages do not survive when the plaintiff in a wrongful death action dies before judgment. Our conclusions that defendant owed no duty of care to intervene in Augustine's medical care related to his preexisting heart disease and there was insufficient evidence of causation to support liability based the duty of care defendant did owe, insofar as administration of the Risperidone test dose was concerned, are dispositive of Liu's appeal.

We note only that the traditional pecuniary/nonpecuniary view of wrongful death damages for loss of a decedent's society and companionship (see, e.g.,

Krouse v. Graham (1977) 19 Cal.3d 59, 68, 137 Cal. Rptr. 863, 562 P.2d 1022) shifted; wrongful death damages for loss of a decedent's society and companionship are now characterized as noneconomic (*Boeken v. Philip Morris USA, Inc.* (2010) 48 Cal.4th 788, 795-796, 108 Cal. Rptr. 3d 806, 230 P.3d 342).[18] And "'noneconomic damages do not survive if the plaintiff dies before judgment.'" (*Sullivan v. Delta Air Lines, Inc.* (1997) 15 Cal.4th 288, 300, 63 Cal. Rptr. 2d 74, 935 P.2d 781.)

DISPOSITION

The judgment in favor of plaintiff individually is reversed. The judgment against plaintiff as the successor in interest to her deceased husband is affirmed. Defendant is awarded costs on both appeals.

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18. See also Civil Code section 1431.2, subdivision (b): "(1) For purposes of this section, the term 'economic damages' means objectively verifiable monetary losses including medical expenses, loss of earnings, burial costs, loss of use of property, costs of repair or replacement, costs of obtaining substitute domestic services, loss of employment and loss of business or employment opportunities. [¶] (2) For the purposes of this section, the term '*non-economic damages' means* subjective, non-monetary losses including, but not limited to, pain, suffering, inconvenience, mental suffering, emotional distress, *loss of society and companionship, loss of consortium*, injury to reputation and humiliation." (Italics added.)

CACI No. 3921 defines the noneconomic damages a wrongful death plaintiff may recover to include the loss of the decedent's "love, companionship, comfort, care, assistance, protection, affection, society, [and] moral support . . . ."

DUNNING, J.*

We concur:

KRIEGLER, Acting P. J.

BAKER, J.

* Judge of the Orange Superior Court, appointed by the Chief Justice pursuant to article VI, section 6, of the California Constitution.

APPENDIX B — TRANSCRIPT EXCERPTS OF PROCEEDINGS OF THE SUPERIOR COURT OF THE STATE OF CALIFORNIA FOR THE COUNTY OF LOS ANGELES, DATED OCTOBER 8, 2015 AND OCTOBER 14, 2015

[2536]SUPERIOR COURT OF THE STATE
OF CALIFORNIA FOR THE COUNTY
OF LOS ANGELES

NO. BC432264

MARION LIU, INDIVIDUALLY AND AS
SUCCESSOR-IN-INTEREST TO
AUGUSTINE LIU, II, *et al.*,

Plaintiff,

vs.

COLLEGE HOSPITAL, INC., *et al.*,

Defendants.

HON. RICHARD L. FRUIN, JUDGE

**REPORTER'S TRANSCRIPT OF PROCEEDINGS
OCTOBER 8, 2015**

***

[2591]YOUR HONOR, THEN BRIEFLY, WE ALSO SEEK A PARTIAL NONSUIT ON THE ISSUE OF NEGLIGENCE OF THE SPONSOR IN FULFILLING

ITS OBLIGATIONS AS A SPONSOR UNDER THE STUDY WITH RESPECT TO HEALTH CARE OF SUBJECTS.

WE BELIEVE THE FEDERAL REGULATIONS AND GUIDANCES ARE CLEAR AND DISPOSITIVE AS TO WHAT SHOULD BE REQUIRED OF A SPONSOR AS COMPARED TO A PRINCIPAL INVESTIGATOR WITH RESPECT TO HEALTH AND SAFETY OF INDIVIDUAL SUBJECTS.

AND THE REGULATIONS AND GUIDANCES MAKE IT CLEAR THAT IT IS THE PRINCIPAL INVESTIGATOR WHO IS TASKED WITH RESPONSIBILITY FOR THE MEDICAL DECISION-MAKING, MEDICAL JUDGMENT, FOR THE CARE OF INDIVIDUAL PATIENTS.

AND WE BELIEVE THAT BECAUSE OF THE HIGHLY REGULATED AND COMPLEX NATURE OF THE FEDERAL REGULATIONS, AND THE EXTENT TO WHICH THEY DEAL WITH THE VARIOUS OBLIGATIONS BETWEEN THE SPONSOR AND PRINCIPAL INVESTIGATOR, THAT IT QUALIFIES FOR A STANDARD OF CARE BEING DICTATED BY THE FEDERAL REGULATIONS UNDER THE [2592]ANALYSIS OF THE CALIFORNIA SUPREME COURT IN THE RAMIREZ VERSUS PLOUGH CASE, WHICH CAN BE FOUND AT 6 CAL.4TH 539, PAGE 539. AGAIN, THAT'S A 1993 CASE. I KNOW THE COURT IS FAMILIAR WITH THAT CASE, SO I WON'T BELABOR THE POINT.

THE COURT: 539, WHAT?

MR. LAZARUS: I'M SORRY. 6 CAL.4TH 539.

THE COURT: I'M SORRY. I AM FAMILIAR WITH IT BECAUSE WE'VE DISCUSS IT BEFORE?

MR. LAZARUS: YES. IN CONNECTION WITH MOTIONS IN LIMINE, THE COURT CITED THE CASE IN ITS MOTIONS IN LIMINE RULING, BUT I'D BE HAPPY TO DISCUSS THE CASE WITH YOU, IF YOU LIKE.

THE COURT: WHAT ARE THE FACTS?

MR. LAZARUS: WELL, THE POINT -- THE ULTIMATE POINT AND THE POINT I THINK THAT IS RELEVANT HERE IN RAMIREZ IS WAS WHETHER OR NOT -- THE QUESTION WAS WHETHER OR NOT MANUFACTURERS OF PHARMACEUTICALS WERE REQUIRED TO INCLUDE ON THEIR LABEL FOREIGN LANGUAGE WARNINGS AND INSTRUCTIONS. I BELIEVE IN THAT CASE IT WAS WHETHER OR NOT WHETHER THEY WERE REQUIRED TO HAVE A SPANISH-LANGUAGE WARNING ON THEIR LABEL. AND THE CALIFORNIA SUPREME COURT SAID IN THAT CASE THAT GIVEN THE NATURE OF THE REGULATIONS CONCERNING WHAT NEEDS TO GO INTO A MEDICINE'S LABEL, THEY'RE COMPLEX, THEY'RE PRETTY WELL COVERING THE FIELD, IF YOU WILL, THAT UNDER CALIFORNIA

LAW WE'RE GOING TO ADOPT THAT AS THE STANDARD OF CARE, AND IF YOU COMPLY WITH THAT, YOU ARE NOT NEGLIGENT, AND BECAUSE YOU DIDN'T INCLUDE A SPANISH-LANGUAGE WARNING ON THE LABEL, AND IT [2593]WASN'T REQUIRED, THEN JUDGMENT FOR DEFENDANT IS REQUIRED UNDER THOSE CIRCUMSTANCES. SO, BASICALLY, WHAT IT MEANS --

THE COURT: I'M SORRY. YOU ARE NOT COMPLAINING --

MR. LAZARUS: I'M SORRY?

THE COURT: -- ABOUT THE -- PLAINTIFF IS NOT ASSERTING THAT THE LABEL SHOULD BE IN SPANISH?

MR. LAZARUS: NO, NO, NO.

THE COURT: YOU ARE ASSERTING THIS RAMIREZ CASE FOR THE PROPOSITION THAT AN FDA-APPROVED DRUG STUDY, IF CONDUCTED IN ACCORDANCE WITH THE FDA-APPROVED PROTOCOL, IMMUNIZES THE SPONSOR FROM ANY LIABILITY?

MR. LAZARUS: NOT EXACTLY, YOUR HONOR. I REALIZE THERE ARE NUANCES TO THIS. SO LET NOW JUST EXPLAIN THAT A LITTLE BETTER. THE STANDARD OF CARE FOR WHAT IS REQUIRED FROM A SPONSOR IN CONNECTION WITH AN

APPROVED DRUG STUDY LIKE THIS ONE IS DICTATED BY THE FEDERAL REGULATIONS AND GUIDANCES WHICH GOVERN THE SPONSOR'S CONDUCT OF A DRUG STUDY.

SO, FOR EXAMPLE, HERE THEY'RE SAYING THAT THE COMPANY SHOULD HAVE CALLED UP THE INVESTIGATOR AND INTERVENED IN INCLUSION AND EXCLUSION CRITERIA DECISIONS, AND CALLED UP THE INVESTIGATOR AND INTERVENED IN MEDICAL-CARE DECISIONS.

AND WHAT WE'RE SAYING IS THAT THAT IS NOT SOMETHING THAT'S REQUIRED OF THE SPONSOR UNDER THE FEDERAL REGULATIONS AND GUIDANCES. AND CALIFORNIA LAW, BECAUSE OF THE NATURE OF THOSE REGULATIONS, SHOULD ADOPT [2594]THAT AS THE STANDARD OF CARE. AND THE NONSUIT IS BECAUSE WE'VE COMPLIED WITH WHAT THE FEDERAL REGULATIONS AND GUIDANCES TOLD US WHAT WE NEEDED TO DO.

THE COURT: SO THIS COULD HAVE BEEN RAISED BY SUMMARY JUDGMENT MOTION?

MR. LAZARUS: PROBABLY NOT, BECAUSE WE DIDN'T KNOW WHAT THE GENERAL, YOU KNOW, UNDERSTANDING OF WHAT THE ALLEGATIONS AND OTHER EVIDENCE WAS GOING TO BE. BUT NOW WE KNOW WHAT THE EVIDENCE IS AND

WE KNOW WHAT THEIR ALLEGATIONS ARE AND WE KNOW WHAT THE CHARGES ARE.

WE ALSO HAVE EVIDENCE IN THE RECORD FROM EXPERT WITNESSES, AS WELL AS FROM THE REGULATIONS AND THE GUIDANCES THEMSELVES, WHICH TELL US WHAT THE SPONSOR'S OBLIGATIONS ARE IN THE CONTEXT OF WHAT THEIR ALLEGATIONS ARE.

SO I BELIEVE THAT THE RECORD IS SUFFICIENT TO SUPPORT OUR MOTION FOR A NONSUIT WITH RESPECT TO THE INDEPENDENT NEGLIGENCE REGARDING THE HEALTH CARE OF THE SUBJECTS.

THE COURT: ALL RIGHT. IS THERE A RESPONSE?

MR. BALABAN: YES, YOUR HONOR. SO, ESSENTIALLY, WHAT MY RECOLLECTION OF RAMIREZ AND THOSE CASES WERE, ESSENTIALLY WHAT WE'RE GETTING IS A PREEMPTION ARGUMENT AT THIS STAGE IN THE FORM OF A NONSUIT.

JUST IN GENERAL WE KNOW THAT IN THIS CASE THE FEDERAL REGULATIONS, WHETHER THEY BE FDA OR OTHER, ARE RELEVANT BUT UNDER CALIFORNIA LAW NOT DISPOSITIVE OF THE DECISIONS IN THIS CASE. AND THAT'S UNDER THE O'NEIL [2595]VERSUS NOVARTIS

CASE, AND I BELIEVE EVEN IF YOU READ RAMIREZ, IT'S PROBABLY IN THERE AS WELL.

HOWEVER, AS THE COURT CAN IMAGINE, WE HAVE A VASTLY DIFFERENT UNDERSTANDING AND INTERPRETATION OF WHETHER JANSSEN COMPLIED WITH THESE REGULATIONS. OUR VIEW OF THE REGULATIONS AS PUT ON THROUGH DR. PLUNKETT AND OTHERS IS THAT ACCORDING TO VARIOUS SECTIONS, INCLUDING 312.50 OF THE CFR, JANSSEN HAS AN OBLIGATION TO ENSURE THAT THE PROTOCOL IS CARRIED OUT. THEY HAVE AN OBLIGATION TO MONITOR THE HEALTH AND SAFETY OF ITS SUBJECTS. THEY HAVE AN OBLIGATION TO VERIFY THAT THE PROTOCOL IS BEING CARRIED OUT TO PROTECT THE HEALTH AND SAFETY OF THE SUBJECTS.

I WOULD ALSO GO ON TO SAY THAT JANSSEN IN ITS PROTOCOL COMMITTED TO FOLLOWING GOOD CLINICAL PRACTICES, WHICH WE'VE ALSO SEEN IN THIS CASE, WHICH IS IN EVIDENCE. AND THAT'S DEFINED BY THIS -- I FORGET THE NAME OF THE GROUP, BUT IN COMMITTING TO FOLLOW GOOD CLINICAL PRACTICES, THEY COMMITTED TO ALSO MONITORING THE HEALTH AND SAFETY OF THEIR SUBJECTS.

IT'S OUR POSITION, WHICH IS WELL WITHIN THE AMBIT OF THE EVIDENCE, THAT WE ARE ENTIRELY CONSISTENT WITH THE FEDERAL REGULATIONS. IN THIS CASE WE THINK THAT THEY BREACHED THEM. THEY DISAGREE.

BUT TAKING A STEP BACK, WE DON'T THINK THAT THAT'S -- WE THINK ARE THE MINIMUM, THE FLOOR, NOT THE CEILING IN THIS CASE, EVEN IF THEY HAD COMPLIED WITH THEM.

[2596]I WOULD GO ON TO STATE WE HAVE ADDITIONAL EVIDENCE OF NEGLIGENCE. HOW DO WE HAVE THAT? WE HAVE THEIR OWN INTERNAL PROTOCOL WHICH WE CLAIM THEY BREACHED. THAT'S EVIDENCE OF NEGLIGENCE UNDER THE LAW WHEN THEY BREAK THEIR OWN RULES.

WE ALSO HAVE EVIDENCE UNDER THE CUSTOM AND PRACTICE IN THE FIELD. THAT'S THROUGH DR. PLUNKETT WHAT REASONABLE SPONSORS SHOULD DO AND HOW THEY BREACHED THOSE RESPONSIBILITIES.

SO ESSENTIALLY WHAT WE HAVE HERE, YOUR HONOR, IS A PREEMPTION CASE. IF WE'RE GOING TO GET INTO THE MERITS OF PREEMPTION, THE BAR IS SUPER HIGH ON THE DEFENDANT. THE DEFENDANT HAS A SUPER HIGH BURDEN TO SHOW, ONE, THAT CONGRESS INTENDED TO PREEMPT THIS EXACT TYPE OF ACTION EITHER EXPRESSLY, WHICH THEY DON'T IN THIS -- OR IMPLIEDLY, WHICH DOESN'T APPLY TO THIS CASE.

SO I DON'T THINK THERE IS ANY ARGUMENT FOR A PREEMPTION HERE FOR THE REASONS

STATED. PRIMARILY, WE THINK THAT WE HAVE GREAT EVIDENCE THAT THEY DIDN'T FOLLOW THESE REGULATIONS. HOWEVER, EVEN IF THEY DID, WE THINK THAT THAT'S NOT THE DISPOSITIVE ISSUE UNDER THE CASE LAW IN CALIFORNIA, INCLUDING THE O'NEIL CASE, IN SETTING OUT THAT THESE REGULATIONS ARE RELEVANT BUT NOT DISPOSITIVE OF THE STANDARD OF CARE, WHICH THE COURT HAS ALREADY, I BELIEVE, EXPRESSED IN THIS CASE ON NUMEROUS OCCASIONS, AND I'LL REST ON THAT.

I THINK THERE IS OTHER -- IF THE COURT IS INCLINED TO LOOK, THERE IS OTHER CASES. I THINK IT'S [2597]CARLIN VERSUS THE SUPERIOR COURT CASE. THAT'S A SUPREME COURT CASE ON A FEDERAL PREEMPTION IN A DRUG LIABILITY CASE. AND THERE IS OTHERS THAT I CAN CITE TO THE COURT. AGAIN, THIS IS COMPLETE -- THIS IS ON THE FLY BECAUSE WE HAVE NO NOTICE THAT THEY'RE MOVING FOR NONSUIT ON PREEMPTION. THIS IS JUST ME REGURGITATING WHAT I REMEMBER FROM OTHER DRUG LIABILITY CASES.

MR. LAZARUS: THIS IS NOT A PREEMPTION MOTION, YOUR HONOR, AND IT'S NOT A PREEMPTION ARGUMENT. I'LL JUST VERY BRIEFLY EXPLAIN THE DIFFERENCE BECAUSE I WANT THE RECORD TO BE CLEAR ABOUT WHAT WE'RE ARGUING ON THAT ONE.

Appendix B

PREEMPTION FLOWS FROM THE FEDERAL CONSTITUTION, ARTICLE VI, WHICH SAYS THAT FEDERAL LAW IS SUPREME. THEREFORE, IT FLOWS DOWN AND PREVENTS STATE COURTS FROM ENTERING AREAS THAT THE FEDERAL COURTS OR FEDERAL LEGISLATIONS ALREADY COVERED. THAT'S NOT WHAT WE'RE SAYING.

THE ARGUMENT IN RAMIREZ AND THE ARGUMENT THAT WE'RE MAKING HERE FLOWS FROM THE CALIFORNIA SUPREME COURT AND FLOWS FROM THE CALIFORNIA STATE COURTS IN WHICH THEY RECOGNIZE THAT SOMETIMES WHEN A FEDERAL REGULATORY BODY OR THE FEDERAL CONGRESS HAS ACTED IN A COMPLEX OR SPECIFIC WAY, THAT CALIFORNIA LAW WILL NOT REQUIRE SOMETHING DIFFERENT, AND THAT'S WHAT WE'RE ARGUING HERE.

FOR EXAMPLE, IN RAMIREZ IT WASN'T THAT THE FEDERAL FOOD AND DRUG ACT HAD SPECIFICALLY SAID THAT STATES CANNOT ACT OR THAT IT WAS FIELD PREEMPTION BECAUSE [2598]OF THE WAY THAT THE FEDERAL GOVERNMENT HAD HANDLED THE ISSUE REGARDING WHETHER OR NOT YOU HAD TO WARN IN A DIFFERENT LANGUAGE ON THE LABEL.

IT WAS THE CALIFORNIA SUPREME COURT SAYING, LOOK, THE FEDERAL REGULATORS HAVE LOOKED AT THIS IN DETAIL. THEY ARE

IN THE BEST POSITION TO DECIDE WHAT IS REQUIRED AS A MATTER OF PUBLIC POLICY WITH RESPECT TO WHICH LANGUAGES YOU HAVE TO WARN ABOUT ON YOUR LABEL; AND, THEREFORE, WE'RE GOING TO DEFER IN SETTING THE STANDARD OF CARE TO WHAT THE FEDERAL REGULATORS HAVE SET UP IN THIS COMPLEX WEB OF REGULATIONS WHICH THEY ENACTED.

AND THAT'S WHAT WE'RE TALKING ABOUT HERE. WE'RE TALKING ABOUT A RAMIREZ TYPE OF ANALYSIS IN WHICH WHAT WE HAVE IS A FEDERAL REGULATORY SCHEME IN WHICH THE FDA, THE DHAS, AND CONGRESS HAVE LOOKED AT WHAT IS REQUIRED IN CLINICAL RESEARCH TO PROTECT THE HEALTH AND WELFARE OF SUBJECTS, AND THEY HAVE IMPOSED RULES BASED ON THOSE POLICIES. AND THOSE RULES ARE SUFFICIENTLY SPECIFIC, WIDE-REACHING, AND COMPLEX THAT A CALIFORNIA COURT SHOULD ADOPT THOSE REGULATIONS AS THE STANDARD OF CARE AND NOT REQUIRE SOMETHING DIFFERENT, ADDITIONAL TO, OR VARY FROM WHAT THE FEDERAL REGULATORS IN CONGRESS HAVE PUT INTO PLACE. THAT'S WHAT WE'RE ARGUING HERE. IT'S NOT PREEMPTION.

THE COURT: SO YOU ARE SAYING AS A TRIAL COURT, I SHOULD DEFER WHAT I'VE HEARD DURING THIS TRIAL AS TO THE

COMPREHENSIVENESS AND THOUGHTFULNESS OF THE FDA REGULATIONS.

[2599]MR. LAZARUS: THAT'S OUR ARGUMENT, YOUR HONOR.

THE COURT: ALL RIGHT. I'LL DENY THE MOTION ON THAT BASIS.

MR. LAZARUS: AND THEN THE FINAL PARTIAL NONSUIT WE HAVE, YOUR HONOR, IS A SPECIFIC ONE THAT GOES VERY SPECIFICALLY TO THE ALLEGATIONS REGARDING NEGLIGENCE IN RECRUITING AND CONSENTING MR. LIU IN THIS STUDY. AND THE REASON WHY WE THINK NONSUIT IS APPROPRIATE IS FOR TWO REASONS.

NUMBER ONE, AS WE'VE BEEN TALKING ABOUT, THE REGULATIONS AND THE GUIDANCES MADE CLEAR THAT THE ENTITY RESPONSIBLE FOR OBTAINING INFORMED CONSENT IS THE PRINCIPAL INVESTIGATOR. AFTER OBTAINING APPROVAL OF THE IRB OF THE INFORMED CONSENT FORM AND THE INFORMED CONSENT PROCESS THAT'S OUTLINED IN THE PROTOCOL, AND, AGAIN, APPROVED BY THE IRB, THE SPONSOR IS NOT RESPONSIBLE TO OBTAIN INFORMED CONSENT FROM INDIVIDUAL SUBJECTS. THAT IS CRYSTAL CLEAR UNDER THE REGULATIONS, THE GUIDANCES, AND THE CUSTOM AND PRACTICE.

IN ADDITION, AS TO THE RECRUITMENT ALLEGATIONS, THE IDEA THAT MR. LIU WAS IMPROPERLY RECRUITED INTO THE STUDY, THERE IS JUST NO EVIDENCE TO SUPPORT THAT OTHER THAN SOME INNUENDO FROM DR. PLUNKETT.

BUT THE MORE IMPORTANT REASON, YOUR HONOR, WHY NONSUIT IS REQUIRED FOR THE CONSENT AND ALLEGATIONS IS CAUSATION. EVEN ASSUMING MR. LIU WAS IMPROPERLY CONSENTED, THERE IS NO EVIDENCE FROM WHICH A JURY COULD FIND THAT A CAUSE CONTRIBUTED TO MR. LIU'S DEMISE TO HAVE [2600]HIM IN THE STUDY, AND HERE IS WHY.

IF MR. LIU WAS NOT RECRUITED INTO THE STUDY OR IF HE DOES NOT GET CONSENTED INTO THE STUDY, HE NEVER GETS THE SCREENING EKG, AND HE NEVER GETS THE SCREENING LABS. INSTEAD, HE'S HOME EXPERIENCING WHATEVER HE'S EXPERIENCING WITHOUT THE BENEFIT OF ANY MEDICAL CARE. THE EVIDENCE IS ABSOLUTELY UNDISTURBED HERE THAT HE WAS ASYMPTOMATIC. HE WAS NOT EXPERIENCING OR COMMUNICATING ANY SYMPTOMS. THERE IS NO NONSPECULATIVE REASON TO BELIEVE THAT HE WOULD HAVE GOTTEN ANY MEDICAL CARE IF HE HAD NOT BEEN IN THE STUDY UP UNTIL THE TIME WHEN IT WAS TOO LATE, WHICH THE EVIDENCE SHOWS WAS ON FEBRUARY 25TH.

ACCORDINGLY, THERE IS NO NONSPECULATIVE EVIDENCE THAT MR. LIU'S PARTICIPATION IN THE STUDY IS THE CAUSE OF HIS DEATH. IN FACT, THE EVIDENCE, I THINK, IS CLEAR THAT THEY GAVE HIM WHATEVER TINY CHANCE HE HAD OF SURVIVING, BUT IT JUST WASN'T ENOUGH TO ALLOW HIM TO BE SAVED. THOSE ARE THE CIRCUMSTANCES.

THAT MEANS THAT THE REAL ISSUES IN THIS CASE WOULD BE THE ISSUES WE SHOULD BE FOCUSING ON WHICH ARE WHETHER HE GOT THE APPROPRIATE MEDICAL CARE AFTER THE SITUATION CAME TO LIGHT, AND THAT HAS NOTHING TO DO WITH THE CONSENTING PROCESS OR THE RECRUITMENT PROCESS. THOSE WERE A BENEFIT TO HIM MORE THAN ANYTHING ELSE.

MR. BALABAN: I'LL START ON THE CAUSATION PART AND WORK BACKWARDS. IF HE WASN'T IN THE STUDY, HE WOULDN'T HAVE BEEN GIVEN THE 1 MILLIGRAM. IF HE WASN'T GIVEN THE 1 MILLIGRAM, ACCORDING TO OUR EVIDENCE AND OUR THEORIES, [2601]HE WOULD NOT HAVE DIED. IT'S CERTAINLY THAT 1 MILLIGRAM WAS A SUBSTANTIAL FACTOR. SO WE ABSOLUTELY FILL THE CAUSATION BOX, IF YOU WILL.

THEN WORKING BACKWARDS, IT'S JANSSEN WHO DESIGNED THE INFORMED CONSENT PROCESS. IT'S JANSSEN THAT WROTE THE FORM. WE HEARD FROM JANSSEN'S OWN EXPERT ALL

THE DIFFERENT WAYS THEY CAN DO THINGS DIFFERENTLY IF THEY CHOOSE TO, INCLUDING INTERACTIVE CONSENT, EDUCATED CONSENT, COMPUTER MODULES, AND ALL THOSE THINGS THAT JANSSEN CHOSE NOT TO DO.

THE EVIDENCE IS ALSO CLEAR THAT JANSSEN -- THAT THERE IS THIS ONGOING DUTY TO CONTAIN INFORMED CONSENT UNDER THE FACTS OF THIS CASE WHICH WE CLAIM HE DIDN'T PROPERLY GET, AS WELL AS THE ISSUE OF -- IT'S CLEAR THAT JANSSEN KNEW DR. VALENCERINA WAS TREATING HER OWN PATIENTS. SHE PUT IT RIGHT IN THE SUBMISSION TO THE IRB. SO THEY WERE AWARE OF THAT FACT. WE CLAIM THAT'S IMPROPER. THERE IS A CONFLICT OF INTEREST WHEN YOU ARE DEALING WITH, ONE, YOUR OWN PATIENT; TWO, A MENTALLY ILL PATIENT. AND I THINK WE HAVE ABUNDANCE SUPPORT FOR THAT, EVEN FROM DEFENDANTS' OWN EXPERT, DR. DUNN, IN REGARDS TO HER OWN WRITINGS IN SOME OF THESE PRACTICES AND HOW THEY'RE QUESTIONED IN THE FIELD. SO I THINK JANSSEN IS ON THE HOOK FOR THAT BOTH ON A NEGLIGENCE ASPECT AS WELL AS CAUSATION.

MR. LAZARUS: YOUR HONOR, THE 1 MILLIGRAM WE'VE ALREADY TALKED ABOUT. AND IF THE -- FIRST OF ALL, WE DON'T BELIEVE THERE IS EVIDENCE TO ALLOW THAT TO GO TO [2602]THE JURY ANYWAYS, BUT PUTTING THAT ASIDE, THAT'S AN AWFULLY SLIM READ FOR THE

ALLEGATION THAT THE STUDY HAD ANYTHING TO DO WITH MR. LIU'S DEATH. REMEMBER, HE WAS ON 800 MILLIGRAMS OF SEROQUEL A DAY. DR. PLUNKETT TESTIFIED THAT IT HAS THE SAME EFFECTS AS RISPERIDONE. I JUST DON'T THINK THAT THERE IS ANY EVIDENCE WHICH WOULD SUPPORT HOLDING US LIABLE FOR BRINGING HIM INTO A STUDY BASED ON THE 1 MILLIGRAM.

THE COURT: DOES PLAINTIFF REALLY WANT TO GO TO THE JURY ON AN ARGUMENT BASED UPON A RECRUITMENT WHICH LOGICALLY CAN BE CHALLENGED?

MR. BALABAN: YEAH, I DO, YOUR HONOR. EVERYBODY HAS THEIR OWN VIEW OF THINGS. MY VIEW OF THIS CASE, THE VERY FIRST FACT I EVER LEARNED ABOUT THE CASE WAS THAT A DOCTOR HAD RECRUITED HER OWN MENTALLY ILL PATIENT INTO A STUDY WHERE SHE WAS GETTING, YOU KNOW, 30 GRAND FOR. THAT TO ME RANG AT SOMETHING JUST ON THE SMELL TEST IS IMPROPER. AND WHEN GOING THROUGH AND NOW HAVING HAD A CHANCE TO SPEAK TO THE EXPERTS, DEFENSE AND PLAINTIFF, I THINK THAT THAT PRACTICE IS ONE THAT SHOULD BE CHALLENGED IN A COURT LIKE THIS. I DON'T THINK IT'S FAIR. I DON'T THINK IT WAS FAIR TO MR. LIU. WE THINK THERE WAS ABUNDANT EVIDENCE BOTH IN THE SCIENTIFIC PAPERS THAT THAT'S SOMETHING THAT SHOULD BE AVOIDED, IF POSSIBLE, ESPECIALLY IN THE

CONTEXT OF THIS STUDY WHERE THERE IS ABSOLUTELY NOTHING IN IT FOR THIS YOUNG MAN, ZERO. I MEAN, HE WAS EVENTUALLY FOR THE BENEFIT OF SCIENCE, AND I DON'T THINK THAT WAS FAIR.

[2603]SO TO ANSWER THE COURT'S QUESTION, YES, WE DO WANT TO GO TO THE JURY ON THAT. AND I THINK THAT, AGAIN, JANSSEN AS THE SPONSOR IS THE ONE THAT SET UP THE INFORMED CONSENT PROCESS. THEY'RE THE ONE THAT HAD THE OPPORTUNITY TO MAKE IT MORE INVOLVED, TO MAKE IT BETTER. THEY'RE THE ONES THAT SET THE STAGE FOR THE WHOLE RECRUITMENT PROCESS.

AND THEY WERE AWARE THAT DR. VALENCERINA WAS RECRUITING MR. LIU AS -- AND YOU REMEMBER THE CHECKED BOXES, AS A MENTALLY DISABLED COGNITIVELY IMPAIRED, UNDEREDUCATED, AND ECONOMICALLY -- I FORGET WHETHER IT WAS IMPOVERISHED OR WHATEVER IT WAS.

I THINK ALL THOSE THINGS ARE UNREASONABLE AND I THINK JANSSEN DOES BEAR THE RESPONSIBILITY FOR THOSE. AND, AGAIN, HAD HE NEVER BEEN ENROLLED INTO THE STUDY, HE DOESN'T GET THE 1 MILLIGRAM.

AND, ALSO, I THINK, THERE HAS BEEN TESTIMONY, YOUR HONOR, ABOUT THE LIKELIHOOD THAT HAD HE NOT BEEN IN

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THE STUDY IN AN ENVIRONMENT WHERE HE THOUGHT HE WAS BEING PROTECTED SURROUNDED BY ALL THESE DOCTORS, IF SOMETHING WOULD APPEARED SYMPTOMOLOGY, HE MORE THAN LIKELY WOULD HAVE ENDED UP IN THE EMERGENCY ROOM. AND I THINK THAT WAS THROUGH DR. VON SCHWARZ AND SOME OTHER DOCTORS, SO --

THE COURT: WELL, WE NEVER HEARD ANY TESTIMONY ABOUT WHAT WOULD ALERT MR. LIU IF HE WAS ASYMPTOMATIC. WE DON'T KNOW WHETHER HE WAS SUFFERING FROM CHEST PAINS OR WHETHER HE JUST WOULD HAVE COLLAPSED OR WHETHER HE [2604]WOULD HAVE DIED IN HIS SLEEP, BUT I ONLY MENTION THAT BECAUSE THERE IS A LOT OF THINGS ABOUT THE SITUATION WE DON'T KNOW.

THE ISSUE PROBABLY IS WHETHER OR NOT BEING ON THE STUDY, HE WOULD NOT HAVE GOTTEN THE SCREENING TESTS WHICH WOULD HAVE ULTIMATELY ALERTED THE PRINCIPAL INVESTIGATOR SUFFICIENTLY TO SEND HIM TO AN EMERGENCY ROOM. AND DOCTOR -- I FORGET HIS NAME RIGHT NOW, BUT THE EMERGENCY ROOM DOCTOR THOUGHT THAT HE HAD SAVED HIM AND PRESERVED HIM.

BUT IF PLAINTIFF IS DETERMINED TO PROCEED ON THAT THEORY, I DON'T THINK THAT I WOULD GRANT A MOTION FOR A NONSUIT TO EXCLUDE IT.

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[2855]REPORTER'S TRANSCRIPT
OF PROCEEDINGS
OCTOBER 14, 2015

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[3007]THE COURT: ALL RIGHT. WELL, I HAVE TO RULE IN THE ABSENCE OF ANY DIRECT AUTHORITY AND IN THE ABSENCE OF ANY WRITING, EXCEPT MR. BALABAN'S RECENT PROVISION OF RELATED AUTHORITY. MY VIEW OF THE MATTER IS THAT A PHYSICIAN/INDEPENDENT INVESTIGATOR IS NOT AN AGENT OF THE SPONSOR AND THERE IS A NUMBER OF REASONS FOR THAT.

TO BEGIN WITH, THE FDA IS TRYING TO OBTAIN UNBIASED INFORMATION. I BELIEVE THAT'S ONE OF THE REASONS THAT IT REQUIRES A PROTOCOL THAT HAS SOME INDEPENDENT OVERSIGHT WITH RESPECT TO THE WAY IN WHICH THE STUDY IS CONDUCTED. I THINK THAT'S ONE OF THE FUNCTIONS OF THE IRB. IT'S ALSO ONE OF THE REASONS THAT [3008]THE PROTOCOL IS APPROVED BY THE FDA.

SECONDLY, I THINK THAT A PHYSICIAN IN A CLINICAL TRIAL, AT LEAST AS DESCRIBED IN THIS CASE, IS MAKING JUDGMENTS WHICH ARE INDEPENDENT OF THE SPONSOR'S INTERESTS AND ARE INTENDED TO BE IN THE INTEREST

OF THE PATIENT OR THE SUBJECT FOR THE PURPOSE OF PROTECTING THE SUBJECT FROM ADVERSE CONSEQUENCES OF THE TRIAL. I THINK THAT THE PHYSICIAN IN HER OR HIS UNFETTERED DISCRETION RECOMMENDS INCLUSION OF THE SUBJECT IN THE TRIAL AND I THINK THAT THE PHYSICIAN'S RESPONSIBILITY DURING THE TRIAL TO MONITOR THE REACTION OF THE SUBJECT TO THE ENVIRONMENT AND TO THE TEST DRUG IS EVIDENCE THAT THE PHYSICIAN IS MAKING DECISIONS WHICH ARE INDEPENDENT OF THE PROGRAM OR THE STRUCTURE IMPOSED BY THE SPONSOR.

CONSEQUENTLY, THIS MAY BE THAT CASE WHICH GOES UP ON APPEAL. I AM GOING TO HOLD THAT THE PHYSICIAN/INDEPENDENT INVESTIGATOR IS NOT THE AGENT OF JOHNSON & JOHNSON -- I DO THINK -- OR JANSSEN.

I DO THINK THAT A SPONSOR HAS INDEPENDENT RESPONSIBILITIES TO THE PATIENT, AND JANSSEN IN THIS PARTICULAR STRUCTURE HAS SEEN TO IT THAT IT WOULD OBTAIN INFORMATION ABOUT THE REACTION OF THE SUBJECT TO THE TEST DRUG AND TO THE PHYSICAL CONDITION OF THE SUBJECT SUCH THAT IT HAD REASONABLY ASSUMED RESPONSIBILITIES TO MAKE ITS OWN JUDGMENT SEPARATELY FROM THE PHYSICIAN AS TO WHETHER OR NOT THIS SUBJECT SHOULD STAY IN THE PROGRAM AND SHOULD BE -- IF

THE CIRCUMSTANCES WARRANTED TAKEN OUT OF THE PROGRAM AND PROVIDED MEDICAL CARE FOR THE [3009]SUBJECT'S BENEFIT.

MR. BALABAN: THANK YOU, YOUR HONOR.

MR. LAZARUS: THANK YOU, YOUR HONOR.

YOUR HONOR, AS TO THE OTHER GROUNDS THAT WE WOULD CITE FOR THE DIRECTED VERDICT, I REALLY DON'T WANT TO BELABOR THOSE POINTS. WE'VE ALREADY DISCUSSED THEM. SUFFICE IT TO SAY, UNLESS THE COURT WANTS ME TO ELABORATE WHAT WE WERE DOING, THE ARGUMENTS THAT WE MADE AND THE ISSUES THAT WE RAISED WITH RESPECT TO OUR MOTIONS FOR PARTIAL NONSUIT AND NONSUIT AND CONVERTING THEM INTO MOTIONS FOR DIRECTED VERDICTS, THAT WOULD INCLUDE THE ARGUMENT THAT THE DUTY OF CARE IS -- UNDER RAMIREZ IS THE STANDARD THAT'S STATED UNDER THE FEDERAL REGULATIONS, AS WELL AS OUR ARGUMENTS REGARDING THE DUTY OF CARE AND CAUSATION WITH RESPECT TO THE ISSUES OF CONSENT AND RECRUITMENT, AND OUR MOTION WITH RESPECT TO THE 1 MILLIGRAM BEING -- 1 MILLIGRAM OF RISPERIDONE BEING THE CAUSE OF MR. LIU'S DEATH OR A SUBSTANTIAL CONTRIBUTING FACTOR, AND, FINALLY, THE OVERARCHING DIRECTED VERDICT BECAUSE WE BELIEVE ALL OF THOSE

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REASONS SUPPORT JUDGMENT IN JANSSEN'S FAVOR.

THE COURT: YOUR MOTION FOR NONSUIT WAS NOT A WRITTEN MOTION. IS YOUR MOTION FOR DIRECTED VERDICT A WRITTEN MOTION?

MR. LAZARUS: IT IS NOT, YOUR HONOR.

THE COURT: DON'T YOU THINK IT'S RATHER DIFFICULT TO PRESENT A MOTION ON THOSE NUMEROUS GROUNDS AT THE END OF THE TRIAL WITHOUT A WRITING TO SUPPORT IT AND A LIST [3010]OF AUTHORITIES TO SUPPORT THE LEGAL ARGUMENT?

MR. LAZARUS: YOUR HONOR, I DO AGREE IT WOULD HAVE BEEN PREFERABLE HAD I PUT TOGETHER A WRITTEN MOTION. IT WOULD HAVE BEEN EASIER FOR THE COURT, I'M SURE. UNFORTUNATELY, I DID NOT HAVE TIME TO PUT THAT TOGETHER AND DECIDED TO MAKE THE MOTION ORALLY, AND THAT'S WHAT WE HAVE DONE.

THE COURT: YOU GOT FOUR ATTORNEYS IN THE ROOM AND PROBABLY MORE BACK AT THE OFFICE. IS IT TOO DIFFICULT TO PREPARE A WRITTEN MOTION SO THAT, YOU KNOW, I CAN THINK ABOUT AND SEE WHAT AUTHORITIES YOU HAVE?

MR. LAZARUS: YOUR HONOR, IF THE COURT WOULD PREFER, WE WILL DRAFT SOMETHING UP AND GET IT TO YOU. RIGHT NOW WE HAVE BEEN FULLY PREOCCUPIED IN TRYING TO GET THIS CASE COMPLETED AND TO THE JURY. I REGRET THAT I HAVEN'T BEEN ABLE TO DO THAT. WE CAN FILE SOMETHING TOMORROW SO THAT THE COURT CAN LOOK AT IT WHILE THE JURY IS OUT. THAT'S THE BEST WE CAN DO ON IT.

THE COURT: WELL, YOU KNOW, THAT DOESN'T REALLY HELP. I MEAN, IT MIGHT HELP ME, BUT IF THERE IS SOMETHING IN WRITING, IT GOES TO THE OTHER SIDE AS WELL, AND THE OTHER SIDE HAS AN OPPORTUNITY TO RESPOND IN WRITING. AND THAT'S THE BENEFIT OF BRIEFING. IT JUST AMAZES ME THAT WE HAVE A TRIAL WHICH IS I THINK TODAY IN THE 15TH DAY AND WE GET A MOTION FOR A DIRECTED VERDICT ON ISSUES THAT YOU WERE WELL AWARE OF BEFORE THE TRIAL BEGAN WHICH IS NOT SUPPORTED BY A BRIEF.

MR. BALABAN: CAN I MAKE ONE COMMENT ON THAT, [3011]YOUR HONOR. WE ARGUED -- AS I UNDERSTAND IT, THESE ARE THE SAME EXACT ISSUES WE ARGUED ON THE MOTION FOR NONSUIT WHICH THE COURT DENIED, EXCEPT FOR THE ONE THAT WAS PENDING REGARDING AGENCY. I DON'T THINK THAT ANYTHING HAS HAPPENED IN THE DEFENSE CASE THAT HAS CHANGED THE LANDSCAPE IN REGARDS TO

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THE EVIDENCE THAT WOULD ALLOW A JURY TO FIND IN PLAINTIFF'S FAVOR A -- GIVEN ALL THE REASONABLE INFERENCES ON EACH AND EVERY ONE THOSE ISSUES WHICH WERE ALREADY DENIED BY THE COURT.

THE COURT: I AM GOING TO DENY THE BALANCE OF THE MOTION FOR DIRECTED VERDICT.

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APPENDIX C — DENIAL OF THE SUPREME COURT OF CALIFORNIA, FILED APRIL 11, 2018

COURT OF APPEAL, SECOND APPELLATE DISTRICT, DIVISION FIVE- NOS. B269318, B270332

IN THE SUPREME COURT OF CALIFORNIA

S247023

En Banc

MARION LIU, AS SUCCESSOR IN INTEREST TO AUGUSTINE LIU, DECEASED,

Plaintiff and Appellant,

v.

JANSSEN RESEARCH & DEVELOPMENT, LLC,

Defendant and Respondent.

Consolidated cases.

The petition for review is denied.

CANTIL-SAKAUYE
Chief Justice

APPENDIX D — RELEVANT STATUTORY PROVISIONS

21 C.F.R. § 312.50

§ 312.50 General responsibilities of sponsors.

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

Appendix D

21 C.F.R. § 312.56

§ 312.56 Review of ongoing investigations.

(a) The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.

(b) A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA–1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with the requirements of § 312.59 and shall notify FDA.

(c) The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors shall make such reports to FDA regarding information relevant to the safety of the drug as are required under § 312.32. The sponsor shall make annual reports on the progress of the investigation in accordance with § 312.33.

(d) A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects shall discontinue those investigations that present the risk, notify FDA, all institutional review boards, and all investigators who have at any time participated

in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding as required by § 312.59, and furnish FDA with a full report of the sponsor's actions. The sponsor shall discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued. Upon request, FDA will confer with a sponsor on the need to discontinue an investigation.