



Assessing the legal duty to use or disclose interim data for ongoing clinical trials

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ABSTRACT

Randomized controlled clinical trials, leading to large-scale meta-analyses, are considered the gold standard for research evaluating new drugs and other therapeutic interventions. To promote scientific integrity and prevent the adoption of potentially fallacious early trends, emerging information is commonly shielded from sponsors, investigators, and other clinical trial actors, including through the use of independent Data and Safety Monitoring Boards (DSMBs). Once established, a DSMB is usually the only body to have access to unblinded information until trial completion or the crossing of pre-specified, and often highly stringent, stopping boundaries. Yet, in certain circumstances, clinical trial actors have legal obligations to trial participants and others to use or disclose emerging information.

This paper canvasses potential legal obligations to use or disclose emerging clinical trial data, including through tort law and securities laws. The analysis is supplemented by a comprehensive search of US cases in which courts have adjudicated upon such allegations. Notably, available cases demonstrate widespread judicial deference to clinical trial practices designed to shield clinical trial actors from emerging information. As a result, despite a theoretical possibility of legal obligations of use or disclosure, it appears that these will rarely be enforceable.

KEYWORDS: Clinical Trials, Confidentiality, Data Monitoring Committees, Disclosure, Liability, Monitoring

1. INTRODUCTION

In Apr. 1992, a clinical trial started enrolling women at a high risk for breast cancer. For the first time, a major, multi-center clinical trial would assess whether a breast cancer *treatment* drug (tamoxifen citrate) could be effective in *preventing* breast cancer.

By 1997, almost 14,000 women had enrolled in the study. Half were randomized to receive tamoxifen, the rest placebo. The two funding agencies, the National Cancer Institute and the National Heart, Lung, and Blood Institute set up a committee to monitor, among other things, study safety and efficacy. The trial's Data and Safety Monitoring Board (DSMB)¹ first saw efficacy data in Mar. 1995. Of the 106 breast cancers so far diagnosed, 70 were in women assigned to receive placebo, and 36 were in women receiving tamoxifen. Although the information seemed favorable to the tamoxifen-treated group, it was not sufficient to cross the pre-specified 'stopping boundary', i.e., the point at which emerging trial results were considered sufficiently conclusive to preclude clinical equipoise between the trial arms. As the study continued, it was increasingly clear that there was a lower incidence of breast cancer diagnoses in participants receiving tamoxifen than those receiving placebo. By the third DSMB review in Mar. 1997, the DSMB identified approximately 50 per cent reduction in invasive breast cancer incidence among women randomized to tamoxifen, with a statistically significant *P* value of 0.000011: that is, a likelihood of 1 in 10,000 of the differences in breast cancer reduction between the two arms having occurred by chance alone. Despite this clear evidence of the intervention's preventative effect, the DSMB voted to continue the study in order to find out more about potential long-term adverse effects. In Mar. 1998, with an even stronger *P*-value,² the DSMB recommended that the study be stopped and participants unblinded.³

By all accounts, the DSMB performed its monitoring role thoughtfully and deliberately, ensuring ongoing trial validity in a context of intense public, media, and governmental scrutiny. Yet, for at least two years before the trial was terminated, the efficacy of tamoxifen in preventing breast cancer in high-risk women was essentially incontrovertible. The confidential nature of DSMB deliberations meant that no indication of efficacy was available to investigators or study participants. Had the information been disclosed, it would likely have changed the willingness of many participants to remain in the trial—particularly given tamoxifen was already in the market and therefore available off-label: presumably a preferable position than continuing in a study involving a 50 per cent chance of receiving placebo.

Now consider a clinical trial sponsored by the publicly listed company NewLink Genetics Corp ('NewLink'). The company's most advanced treatment candidate was a vaccine intended to treat pancreatic cancer. NewLink developed a phase 3 clinical trial designed to pursue marketing approval. The Immunotherapy for Pancreatic Resectable cancer Study (IMPRESS), which commenced in May 2010, was structured around four major milestones, the first being recruitment of all 722 participants, the second, third, and fourth being periodic DSMB review after pre-specified numbers of

¹ For the sake of clarity, in this article, the term Data and Safety Monitoring Board (DSMB) will be used to capture all bodies established with the function of performing an independent and ongoing review of emerging trial data. In the Breast Cancer Prevention Trial, this body was named the Endpoint Review, Safety Monitoring and Advisory Committee (ERSMAC).

² At this point, the *P*-value for efficacy reached $P < 0.000006$: that is, a chance of 6 in 100,000 of having occurred by chance alone.

³ Carol K. Redmond, Joseph P. Constantino & Theodore Colton, *Challenges in Monitoring the Breast Cancer Prevention Trial*, in *Data Monitoring in Clinical Trials: A Case Studies Approach* 118-135 (David L. DeMets, Curt D. Furberg, & Lawrence M. Friedman eds., 2006), <http://public.eblib.com/EBLPublic/PublicView.do?ptiID=302575> (last visited Apr 5, 2013).

participant deaths. Each DSMB review permitted study termination if the overall survival of treatment group participants exceeded that of control arm participants at a requisite level of statistical significance.⁴ Otherwise, the study was to continue.

After the first interim analysis, the DSMB recommended that the trial continue. NewLink explained to investors that trial continuation was an ‘anticipated outcome’, and that they ‘look[ed] forward to continuing the study and to gathering additional, more mature data in support of [NewLink’s] mission to provide improved treatment options for patients with pancreatic cancer’.⁵ Similarly, after the second interim analysis, NewLink issued a press release announcing that the DSMB found that the results again did not justify seeking marketing approval, again making statements signaling an expectation of clinical and commercial success. In May 2016, NewLink reported that the IMPRESS trial did not achieve its primary endpoint, which was a statistically significant difference in overall survival between the treatment and control arms. More concerning, final trial results reported that the treatment arm had a three-month *lower* survival time than the control arm. Investors brought class action proceedings claiming that company had made fraudulent misstatements to them.⁶

The above scenarios raise a wealth of questions—What are the ethical principles that should govern trial stopping decisions? What should be the roles and qualifications of the persons entrusted with making these decisions? Should there be additional accountability mechanisms to oversee trial stopping decisions? This article focuses only on one part of this landscape: the potential *legal* obligations of clinical trial actors to disclose or otherwise act upon emerging trial information. For the purpose of this analysis, the category of clinical trial actors is conceptualized broadly to include sponsor companies, universities, hospitals, individual researchers, and reviewing Institutional Review Boards (IRBs).⁷ Although no litigation has so far been brought against them, DSMBs could also fall within this list of potential defendants.

Part two of this article provides contextual information on clinical trial monitoring, including the growing prevalence of independent DSMBs to provide expert, ongoing assessment of potentially emergent safety or efficacy signals. Most notably, modern trial monitoring practices commonly involves the siloing of the vast preponderance of interim trial data within DSMBs until such time as the data reaches stringent thresholds for statistical certainty. That is, sponsors and researchers have no access to this data until those thresholds are reached. The rationales for this confidentiality are well defined: to protect a trial’s scientific integrity, as well as to prevent trial sponsors, investigators, and/or participants from the potentially premature adoption of trial results. However, the resultant informational asymmetries may also prevent other clinical trial actors from satisfying obligations to disclose or otherwise act upon emerging trial information. Part three canvasses these potential legal claims that may be brought against clinical trial

⁴ At 222 deaths, approximately a 99.5 per cent likelihood that algenpantucel-L patients were outliving control group patients because of the NewLink treatment or *P*-value of 0.004; at 33 deaths a *P*-value of 0.019, or about a 98 per cent likelihood; at 444 patient deaths, a *P*-value of 0.043, or about 95.5 per cent likelihood: Amended Class Action Complaint For Violations Of Federal Securities Laws, *Nguyen v. New Link Genetics Corp.*, No. 1:16-CV-3545-WHP (S.D.N.Y., Nov. 10, 2016)

⁵ *Nguyen v New Link Genetics Corporation*, 297 F.Supp.3d 472 (S.D.N.Y. Mar. 29, 2018).

⁶ *Id.*

⁷ Michelle M. Mello, David M. Studdert & Troyen A. Brennan, *The Rise of Litigation in Human Subjects Research*, 139 ANN. INTERN. MED. 40 (2003).

actors for failure to disclose or otherwise act upon clinical trial data, including lack of informed consent, negligent conduct, product liability, fraud, and breach of contract. For trials sponsored by publicly listed companies, non-disclosure also might constitute securities fraud.

Evident in part three is a disconnection between legal actions that include potential obligations on clinical trial actors to use or disclose interim trial data, and clinical trial practices directed toward maintaining the confidentiality of interim trial data. Navigating this divide will depend on the principles and values that judges determine to be applicable, and the respective weight to which they should be accorded.⁸ To investigate the manner in which judges have so far balanced these responsibilities, part four sets out the results of a comprehensive search and analysis of US case law in which a plaintiff has alleged an obligation for a clinical trial actor to have disclosed, or otherwise acted upon, interim trial data. This provides an indication of the way in which courts might use their discretion in cases going forwards. Part five draws lessons from these cases to inform law and policy going forwards.

2. MONITORING CLINICAL TRIALS FOR EMERGING INFORMATION

2.1 An Obligation to Monitor Emerging Trial Safety and Efficacy Data

Randomized controlled clinical trials, leading to large-scale meta-analyses, are considered the gold standard for research evaluating new drugs and other therapeutic interventions. The clinical trial process is typically long and complex, divided into roughly four phases. Phase 1 trials enroll a small group of people to establish an intervention's safety in a participant population, including identification of a safe dosage range. Phase 2 trials enroll a larger group of participants to get additional information on safety and preliminary efficacy information. Phase 2 trials typically last from several months to two years, and are often when a control group and potential blinding is introduced. Phase 3 trials provide more definitive information about the intervention's safety and efficacy. These usually enroll large groups of participants (from several hundred to several thousand) and last from one to four years. Phase 4 trials are conducted after an intervention has been marketed, to further monitor the intervention's action in the general population.⁹ Accordingly, an imperative to monitor ongoing trials for emerging safety or efficacy signals—and to take action based upon such signals—increasingly has been recognized.

Monitoring obligations extend to a variety of clinical trial actors, including clinical trial sponsors, investigators, and reviewing IRBs (in some countries, termed research ethics committees or human research ethics committees). Most pertinently, trial sponsors are required to regularly assess a trial's emerging safety and efficacy profile. In the US, the Code of Federal Regulations (CFR) (21 CFR 312.56, Investigational New Drug Application) sets out monitoring responsibilities for sponsors of clinical drug trials. This includes 'review[ing] and evaluat[ing] the evidence relating to the safety and effectiveness of the drug' and notifying the Food and Drug Administration (FDA) and

⁸ Kent Greenawalt, *Discretion and Judicial Decision: The Elusive Quest for the Fetters That Bind Judges*, 75 COLUMBIA LAW REV. 359, 399 (1975).

⁹ Office of the FDA Commissioner, THE DRUG DEVELOPMENT PROCESS - STEP 3: CLINICAL RESEARCH, https://www.fda.gov/forpatients/approvals/drugs/ucm405622.htm#Clinical_Research_Phase_Studies (accessed Oct 26, 2018).

participating investigators of potentially serious safety findings. The regulations specify that a sponsor who determines that an investigational drug ‘presents an unreasonable and significant risk to subjects’ shall—within five working days of making such determination—discontinue the relevant investigations, and notify the FDA, trial investigators, and reviewing IRBs.¹⁰ Additionally, 21 CFR 312.50 requires clinical drug trial sponsors to ensure that the FDA and participating investigators ‘are promptly informed of significant new adverse effects or risks with respect to the drug’.¹¹ The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice extends this notification obligation to all findings that ‘could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC’s approval/favorable opinion to continue the trial’¹²

2.2 The Emergence of DSMBs as a Strategy for Trial Monitoring

Recognition of the need for regular monitoring of accumulating trial data, and of the scientific and ethical benefits of independence in this monitoring role, has fostered the establishment of DSMBs: committees tasked with assessing the appropriateness of continuing a clinical trial based on emerging trial data.¹³ DSMBs are required for all NIH-funded multi-site clinical trials ‘involving interventions that entail potential risk to the participants’.¹⁴ Additionally, under the Exception from Informed Consent Rule,¹⁵ an independent DSMB is mandatory for emergency research trials seeking a waiver of subject’s informed consent.

In combination with considerable uptake in commercially sponsored trials, the result is the establishment of DSMBs in many—and possibly most—clinical trials. Jennifer Gewandter and her colleagues published a systematic review of randomized controlled trials published in six high-impact, general medical journals in 2014, and assessed the reported use of DSMBs. Out of 294 articles, 174 (59 per cent) mentioned the use of a DSMB. Of the remaining 119 articles, 59 had advised of the intended use of a DSMB in a clinical trials registry entry or a published protocol. Accordingly, 237 (81 per cent) of the trials reviewed likely included a DSMB.¹⁶ This is markedly higher than reported in a 2004 review of clinical trials in similar high-impact medical journals, which found the use of DSMBs in approximately 25 per cent of such trials.¹⁷ This could be a function of expanding use of DSMBs over time, or it could

¹⁰ 21 CFR 312.56(d).

¹¹ Equivalent obligations for sponsors of clinical device trials are set out at 21 CFR 812.40 and 21 CFR 812.46.

¹² International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2) 5.16.2 (2016), https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4_2016_1109.pdf.

¹³ Califf RM Morse MA, *Monitoring and ensuring safety during clinical research*, 285 JAMA 1201–1205 (2001). The background and history of DSMBs is further explained in Lisa Eckstein, *Building a More Connected DSMB: Better Integrating Ethics Review and Safety Monitoring*, 22 ACCOUNT. RES. 81, 105 (2015).

¹⁴ National Institutes of Health, NIH POLICY FOR DATA AND SAFETY MONITORING (1998), <http://grants.nih.gov/grants/guide/notice-files/not98-084.html> (accessed Apr 25, 2013).

¹⁵ 21 CFR 50.24(a).

¹⁶ Jennifer S. Gewandter et al., *Reporting of data monitoring boards in publications of randomized clinical trials is often deficient: ACTION systematic review*, 83 J. CLIN. EPIDEMIOL. 101, 107 (2017).

¹⁷ Matthew R. Sydes et al., *Reported use of data monitoring committees in the main published reports of randomized controlled trials: a cross-sectional study*, 1 CLIN. TRIALS 48, 59 (2004). A similar figure was reported in Mihaela

reflect the more comprehensive search methodology conducted by Gewandter and her colleagues, which included a search of published protocols and clinical trial registry entries for all published trials that failed to mention whether a DSMB had been constituted.

The DSMB is appointed by, and principally advises, the trial sponsor on the ongoing safety of trial participants and, often, whether the trial arms remain in a state of clinical equipoise. Membership typically includes a small number of experts, including clinicians in the relevant disease area and one or more statisticians.¹⁸ Most DSMBs perform their monitoring functions in accordance with a written charter, often drafted by the trial sponsor, or by the DSMB with subsequent agreement by the sponsor.¹⁹ In its Guidance Document *Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors*, the FDA advises that topics to be addressed in such a charter

would normally include a schedule and format for meetings, format for presentation of data, specification of who will have access to interim data and who may attend all or part of [DSMB] meetings, procedures for assessing conflict of interest of potential [DSMB] members, the method and timing of providing interim reports to the [DSMB], and other issues relevant to committee operations.²⁰

2.3 Informational Asymmetries Resulting from DSMB Review

Once a DSMB is established, with very limited exceptions, it is usually the only body to have access to unblinded interim trial safety and efficacy data. Sponsors have requirements to monitor trials for adverse events and, in certain cases, to inform regulators such as the FDA and trial investigators of such events either as individual cases or in an aggregated form.²¹ While these safety reports will usually be unblinded, the FDA has clarified that satisfying these requirements does not entail the need for sponsors to unblind themselves to trial results more generally. The Agency explains that:

Knowledge of the treatment received is necessary for interpreting [a serious adverse] event, may be essential for the medical management of the subject, and may provide critical safety information about a drug that could have implications for the ongoing conduct of the trial (e.g., monitoring, informed consent). *The Agency does not believe that unblinding single or small numbers of serious and unexpected adverse event cases will compromise the integrity of the study, in part because such unblinding should be infrequent.* (Emphasis added.)²²

Stegert et al., *An analysis of protocols and publications suggested that most discontinuations of clinical trials were not based on preplanned interim analyses or stopping rules*, 69 J. CLIN. EPIDEMIOL. 152, 160 (2016), which analysed the use of DSMBs in randomised clinical trial protocols approved by six research ethics committees in Switzerland, Germany, and Canada between 2000 and 2003.

¹⁸ Sydes et al., *supra* note 17.

¹⁹ FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR CLINICAL TRIAL SPONSORS: ESTABLISHMENT AND OPERATION OF CLINICAL TRIAL DATA MONITORING COMMITTEES 4.3 (2006), <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf> (accessed Aug 13, 2013).

²⁰ *Id.* at 4.3.

²¹ Safety reporting requirements are set out at 21 CFR 312.32.

²² Food and Drug Administration, SAFETY REPORTING REQUIREMENTS FOR INDs AND BA/BE STUDIES 16 (2012), <https://www.fda.gov/downloads/Drugs/Guidances/UCM227351.pdf> (accessed Nov 14, 2018).

Trial investigators are also required to send emerging safety information to reviewing IRBs, but again this information is limited in nature and often not associated with the contextual information necessary for any meaningful assessment.²³

Tight control over the use and disclosure of interim data is essential to maintain a trial's scientific integrity, including forestalling any concerns that a trial's sponsor might seek to change aspects of a trial's design to improve the chances of a positive finding. This was an issue, for example, in the 2013 Light Study, which sought to assess the cardiovascular risks associated with the anti-obesity drug Contrave. Although the study was blinded and a DSMB established, a (initially) small team at the sponsor company was given confidential access to interim data in order to file for FDA approval. At the time of access (25 per cent of primary endpoint events), the interim data appeared highly promising: if accurate, they would make Contrave one of the most effective cardiovascular drugs in history. What followed was a widespread leak of this information to over 100 people, including members of the sponsor company's board of directors who had a financial interest in the outcome of the trial. As a consequence of the widespread dissemination of unblinded data, and its potential to compromise trial integrity, the FDA advised that the Light Study would not be sufficient to satisfy the requirement of characterizing Contrave's cardiovascular effects. Instead, a new trial would be needed.²⁴ The Light Study's Executive Steering Committee subsequently voted to terminate the trial on the basis that 'the premature release of interim data had compromised the scientific integrity of the ongoing study'.²⁵

Maintaining the confidentiality of interim trial data also prevents sponsors, trial investigators, participants, and possible patients from prematurely adopting potentially fallacious trial results; in particular, prior to an expert determination of statistical and clinical significance.²⁶ To illustrate, the 25 per cent results detailed in the Light study disappeared once 50 per cent of primary endpoint events were analyzed.²⁷ In another trial, which assessed the potential survival advantages of five courses, as compared with four courses of chemotherapy for acute myeloid leukemia, interim reviews suggested large survival benefits for the additional course. The trial DSMB decided not to terminate the trial early for efficacy based on a lack of medical plausibility for the magnitude of the treatment effect along with a lack of associated reduction in relapse risk and, therefore, a likelihood that it was the result of chance. By the time the trial concluded, no survival differences were evident between the treatment arms.²⁸

²³ David L. DeMets, Norman Fost & Madison Powers, *An Institutional Review Board dilemma: responsible for safety monitoring but not in control*, 3 CLIN. TRIALS 142, 148 (2006); Eckstein, *supra* note 13.

²⁴ Center for Drug Evaluation and Research, SUMMARY REVIEW: APPLICATION NUMBER 200063ORIG1S000 (2014), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/200063Orig1s000SumR.pdf (accessed Nov 15, 2018).

²⁵ Steven E. Nissen et al., *Effect of Naltrexone-Bupropion on Major Adverse Cardiovascular Events in Overweight and Obese Patients With Cardiovascular Risk Factors: A Randomized Clinical Trial*, 315 JAMA 990, 1004 (2016).

²⁶ Thomas R. Fleming, Susan Ellenberg & David L. DeMets, *Monitoring clinical trials: issues and controversies regarding confidentiality*, 21 STAT. MED. 2843, 2851 (2002).

²⁷ Nissen et al., *supra* note 25.

²⁸ Keith Wheatley & David Clayton, *Be skeptical about unexpected large apparent treatment effects: the case of an MRC AML12 randomization*, 24 CONTROL. CLIN. TRIALS 66, 70 (2003).

For the above reasons, extensive DSMB practices and procedures have developed to limit the disclosure of emerging trial data. One common practice, for example, is the use of ‘open’ and ‘closed’ sessions of DSMB meetings. Open sessions review the general progress of the trial—for example, participant recruitment and data quality. In addition to DSMB members, open sessions may be attended by trial investigators and sponsor representatives. In comparison, unblinded efficacy and safety data is usually analyzed only in closed DSMB meetings, with attendance restricted to DSMB members and a trial statistician.²⁹ The importance of confidentiality is emphasized in the FDA *Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees*, which states that ‘Unblinded interim data and the results of comparative interim analyses ... should generally not be accessible by anyone other than [DSMB] members or the statistician(s) performing these analyses and presenting them to the [DSMB]’.³⁰ A Health Technology Assessment commissioned by the UK National Health Service on the use of DSMBs reported ‘near unanimity’ in the literature that interim data and DSMB deliberations should be kept confidential. It went on to stress the need for breaches of confidentiality to be treated ‘extremely seriously’.³¹

2.4 Stopping Rules as the Parameters for Disclosure

As evident from the above, clinical trials pose something of an informational quandary. On one hand, trial sponsors and investigators have ongoing obligations to ensure the legal, ethical, and commercial acceptability of trials. On the other hand, modern clinical trial practices shield sponsors and investigators from the vast majority of accruing trial information, which instead is kept tightly locked within an independent DSMB. ‘Stopping rules’ provide a means of bridging these competing requirements.

As their name suggests, stopping rules specify the circumstances in which a DSMB may alert a trial sponsor of information suggesting the need for early trial termination. A threshold issue in this regard is the form of stopping rule(s) to be implemented, including one or more of the following: ‘first, if the experimental treatment is clearly better than the control; second, if it is clearly worse than the control; and third, if it is clearly not going to be shown to be better than the control’.³² These can be summarized as stopping for efficacy, stopping for inferiority, and stopping for futility. Stopping rules also can relate to ‘excess risk’ or other emerging adverse events, summarized as ‘stopping for safety’. Stopping rules are commonly drafted by trial sponsors or investigators, and agreed to by DSMB members, sponsors, and investigators.³³ In a survey of researchers and biostatisticians who had served on a DSMB, the vast majority of researchers (83.8 per cent) and biostatisticians (75 per cent) reported that the stopping rule had been written into the trial protocol.³⁴ The FDA and IRBs review data monitoring plans,

²⁹ A M Grant et al., *Issues in data monitoring and interim analysis of trials*, 9 HEALTH TECHNOL. ASSESS. WINCH. ENGL. 1, 238, iii–iv (2005); Eckstein, *supra* note 13.

³⁰ FOOD AND DRUG ADMINISTRATION, *supra* note 19 at 10.

³¹ Grant et al., *supra* note 29 at 24.

³² John Whitehead, *Stopping clinical trials by design*, 3 NAT. REV. DRUG DISCOV. 973, 974 (2004).

³³ Matthew R. Sydes et al., *Systematic qualitative review of the literature on data monitoring committees for randomized controlled trials*, 1 CLIN. TRIALS 60, 79 (2004).

³⁴ Patti M. Tereskerz et al., *An Opinion and Practice Survey on the Structure and Management of Data and Safety Monitoring Boards*, 18 ACCOUNT. RES. 1, 30 (2011).

including any specified stopping rules, as a part of their risk-benefit assessment, but the criteria on which these plans are assessed is unclear.

Which stopping rules DSMBs operate within and the degree of specificity of these rules has not been comprehensively catalogued. Nevertheless, at least some trials have adopted extremely stringent boundaries, tightly constraining the circumstances in which a DSMB would alert a trial sponsor or trial steering committee of emerging trends. One such example is the Neonatal Oxygen Prospective Meta-analysis (NeO-ProM) Collaboration: a set of five trials that collectively set out to compare the effects of a lower oxygen-saturation target range (85 to 89 per cent) versus a higher target range (91 to 95 per cent) in extremely pre-term infants.³⁵ Two of these protocols specified that the DSMB should advise the trial steering committee of interim trial data if, in the DSMB's view, there is 'proof beyond reasonable doubt' of net clinical benefit or harm. The protocols went on to specify that a difference of at least three standard deviations in the interim analysis of a major endpoint may be needed to satisfy this threshold.³⁶

An obligation on the DSMB to establish 'proof beyond reasonable doubt'—again equated with a difference of greater than three standard deviations—also was included in the Heart Protection Study, reported in 2003. The stopping criterion was based on an increase or decrease in all-cause mortality: the primary endpoint for the trial.³⁷ Differences in secondary 'major morbidity' outcomes such as non-fatal myocardial infarction, stroke, and revascularization were not incorporated. By the second year of the trial, statistically significant differences in these major morbidity outcomes became apparent at a level of $P < 0.001$, 1.7 per cent absolute risk reduction (30 per cent relative risk reduction). Given these clear and compelling differences, commentators questioned whether the trial should have been stopped. On the one hand, this would have meant that the trial would never have answered the question of mortality and had a greater potential for type 1 (false positive) errors. On the other hand, Migrino and Topol noted that

from the perspective of subject safety and well-being, it does not appear to us that there is any choice other than to include major morbidity adverse events as stopping criteria. It is difficult to contemplate a compelling reason to continue a trial that has proven benefit (or harm) 'beyond a reasonable doubt' (or its statistical correlate) in terms of major morbidity such as myocardial infarction or stroke even if it means that the issue of mortality effect is not established'.³⁸

Further informational asymmetries can arise from a DSMB's *application* of stopping rules, particularly given the widely held position that the statistical boundaries

³⁵ Notably, this group of studies was the subjective of considerable ethical controversy, including the adequacy of the consent obtained from participants and the relative risks in comparative effectiveness research. See, e.g., John D. Lantos, *Learning the right lessons from the SUPPORT study controversy*, 99 ARCH. DIS. CHILD. - FETAL NEONATAL ED. F4, F5 (2014); Lois Shepherd, *SUPPORT and Comparative Effectiveness Trials: What's at Stake?*, 45 HASTINGS CENT. REP. 44, 45 (2015); ALAN R. FLEISCHMAN, *The Controversy over SUPPORT Continues and the Hyperbole Increases*, 45 HASTINGS CENT. REP. 42, 44 (2015).

³⁶ Outcomes of Two Trials of Oxygen-Saturation Targets in Preterm Infants, , 374 N. ENGL. J. MED. 749, 760 (2016), supplementary material.

³⁷ Raymond Q Migrino & Eric J Topol, *A matter of life and death? The Heart Protection Study and protection of clinical trial participants*, 24 CONTROL. CLIN. TRIALS 501, 505, 502 (2003).

³⁸ *Id.* at 503.

operate as guidelines rather than rules.³⁹ In other words, it is often within the permissible discretion of a DSMB to recommend trial continuation even after emerging trial data has reached a pre-specified stopping boundary. This was the case in the Breast Cancer Prevention Trial, presented in part one.⁴⁰ Other recently reported studies expressly acknowledge having progressed past a stopping boundary without the knowledge of sponsors and/or investigators.⁴¹ A DSMB may decide that trial continuation is warranted, for example, to gain additional information about potential adverse effects (e.g., the Breast Cancer Prevention Trial) or to obtain further information about secondary endpoints.⁴² John Lantos and Chris Feudtner explain these value-laden trade-offs as core to the role of DSMBs:

There is no completely objective way to determine whether a study ought or ought not to continue. If there were, then there would be no need for DSMBs. Instead, there would be straightforward stopping rules that could be invoked by study statisticians whenever the predetermined statistical threshold was reached. Instead, DSMBs must make difficult judgment calls when interim analyses show worrisome trends that have not yet—or have just barely—reached statistical significance.⁴³

The information feeding into any DSMB decision to recommend trial continuation past the point of a pre-specified stopping boundary will not be available to a reviewing IRB or the FDA, nor will these bodies necessarily be told that the data has reached any such a point. Accordingly there is very limited potential for contemporaneous decision-making oversight.⁴⁴ This raises the question of what other oversight mechanisms might be available, including post hoc review by courts of law.

3 LEGAL OBLIGATIONS ATTACHING TO EMERGING TRIAL INFORMATION

Part two demonstrated the tight confidentiality with which emerging trial information is held; in particular, by DSMBs. Often, this includes a siloing of information from clinical trial actors until an emerging trend can satisfy highly stringent tests for statistical certainty (and, perhaps, even beyond this point). Part three will canvass the key legal obligations that might compel clinical trial actors to disclose or otherwise act upon emerging trial information, including any potential for these obligations to conflict with common DSMB confidentiality practices. At least theoretically, actions could include allegations of lack of informed consent, negligent conduct, product liability, fraud, and breach of contract. For trials sponsored by publicly listed companies, non-disclosure might constitute securities fraud.

³⁹ Sydes et al., *supra* note 33; Wheatley and Clayton, *supra* note 28.

⁴⁰ Redmond, Constantino, and Colton, *supra* note 3.

⁴¹ For example, N. Jewel Samadder et al., *Effect of Sulindac and Erlotinib vs Placebo on Duodenal Neoplasia in Familial Adenomatous Polyposis: A Randomized Clinical Trial*, 315 JAMA 1266, 1275 (2016); Bhakti K. Patel et al., *Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial*, 315 JAMA 2435, 2441 (2016).

⁴² This was the rationale, for example, in Patel et al., *supra* note 41.

⁴³ John D. Lantos & Chris Feudtner, *SUPPORT and the Ethics of Study Implementation: Lessons for Comparative Effectiveness Research from the Trial of Oxygen Therapy for Premature Babies*, 45 HASTINGS CENT. REP. 30, 40 (2015).

⁴⁴ Eckstein, *supra* note 13.

3.1 Lack of Informed Consent

Obligations in US tort law to obtain the informed consent of a patient or clinical trial participant are well established, with the typical legal action alleging that a person was not given adequate information to allow him or her to meaningfully decide whether to participate in a clinical trial.⁴⁵ In *Lenahan v Univ. of Chicago*, for example, a participant in a clinical cancer trial successfully pleaded that the defendants (the University, University Hospital, and trial researchers) had a duty to provide him with an ‘adequate informed consent’.⁴⁶ This was equated with a consent compliant with FDA and DHHS rules and regulations—in particular, a consent form that specified ‘all the risks and alternatives to treatment’.⁴⁷

Implicit within consent requirements may be an obligation to seek *reconsent* from trial participants in certain circumstances, including on the basis of emerging trial information. An articulation of this duty was given in the case of *Mink v University of Chicago*, brought forward by 1,000 women who had been administered diethylstilbestrol in their prenatal care without their knowledge or consent as a part of a clinical trial.⁴⁸ The plaintiffs claimed that DES exposure had led to an increased risk of cancer for themselves and their children: a relationship that was known to the medical community by 1971 but was not notified to participants until as late as 1975 or 1976. Although the action was unsuccessful based on an absence of attributable injury, the U.S. District Court for the Northern District of Illinois agreed that the defendants had an ongoing duty to notify participants of emerging risks, including risks that came to light after treatment had concluded.⁴⁹

More recently, the Court of Appeals of Maryland emphasized the ongoing nature of informed consent obligations in *Grimes v Kennedy Krieger Institute*.⁵⁰ This lawsuit was brought forward by two children who had been recruited into a lead abatement study. Among other actions, they alleged a lack of informed consent because the research institute had failed to warn participants in a timely manner of unsafe blood lead levels. The *Grimes* court agreed that the requirement of informed consent ‘continues during the duration of the research study and applies to new or changing risks’.⁵¹

Notably, the FDA and DHHS rules and regulations specify the need for clinical trial consent forms to include a statement, ‘when appropriate,’ that participants will be provided with ‘significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation’.⁵² Statements to this effect have been adopted in a number of template patient information sheets and consent forms (PISCFs). As an example, the National Cancer Institute *Informed Consent Template for Adult Clinical Trials* includes the heading ‘If I Decide to Take Part Can I Stop Later?’ In part, this states, ‘Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the

⁴⁵ Mello, Studdert, and Brennan, *supra* note 7.

⁴⁶ *Lenahan v. Univ. of Chicago*, 348 Ill. App. 3d 155, 160, (2004).

⁴⁷ *Id.*

⁴⁸ *Mink v. University of Chicago* 460 F. Supp. 713 (N.D. Ill. 1978).

⁴⁹ *Id.*

⁵⁰ *Grimes v. Kennedy Krieger Inst., Inc.*, 366 Md. 29, 98, (2001).

⁵¹ *Id.*

⁵² 45 CFR 46.116 (b)(5) and 21 CFR 50.25 (b)(5).

study'.⁵³ The Stanford University Sample Consent Form includes a similar statement under the heading 'Participant Rights',⁵⁴ advising participants that 'You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study'.

The inclusion of a commitment to alert trial participants to 'significant new findings' in PISCFs also might constitute a stand-alone contractual obligation. In a few cases, courts have been willing to characterize PISCFs as a 'unilateral contract' between a researcher or a research institution and a participant.⁵⁵ As Mello and Joffe explain, in this kind of contract 'a promise (by the investigators and institution) is exchanged for a 'performance' (the subject's participation in a trial)'. They go on to note that 'this kind of contract does not bind the subjects to go through with the performance, but if they do, the promisor must fulfill the promise'.⁵⁶

3.2 Negligent Conduct

A failure to disclose or otherwise act upon emerging trial information also might form the foundation of a broader action in negligent trial conduct. That is, that a clinical trial actor has failed to 'carry out their defined obligations and duties with due care for participant safety'.⁵⁷

An action in negligent conduct is likely to be successful where a clinical trial actor has clear knowledge of an investigational product's lack of safety or efficacy. Analogous in this regard is E. Haavi Morreim's explanation of the litigation arising from highly experimental investigations conducted on glioblastoma patients at the Massachusetts Institute of Technology and the Massachusetts General Hospital. She recounts that, according to the federal district court, Dr. Sweet, the principal investigator,

had actual knowledge of the imprecision of the localization of the boron injections to the cancerous brain tissue and the related imprecision of the neutron radiation, with the result that unacceptably high degrees of radiation necrosis were occurring in these and other of his patients. In short, Sweet well knew during his care of these patients that his [experimental] treatments were not helping them, and, in fact, were causing severe side effects unrelated to the progressive effect of the fatal brain tumors. He pressed ahead anyway, believing in complete good faith that such experimentation on dying patients held out hope for other cancer victims. However praiseworthy his goal, his conduct with respect to the patients involved here was, as the jury found, negligent.⁵⁸

⁵³ National Cancer Institute, INFORMED CONSENT TEMPLATE (2017), https://ctep.cancer.gov/protocolDevelopment/informed_consent.htm (accessed Oct 26, 2018).

⁵⁴ Stanford University IRB, SAMPLE CONSENT FORM (2018), http://researchcompliance.stanford.edu/hs/new/resources/forms_templates/medical.html. (accessed Oct 26, 2018)

⁵⁵ E.g., *Abney v Amgen*, 443 F.3d 540 (2006); *Dahl v HEM Pharmaceuticals Corp*, 7 F.3d 1399 (1993). In other cases, PISCFs have not been accepted as a legal contract, e.g., *Smith v. Kennedy Krieger Inst., Inc.*, No. 2241, Sept Term 2014, 2017 WL 1076481 (Md. Ct. Spec. App. Mar. 22, 2017).

⁵⁶ Michelle M. Mello & Steven Joffe, *Compact versus Contract — Industry Sponsors' Obligations to Their Research Subjects*, 356 N. ENGL. J. MED. 2737, 2743 (2007).

⁵⁷ *Zeman v. Williams*, No. CIV.A. 11-10204-GAO, 2014 WL 3058298 at *3 (D. Mass. July 7, 2014).

⁵⁸ E. Haavi Morreim, *Medical Research Litigation and Malpractice Tort Doctrines: Courts on a Learning Curve*, 4 HOUST. J. HEALTH LAW POLICY 1, 40 (2003), citing *Heinrich ex rel. Heinrich v. Sweet*, 118 F. Supp. 2d 73, 90, 91 (D. Mass. 2000).

However, as explained in part two, modern clinical trial practices mean that unblinded safety and efficacy information most commonly is siloed within the confines of a DSMB. Accordingly, an action in negligence based on a failure to use or otherwise disclose clinical trial data would likely take the form of one of the following:

1. *An action against a trial DSMB for failure to undertake its monitoring obligations with due care for participant well-being.* Concerns about the potential for litigation to be brought directly against a DSMB or its members have been raised in the literature,⁵⁹ but has yet to be tested in a court in the US or elsewhere. However, scope for an action in negligent monitoring appear especially acute where a stopping boundary has been reached but a DSMB makes a decision to continue the trial—for example, to establish additional information about potential adverse effects or secondary efficacy endpoints. This assumes, however, that a potentially harmed participant *knows* about the DSMB decision and is able to overcome associated causation issues.⁶⁰
2. *An action against a trial sponsor or another clinical trial actor for failing to establish a safe study design.* Litigation could also focus on the monitoring processes and practices as articulated in the trial protocol and any available DSMB charter. This could stem from a duty on actors to ‘monitor the progress of their studies to ensure compliance with study protocols and the health and safety of participants’ in order to ‘protect participants generally from foreseeable harm caused by the drug studies themselves’, as articulated by the California Second District Court of Appeal in the unpublished case of *Liu v Janssen Research & Dev., LLC*.⁶¹ The case involved an action in negligence for the death of 17-year-old Augustine Liu. Despite early indications of a cardiac condition, Augustine was enrolled in a trial assessing the use of a new drug, risperidone, for schizophrenia. After receiving his first dose, Augustine developed cardiomyopathy, pneumonia, and failing liver function. He died four days later. The Court of Appeals overturned the jury’s finding of negligence on the basis that the sponsor’s duty did not extend to an obligation to diagnose or treat Augustine’s pre-existing disease or to intervene in his subsequent medical care.⁶² At least theoretically, however, the duty formulation proposed by the Court of Appeals could support an obligation for a trial sponsor or another clinical trial actor to suspend or terminate a trial for emerging safety or efficacy signals.

3.3 Other Tort Actions

Persons harmed by an alleged failure to monitor the safety or efficacy of a clinical trial also may seek to bring actions in other torts, most notably, product liability or fraud. Under product liability tort, a manufacturer—commonly the clinical trial sponsor—has obligations to warn of dangers in its products of which it knows, or which are

⁵⁹ David L. DeMets et al., *Liability issues for data monitoring committee members*, 1 CLIN. TRIALS 525, 531 (2004).

⁶⁰ See, e.g., Elizabeth R. Pike, *Recovering from Research: A No-Fault Proposal to Compensate Injured Research Participants*, 38 AM. J. LAW MED. 7, 62, 28 (2012).

⁶¹ *Liu v. Janssen Research & Dev., LLC*, No. B269318, 2018 WL 272219, at *6 (Cal. Ct. App. Jan. 3, 2018), review denied (Apr. 11, 2018), cert. denied, No. 18-97, 2018 WL 3536949 (US Oct. 1, 2018).

⁶² *Id.*

reasonably foreseeable.⁶³ The extent to which ‘reasonable foreseeability’ of dangers in a clinical trial product fits with stringent DSMB confidentiality conditions for unblinded trial data is unclear.

A failure to warn of interim trial data potentially could also support an action in fraud, as was alleged in the case of *Gelsinger v University of Pennsylvania Hospital*, stemming from the death of an 18-year old in a phase I gene therapy trial.⁶⁴ The Gelsinger family alleged that the researchers’ failure to reveal the death of monkeys injected with the virus and the serious adverse effects suffered by previous trial participants constituted fraud.⁶⁵ The case was settled confidentially.⁶⁶

3.4 Securities Fraud

Publicly listed pharmaceutical companies have duties of disclosure to their shareholders, including, in some instances, of emerging clinical trial data. The U.S. Securities and Exchange Commission requires publicly-listed companies to submit periodic updates, including, a statement of ‘management’s discussion and analysis of financial condition and results of operations’. Among other matters, this should include information on ‘any known trends or uncertainties that have had or that the registrant reasonably expects will have a material favorable or unfavorable impact on net sales or revenues or income from continuing operations’.⁶⁷

Under Rule 10(b) of the Securities Exchange Act of 1934, it is unlawful to ‘make any untrue statement of a material fact or to omit to state a material fact necessary in order to make the statements made, in the light of the circumstances under which they were made, not misleading’. Courts have implied a private cause of action into this rule. To succeed, a plaintiff must demonstrate all the following: ‘(1) a material misrepresentation or omission by the defendant; (2) scienter (explained below); (3) a connection between the misrepresentation or omission and the purchase or sale of a security; (4) reliance upon the misrepresentation or omission; (5) economic loss; and (6) loss causation’.⁶⁸

This raises the question of what constitutes a ‘material misrepresentation or omission’ for the purpose of Rule 10(b). Through the case of *Basic v Levinson*, the Supreme Court has held that the materiality element is satisfied when there is ‘a substantial likelihood that the disclosure of the omitted fact would have been viewed by the reasonable investor as having significantly altered the “total mix” of information made available’.⁶⁹ The Supreme Court has since clarified in the case of *Matrixx Initiatives, Inc. v Siracusano*, that materiality is not necessarily equivalent to statistical significance.⁷⁰ Depending on their source, content, and context, adverse event reports may significantly alter the total mix of information available to investors, despite not reaching the level of

⁶³ *Mulhall v. Hannafin*, 45 A.D.3d 55, 58 (2007).

⁶⁴ *Gelsinger v. University of Pennsylvania Hospital* (Pa. C., No. 001885, complaint filed Sept. 18, 2000)

⁶⁵ *Id.*

⁶⁶ Mello, Studdert, and Brennan, *supra* note 7.

⁶⁷ 17 CFR 229.303(a)(3)(ii).

⁶⁸ Joseph G. Milner, *Sunlight and Other Disinfectants: Disclosure Obligations under the Federal Securities and Drug Regulatory Regimes* H. Thomas Austern Writing Competition Winners, 72 FOOD DRUG LAW J. 141, 188 (2017); Katherine Cohen, Joseph W. Cormier & Mahnu V. Davar, *Predictable Materiality: A Need for Common Criteria Governing the Disclosure of Clinical Trial Results by Publicity-Traded Pharmaceutical Companies*, 29 J. CONTEMP. HEALTH LAW POLICY 201, 232 (2012).

⁶⁹ *Basic Inc. v. Levinson* 485 U.S. 224 (2010).

⁷⁰ *Matrixx Initiatives, Inc. v. Siracusano* 563 U.S. 27 (2012).

statistical significance or known causation. Rather, the Court held that a fact-specific inquiry was necessary to ascertain whether adverse events were material and needed to be disclosed.⁷¹

Beyond materiality, a plaintiff will also need to show that company representatives acted with *scienter*—the required state of mind. Any such action will depend on actual knowledge or, potentially, deliberate recklessness. Moreover, while the *Basic* standard imposes liability for material omissions, it exempts ‘pure omissions’. In order to be liable for an omission, the issuer must have a duty to disclose information.⁷² In the context of interim clinical trial results, such a duty of disclosure may arise if the company makes statements that—in the absence of information about the interim results—will mislead investors.⁷³

4 COURT ASSESSMENT OF ALLEGED DUTIES TO USE OR DISCLOSE INTERIM TRIAL DATA

Evident in the legal analysis set out in part three is the scope for considerable discretion in the manner in which a court might assess a legal claim stemming from an alleged failure to disclose or otherwise act upon interim clinical trial data. This is especially the case given the *prima facie* disconnect between accepted DSMB practices (i.e., confidentiality until interim trial data can satisfy stringent causative thresholds) and much broader legal disclosure obligations: for example, of information for which there is ‘reasonable evidence’ of adverse effect, or that might have a ‘material’ impact on a sponsor company’s revenues or impact.

The question for this paper was the manner in which US courts were assessing allegations that clinical trial actors had a duty to use or disclose emerging trial information, and how any such duties interacted with the siloing of information within independent DSMBs. A comprehensive search was conducted for US cases involving allegations that a clinical trial actor was under an obligation to disclose interim clinical trial data. Two large legal databases—*Thomson Reuters Westlaw* and *LexisNexis International*—were interrogated in July 2018 for all federal and state US decisions using various combinations of the following search terms: *clinical trial, research, drug, investigation, study, disclose, terminate, monitor, blind, Data and Safety Monitoring Board (DSMB), Data Monitoring Committee (DMC)*. Results were filtered manually for cases in which an obligation of disclosure of information relating to ongoing clinical trials or medical research was at issue. Excluded from analysis were cases such as *McDarby v Merck & Co., Inc.*, 401 (the Vioxx product liability case)⁷⁴ and *N.J. Carpenters Pension & Annuity Funds v Biogen* 537 F. 3d 35,⁷⁵ in which plaintiffs alleged a duty to interpret, disclose, or otherwise act upon data from *finalized* trials. The 21 cases that met these criteria are set out in Table 1.

4.1 Cases Brought Forward by Trial Participants or Patients

Only four cases were identified in which US courts adjudicated upon an action brought forward by a patient or research participant alleging that a trial sponsor or researcher

⁷¹ For discussion, see Milner, *supra* note 69; Cohen, Cormier, and Davar, *supra* note 69.

⁷² Milner, *supra* note 69.

⁷³ Cohen, Cormier, and Davar, *supra* note 70.

⁷⁴ *McDarby v. Merck & Co., Inc.*, 401 N.J. Super. 10, 28 (App.Div. May 29, 2008).

⁷⁵ *N.J. Carpenters Pension & Annuity Funds v Biogen* 537 F. 3d 35 (U.S. App., 2008).

Table 1. US cases alleging a duty to disclose or use interim trial data.

	<i>Case name</i>	<i>Citation</i>	<i>Legal action</i>
1	Grimes <i>v</i> Kennedy Krieger Institute	782 A.2d 807 (Md. Aug. 16, 2001)	Negligence
2	White <i>v</i> Kennedy Krieger Institute	221 Md.App. 601 (Md. Feb. 26, 2015)	Negligence
3	Parks <i>v</i> Howmedica Osteonics Corp.	No. 8:15-cv-75, 2015 WL 3581714 (M.D.Fla. Feb. 27, 2015)	Range of tort law actions, including design defect, manufacturing defect, failure to warn, negligence fraud by concealment, fraudulent misrepresentation, negligent misrepresentation, and breach of contract
4	Kinkaid <i>v</i> Inzucchi	No NNHCV126035005S, 2013 WL 5496537 (Conn. Super. Ct., Sept. 16, 2013)	Compulsion of discovery
5	In re Pfizer Inc. Securities Litigation	538 F.Supp.2d 621 (S.D.N.Y. Feb. 28, 2008)	Securities fraud
6	Lerner <i>v</i> Northwest Biotherapeutics	273 F.Supp.3d 573 (D. Md. Mar. 31, 2017)	Securities fraud
7	In re Alliance Pharmaceutical Corp. Securities Litigation	279 F.Supp.2d 171 (S.D.N.Y. Aug. 13, 2003)	Misrepresentation in violation of Securities Act

Table 1. continued

	<i>Case name</i>	<i>Citation</i>	<i>Legal action</i>
8	In re Human Genome Sciences Inc. Securities Litigation	933 F.Supp.2d 751 (D. Md. Mar. 26, 2013)	Securities fraud
9	Sanders v AVEO Pharmaceuticals, Inc.	No. 13-11157-DJC., 2015 WL 1276824 (D. Mass. Mar 20, 2015)	Securities fraud
10	In re Ariad Pharmaceuticals, Inc. Securities Litigation	98 F.Supp.3d 147 (D. Mass. Mar. 24, 2015) Appeal affirmed in part, reversed in part in 842 F.3d 744	Securities fraud
11	In re Elan Corp. Securities Litigation	543 F.Supp.2d 187 (S.D.N.Y. Mar. 27, 2008)	Securities fraud
12	Nguyen v New Link Genetics Corp.	297 F.Supp.3d 472 (S.D.N.Y. Mar. 29, 2018)	Securities fraud
13	Weinstein v. Kirkman	No. C13-0769-JCC, 2013 WL 12121125 (W.D. Wash. Sept. 16, 2013)	Securities fraud
14	Fortunato v Akebia Therapeutics, Inc.	34 Mass.L.Rptr. 78 (Mass. Super. Feb. 21, 2017)	Misrepresentation in violation of Securities Act
15	Erste-Sparinvest Kapitalanlagegesellschaft MBH v Seres Therapeutics, Inc.	No. 16-111943, 2018 WL 1567614 (D. Mass. Mar. 30, 2018)	Securities fraud

Table 1. continued

	<i>Case name</i>	<i>Citation</i>	<i>Legal action</i>
16	Vallabhaneni <i>v</i> Endocyte, Inc.	No. 1:14-cv-01048-TWP-MJD, 2016 WL 51260 (S.D. Ind., Jan. 4, 2016)	Securities fraud
17	In re Intrabiotics Pharmaceuticals, Inc. Securities Litigation	No. C 04-02675 JSW, 2006 WL 708594 (N.D. Cal., Jan. 23, 2006), motion to dismiss second consolidated complaint granted on Aug. 1, 2006.	Securities fraud
18	City of Bristol Pension Fund <i>v</i> Vertex Pharmaceuticals Inc.	12 F.Supp.3d 225 (D. Mass. Mar. 31, 2014)	Securities fraud
19	Huang <i>v</i> Avalanche Biotechnologies, Inc.	No. 15-cv-03185-JD, 2016 WL 6524401 (N.D. Cal. No <i>v</i> 3, 2016)	Securities fraud
20	Shah <i>v</i> GenVec, Inc.	No. DKC 12-0341., 2013 WL 5348133 (D. Md, Sept, 20, 2013)	Securities fraud
21	Security Police and Fire Professionals of America Retirement Fund <i>v</i> Pfizer, Inc., appealed in City of Edinburgh Council <i>v</i> Pfizer, Inc.	No. 10-cv-3105, 2013 WL 1750010 (D.N.J., Apr. 22, 2013)	Securities fraud

was under a duty to disclose or otherwise act upon interim trial data. This likely reflects challenges that have been more broadly identified for research participants face in mounting successful tort actions.⁷⁶ However, the available cases show a clear willingness to accept FDA review of trial methodology and the blinding process. In particular, the cases evidence a judicial unwillingness to unblind, or to require unblinding, when there is evidence of an operational (though not necessarily detailed) monitoring process.

The strongest support for a duty on researchers and others to provide participants with information obtained during the course of research comes from the case of *Grimes v Kennedy Krieger Institute*.⁷⁷ This case surrounded a research study investigating lead abatement procedures, specifically more cost-effective partial abatement. Effectiveness was to be determined by levels of lead dust in the home, as well as blood lead levels of child participants living in the selected homes. Plaintiffs brought forward an action in negligence arguing that researchers had a duty to inform them more clearly of the fact that some lead dust was expected to accumulate in their children despite the ablation procedures that had been conducted, and to promptly advise them of individual lead test results.

The Court of Appeals of Maryland held that researchers entered into a ‘special relationship’ with child participants, which included a duty to—at a minimum—promptly provide them and their parents with ‘any information that might bear on their willingness to continue to participate in the study’ including ‘full, detailed, prompt, and continuing warnings as to all the potential risks and hazards inherent in the research or that arise during the research’.⁷⁸ The Court put forward a strong role for the judiciary in overseeing the medical and scientific community, including the decisions of reviewing IRBs, opining that ‘IRBs, are, primarily, in-house organs’ which are ‘not designed, generally, to be sufficiently objective in the sense that they are as sufficiently concerned with the ethicality of the experiments they review as they are with the success of the experiments’.⁷⁹ In noting the limits of participant consent in defining the scope of researcher duties, the Court stated:

The duty to a vulnerable research subject is independent of consent, although the obtaining of consent is one of the duties a researcher must perform. . . . Such legal duties, and legal protections, might additionally be warranted because of the likely conflict of interest between the goal of the research experimenter and the health of the human subject, especially, but not exclusively, when such research is commercialized. There is always a potential substantial conflict of interest on the part of researchers as between them and the human subjects used in their research. If participants in the study withdraw from the research study prior to its completion, then the results of the study could be rendered meaningless. There is thus an inherent reason for not conveying information to subjects as it arises, that might cause the subjects to leave the research project. That conflict dictates a stronger reason for full and continuous disclosure.⁸⁰

⁷⁶ Pike, *supra* note 60.

⁷⁷ *Grimes v Kennedy Krieger Institute*, 366 Md. 29, (2001).

⁷⁸ *Id* at 843.

⁷⁹ *Id* at 817.

⁸⁰ *Id* at 850–51. Emphasis added.

The strong judicial oversight of research advocated by the *Grimes* Court was subject to immediate discussion and controversy,⁸¹ and, following on from a motion for reconsideration, the judgment's precedent was limited only to the conclusion that summary judgment was improperly granted.⁸² The lack of weight that the *Grimes* precedent may have for subsequent courts, and a marked shift towards judicial deference for the scientific process, was evident in the subsequent case of *White v Kennedy Krieger Institute*.⁸³ This case arose from a related lead abatement study conducted by KKI in the 1990s. The Treatment of Lead-Exposed Children Study ('TLC Study') was designed to study methods to lower lead poisoning in inner cities, through some environmental modifications and nutritional supplements, as well as a double-blinded component investigating the effects of the drug succimer—which had already been approved for use in children with extremely elevated lead blood levels—in children with moderate lead exposure. As a part of this investigation, blood levels were taken from study participants two weeks after each round of treatment. Test results were reported to the Data Coordinating Center, which would notify KKI if a child's blood lead level exceeded pre-specified thresholds.⁸⁴ The plaintiff, Tyron White, brought an action against KKI alleging that, due to the Institute's negligent conduct in this study he was exposed to harmful levels of lead resulting in irreparable brain injuries.

At trial, a jury deliberated on whether KKI was negligent in planning and implementing the TLC study, including whether it had breached a duty to participants. The jury ultimately decided that it had not. In his jury instruction, the trial judge described the researchers' duty as being to use reasonable care to ensure 'the protection of the study participants from unreasonable harm' including 'completely and promptly inform[ing] the participants of potential hazards existing during the study'. The plaintiffs appealed this instruction as failing to capture the full extent of researcher duties, as set out in *Grimes*, being to provide 'full, detailed, prompt, and continuing warnings as to all the potential risks and hazards inherent in the research or that arise during the research'. This more extensive duty formulation was rejected on appeal. For the Maryland Court of Special Appeals, the double-blinded nature of the study was particularly pertinent in limiting any 'special duties' that might be imposed on researchers, including any duty to warn about a child's elevated blood lead levels:

Even if White's proposed instruction ... properly reflected the holding of the *Grimes* Court (that a special relationship may be created by the researcher's special knowledge that in turn gives rise to a duty to warn), it would still fail on the facts of the TLC

⁸¹ For example, Leonard H. Glantz, *Nontherapeutic Research with Children: Grimes v Kennedy Krieger Institute*, 92 AM. J. PUBLIC HEALTH 1070–1073 (2002); Loretta M. Kopelman, *Pediatric Research Regulations under Legal Scrutiny: Grimes Narrows Their Interpretation*, 30 J. LAW. MED. ETHICS 38–49 (2002); Diane E. Hoffmann & Karen H. Rothenberg, *Whose Duty Is It Anyway: The Kennedy Krieger Opinion and Its Implications for Public Health Research Symposium: Research with Children: The New Legal and Policy Landscape: The Kennedy Krieger Case*, 6 J. HEALTH CARE LAW POLICY 109, 147 (2002).

⁸² Discussed in *White v. Kennedy Krieger Institute* 221 Md.App. 601 (Md. Feb. 26, 2015).

⁸³ *Id.*

⁸⁴ If a child's blood lead level was 45 mcg/dL or higher, KKI was to retest within three days. If the level remained 45 mcg/dL or higher after retesting, participation in the study treatment would pause, and the child would be treated in accordance with normal protocol for children with moderate blood lead levels. If the child's blood lead level measured above 60 mcg/dL, participation in the study would end immediately and the child be treated according to normal treatment protocols for children with extreme blood lead levels.

Study. In *Grimes*, the special knowledge that the researchers had—but that the parents lacked—was knowledge of the child subjects' elevated blood lead levels. Here, however, the TLC Study was double blind, and pursuant to the TLC Study Protocol, KKI was not notified of the results of an individual child's blood lead levels unless the child's blood lead level went above 44 mcg/dL. At any point that a child's lead levels were confirmed to be higher than 44 mcg/dL during the TLC Study, KKI was required to notify the parent, end the child's participation in the TLC Study, and begin treating the child according to KKI's standard procedure for treating children with blood lead levels above 44 mcg/dL. Prior to a child's blood lead level reaching above 44 mcg/dL, KKI was not notified of fluctuations in blood lead levels, and therefore could not pass along that information to the parents. Thus, the TLC Study Protocol by design prevented KKI from having the specific knowledge of a child's elevated lead levels that in *Grimes* were found to, at times, give rise to special duties.⁸⁵

In one of the few other cases in which a US court has adjudicated on an alleged duty to use and disclose interim trial data, the court dismissed any such duty based on FDA pre-emption through the Medical Devices Act of 1976 (MDA), thereby excluding the application of state tort laws. The unreported judgment of *Parks v Howmedica Osteonics Corp.* involved a range of actions in tort stemming from a clinical trial of CerviCore Intervertebral Disc ("CerviCore").⁸⁶ The sponsor company Howmedica Osteonics Corp. (HOC) developed CerviCore as an alternative to anterior discectomy and fusion procedures. HOC obtained an FDA Investigational Device Exemption (IDE) under the MDA to initiate a randomized clinical trial of the unit. According to the plaintiff complaint, considerable adverse events materialized during the course of the trial, including evidence of device failure and the release of metal debris into participants' bodies. HOC ultimately terminated device development and the CerviCore trial. The plaintiff—a trial participant who was randomized to receive the CerviCore unit—brought forward a range of actions (defective product design and manufacture, failure to warn, negligence and gross negligence, and fraudulent and negligent misrepresentation) against HOC grounded in a failure to protect trial participants from dangers of which it should have been aware. The United States District Court Middle District of Florida held that the FDA's granting of an IDE pre-empted any such causes of action,⁸⁷ given that a fact-finder could find liability even if a manufacturer had complied with all relevant FDA regulations. This was consistent with other cases in which courts have assessed the application of state tort laws such as product liability and failure to warn in the context of devices for which a sponsor has obtained an IDE.⁸⁸

A quite different action was brought forward by Sara Kinkaid, a plaintiff in a class action against the manufacturer of Actos (pioglitazone) alleging a lack of warning about

⁸⁵ *Id* at 740.

⁸⁶ *Parks v. Howmedica Osteonics Corp.*, No. 8:15-cv-75, 2015 WL 3581714 (M.D.Fla. Feb. 27, 2015).

⁸⁷ This was based upon the provision in the Medical Device Act of 1976 stating that, 'no State or political subdivision of a State may establish or continue in effect with respect to a device intended for human use any requirement—(1) which is different from, or in addition to, any requirement applicable under this chapter to the device, and (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under this chapter'.

⁸⁸ For example, *Blinn v. Smith & Nephew Richards, Inc.*, 55 F. Supp. 2d 1353, 1359 (M.D. Fla. 1999); *Fowler et al. v. Smith & Nephew Richards, Inc.*, No. 97-1380-CIV-J-10B, 1999 WL 1132967 (M.D. Fla. Sept. 27, 1999); *Slater v. Optical Radiation Corp.*, 961 F.2d 1330 (7th Cir. 1992); *Dorsey v. Allergan, Inc.*, No. 3:08-0731, 2009 WL 703290 (M.D. Tenn. Mar. 11, 2009).

the link between Actos and bladder cancer. In the case of *Kinkaid v Inzucchi*, Ms Kinkaid sought data from an ongoing clinical trial being conducted by the Yale School of Medicine assessing whether pioglitazone is effective in lowering the risk of stroke or myocardial infarction among non-diabetic persons who have suffered recent ischemic stroke or transient ischemic attack and who are insulin resistant ('the IRIS study').⁸⁹ Ms Kinkaid sought to compel information on the incidence of bladder cancer in IRIS study participants, including unblinding of the treatment group for the eleven study participants at that time diagnosed with bladder cancer. The Connecticut Superior Court denied the request based on the need to maintain the integrity of the IRIS trial: 'While the court recognizes that the discovery of the sought information may potentially be useful to the plaintiff if statistically significant, the risk of jeopardizing the integrity of the study outweighs the potential benefit to the plaintiff'.⁹⁰ It further noted that

the DSMB, which is responsible for assuring the scientific conduct and the safety of the study, has reviewed the treatment arm data biannually, has reviewed the actual treatment assignments since 2011 and has not indicated in any of its reports that it has concerns regarding the nexus between pioglitazone and bladder cancer.⁹¹

Although the IRIS study protocol provided the DSMB with significant leeway in terms of adverse event monitoring, the monitoring process for the study was not raised in party filings or the judgment. Under the heading 'Analysis of Adverse Events', the protocol specified that 'The incidence of serious adverse events ... and any adverse events ... will be calculated and compared among the treatment groups using statistics appropriate for discrete or count data. Time to adverse events will also be monitored and compared between treatment arms'.⁹² The only additional guidance comes under the heading 'Responsibilities' and tasks the DSMB with 'monitor[ing] interim data regarding the safety and efficacy of the study regimen so that the trial will be concluded as soon as there is convincing evidence of the treatment effect' and 'advise[ing] the [trial sponsor] and the investigators as to whether a protocol should continue as scheduled or undergo modification due to a finding from the monitoring process'.⁹³ This is in no way intended to criticize the protocol, especially given the challenge of meaningfully specifying stopping criteria for safety in the absence of prior knowledge of likely adverse events and rates. Yet the result is considerable DSMB discretion in determining the threshold at which to advise sponsors and investigators of any emerging concerns: a discretion that warrants (at a minimum) recognition when it comes to the weight the judiciary and others place on DSMB reviews.

⁸⁹ No NNHCv126035005S, 2013 WL 5496537 (Conn. Super. Ct., Sept. 16, 2013).

⁹⁰ *Kinkaid v. Inzucchi*, No NNHCv126035005S, 2013 WL 5496537 (Conn. Super. Ct., Sept. 16, 2013) at *4.

⁹¹ *Id.*

⁹² Walter N. Kernan et al., *Pioglitazone after Ischemic Stroke or Transient Ischemic Attack*, 374 N. ENGL. J. MED. 1321, 1331 (2016), supplementary materials. Notably, the pivotal trial publication advised that incident bladder cancer occurred in 12 patients in the pioglitazone group and in 8 in the placebo group ($P = 0.37$). The total incidence of cancer did not differ significantly between the two groups (133 patients and 150 patients, respectively; $P = 0.29$): *Id.*

⁹³ Kernan et al., *supra* note 92, supplementary materials.

4.2 Cases Brought Forward by Sponsor Company Shareholders

A total 17 cases were identified in which shareholders of a sponsor company brought an action alleging securities fraud based on the non-disclosure of interim trial information. Once again, the prevailing trend was clear judicial acceptance of arguments grounded in scientific methodology and the availability of oversight through specialized regulators such as the FDA.

4.2.1 Allegations of Non-Disclosure Through Study Design

Only one case expressly dealt with trial design and stopping rules as a tool available to sponsor companies to limit their knowledge of interim trial data and, accordingly, their disclosure obligations. *In Re Pfizer, Inc. Securities Litigation* stemmed from clinical trials of a drug torcetrapib, which Pfizer was developing as a potential treatment for coronary heart disease.⁹⁴ Phase 3 trials of the drug were terminated after a DSMB recommendation citing an imbalance of mortality and cardiovascular events. Shareholders argued that Pfizer had acted misleadingly by failing to disclose facts that lessened the likelihood that torcetrapib would prove safe and effective. Most relevantly, that Pfizer had ‘designed the phase 3 trials to allow the trial to continue until an unreasonably high standard of statistical certainty was met’.⁹⁵ The Amended Class Action Complaint substantiated this claim, advising that the trial stopping rule was set at a level of $P < 0.01$, arguing that:

While such a degree of certainty might have application where a patient population is terminally ill—and therefore the risk of death from continuation of the trial is lessened—it clearly had no application here where the patient population was generally healthy. Using a 95 per cent certainty level that adverse results were caused by torcetrapib would have had no negative impact on the study other than to end it earlier and potentially save lives.⁹⁶

The United States District Court for the Southern District of New York granted Pfizer’s motion to dismiss. To the extent that the Court engaged with the claimed misbehavior surrounding trial design, it accepted the stopping boundary as ‘an appropriate measure of statistical significance’.⁹⁷ Moreover, it noted that—without more—a ‘conclusory allegation’ based on trial design is insufficient evidence of a defendant’s fraudulent intent.

Plaintiffs in the case of *Lerner v Northwest Biotherapeutics* also sought to draw links between alleged deficiencies in oversight processes and non-fulfillment of sponsor disclosure obligations.⁹⁸ At issue in this case were sponsor press releases citing ‘encouraging results’ from an ongoing phase 3 trial of a cancer immunotherapy, DCVax-L. On Aug. 21, 2015, the FDA issued a clinical hold on trial recruitment, leading to a 22 per cent drop in share prices.

⁹⁴ *In re Pfizer, Inc. Sec. Litig.*, 538 F. Supp. 2d 621, 636 (S.D.N.Y. 2008).

⁹⁵ *Id.*

⁹⁶ Amended Class Action Complaint, 94-98, *In re Pfizer, Inc. Sec. Litig.*, No. 1:06-cv-14199-LAK (S.D.N.Y., Apr. 2, 2007).

⁹⁷ *In re Pfizer, Inc. Sec. Litig.*, 538 F. Supp. 2d 621, 637 (S.D.N.Y. 2008).

⁹⁸ *Lerner v Northwest Biotherapeutics* 273 F.Supp.3d 573 (D. Md. Mar. 31, 2017).

One of the statements with which plaintiffs took issue was a sponsor company press release issued on Mar. 7, 2014 stating that the DSMB had made an ‘unblinded review of the safety data ... and recommended that the trial continue as planned. The DSMB’s review of the efficacy data is still pending’. Plaintiffs alleged that the interim review had actually commenced in 2013 and would only have taken a few weeks to complete and, accordingly, the review ‘was either completed and buried, or the DSMB had been directed not to complete it’.⁹⁹ The United States District Court for the District of Maryland dismissed the action. Based on the available facts, Justice Hazel did not accept that an efficacy review had, in fact, been conducted. He further emphasized the separation between DSMB processes and the sponsor company, stating that ‘it is unclear from the Complaint how Plaintiffs attribute the alleged shortcomings of the safety board review to Defendants given their stated lack of involvement’.¹⁰⁰

4.2.2 *Inferences Regarding Sponsor Knowledge About Relative Safety or Efficacy of Trial Interventions*

Other cases have sought to base sponsor company disclosure obligations on inferences about what information the company know, or should have known, about the respective merits of trial interventions.

(a) *Unblinded Data*. For unblinded trials, the availability of information to the sponsor company is relatively straightforward, with the criteria for disclosure therefore depending on judicial determinations of the materiality of the information and any scientist in sponsor decision-making. *In re Alliance Pharmaceutical Corp. Securities Litigation* provides one of the few examples in which a court has upheld the sufficiency of plaintiff shareholder pleadings with respect to duties to disclose emerging trial information.¹⁰¹ One of the issues in this trial was the disclosures necessary to shareholders of MBI—a company with which the defendant company Alliance was merging. Shareholders of MBI voted to approve the merger on Dec. 29, 2000. A prospectus had been issued in connection with the merger on Nov. 9, 2000, with updates on Nov. 22 and 29, 2000. At the time the merger was on foot, information was emerging about Oxygent, Alliance’s ‘premiere’ investigation product: an oxygen carrier being developed to reduce the need for blood transfusions during surgery. Most importantly, an ongoing phase 3 trial had begun to show an imbalance of stroke events between the investigational and control arm. On Dec. 19 and 20, 2000 this imbalance became statistically significant, a fact that was known to sponsor company personnel. Based on this imbalance, the sponsor company amended the trial inclusion criteria to exclude persons who appeared to be at a higher risk of stroke. Trial investigators were informed of these amended criteria on Dec. 22, 2000. Further adverse event information was received in early January, leading to suspension of the trial on January 8, 2001 and an associated press release. Plaintiffs argued that Alliance was under a duty to amend its registration statement to reflect this imbalance in adverse events prior to the time it became effective (Dec. 29, 2000 or possibly several days later at the time the merger was finalized).

While the United States District Court for the Southern District of New York emphasized that there was no duty on sponsor companies to provide ‘status updates’ on

⁹⁹ *Id* at 57.

¹⁰⁰ *Id*.

¹⁰¹ *In re Alliance Pharmaceutical Corp. Securities Litigation* 279 F.Supp.2d 171 (S.D.N.Y., 2003).

clinical trial activities, it accepted that clinical trial developments adverse enough to cause changes in the trial protocol had at least the potential to satisfy disclosure requirements. In upholding the adequacy of the pleadings in this regard, Justice McMahon adopted a cautionary tone:

Plaintiffs will have their day in court, but they obviously face a much greater burden in convincing a trier of fact of defendants' liability than they have overcome here by defeating defendants' motion for summary judgment. Plaintiffs must show that, under the totality of the circumstances, defendants were aware, as of the materiality date, that the increase in adverse events cast doubt on the previous positive results of Oxygent.¹⁰²

Similar caution in interpreting and enforcing disclosure requirements was evident in *In Re Human Genome Sciences Inc Securities Litigation*, in which the United States District Court for the District of Maryland was unwilling to infer scienter from a sponsor company's non-disclosure of attempted and actual suicides in an ongoing, unblinded extension study. Justice Titus noted that, 'While it is possible to infer that HGS executives deliberately omitted facts about the attempted and actual suicides in order to hoodwink investors, it is just as plausible, indeed more so, to infer that they only offered vague details about the study because it was ongoing'.¹⁰³

Other judgments that have sought to assess disclosure obligations attaching to emerging trial information have used FDA actions as a marker for the materiality of the information. In *Sanders v Aveo Pharm., Inc.*, for example, evidence began to emerge during unblinded phase 3 trials of an investigational kidney cancer drug of higher death rates in the intervention as compared with the control arm.¹⁰⁴ The FDA held a meeting with the sponsor in which it raised concerns about the adverse overall survival trend. Although the overall survival data were not 'fully mature', the United States District Court for the District of Massachusetts agreed that the sponsor's failure to disclose 'an unmistakable and worsening trend'—in particular, one that had been the subject of FDA warnings—was materially misleading.

This can be compared with *In re Ariad Pharm. Inc.*, in which the Court did not accept that likely sponsor knowledge of an 'increasing rate and pattern' of adverse events in trials for ponatinib, an investigational chronic myeloid leukemia drug required disclosure in stock offering materials.¹⁰⁵ This was based on the fact that only six months' worth of trial data would be covered in the disputed period. Influential for the court in assessing the materiality of the information was an FDA requirement from the preceding year for data to be resubmitted after an additional 12 months. The Court reasoned from this that data from a six-month period—as compared with a 12-month period—was too preliminary from which to draw sound conclusions.¹⁰⁶ Similar caution was evident in

¹⁰² *Id.*

¹⁰³ *In Re Human Genome Sciences Inc Securities Litigation* 933 F.Supp. 2d 751 (D. Md. Mar 22, 2012).

¹⁰⁴ *Sanders v. Aveo Pharm., Inc.*, No. CIV.A. 13-11157-DJC, 2015 WL 1276824 (D. Mass. Mar. 20, 2015).

¹⁰⁵ *In re Ariad Pharm. Inc* 98 F.Supp. 3d 147 (D. Mass. 2015).

¹⁰⁶ An appeal of this finding was dismissed by the U.S. Court of Appeals, First Circuit, based on insufficient evidence that the plaintiffs satisfied the requirement of having purchased shares that were the direct subject of the prospectus and registration statement: *In re Ariad Pharm., Inc. Sec. Litig.*, 842 F.3d 744 (1st Cir. 2016). The Court of Appeal overturned one District Court grant of a motion to dismiss, being a failure of the sponsor company to identify the high incidence of serious cardiovascular events in the trial after the FDA had raised concerns about the events, and dismissed the sponsors proposed label to better reflect these events.

In *Re Elan Corp Securities Litigation*, in which the United States District Court for the Southern District of New York failed to uphold the materiality of non-disclosures of emerging safety events in phase 3 clinical trials based on a lack of evidence of a statistically significant relationship with the product.¹⁰⁷

(b) *Blinded Information*. In a number of trials involving blinded safety and efficacy data, courts were asked to make inferences about sponsor knowledge of emerging trends. These were rejected unanimously.

The facts of *Nguyen v NewLink Genetics Corp.*, for example, were presented briefly in the introduction to this paper.¹⁰⁸ It involved a securities fraud action that shareholders brought against a clinical-stage biopharmaceutical company. The action alleged that the company fraudulently failed to disclose emerging information from a phase 3 trial showing lack of efficacy of the company's most progressed treatment candidate—the HyperAcute Pancreas. The trial protocol allowed for four DSMB reviews after pre-specified numbers of participant deaths. If the overall survival of participants in the treatment group exceeded that of control arm participants by pre-specified amounts, the DSMB could recommend trial termination. Otherwise, the study was to continue. The trial continued for its full duration. On completion, NewLink reported that the treatment arm of the study had a lower overall survival than the control arm (27.3 months and 30.4 months respectively). NewLink share prices dropped precipitously.

The question for the Court was whether NewLink acted fraudulently in press releases while the trial was ongoing, including making a statement after the first interim review that 'it is reassuring that no unexpected safety issues or other concerns were raised by the independent data safety monitoring committee'. The Court held that it had not. A key consideration was the lack of sponsor knowledge of accruing survival rates:

Importantly, NewLink and its officers and directors *were blinded to the results of the clinical trial*. At each clinical trial milestone, an independent monitoring committee analyzed data to determine whether the overall survival of trial participants receiving NewLink's immunotherapy exceeded that of a separate group of participants treated with standard chemotherapy.¹⁰⁹

Other judgments further stressed the separation between DSMB oversight and review of blinded information and sponsor knowledge that could lead to duties of disclosure. In the case of *Weinstein v Kirkman*, the United States District Court for the Western District of Washington assessed allegations of security fraud based on the non-disclosure of emerging efficacy information of the investigational drug L-BLP25 from phase 3 clinical trials.¹¹⁰ The Court did not accept the fact that the DSMB had conducted two interim efficacy reviews as allowing an inference that the sponsor company had been informed of results. In allowing the motion to dismiss, the District Court

¹⁰⁷ *In Re Elan Corp Securities Litigation* 543 F.Supp.2d 187 (S.D.N.Y. Mar. 27, 2008). This reasoning would likely be inconsistent with the subsequent Supreme Court case of *Matrixx Initiatives Inc. v. Siracusano*, 131 S. Ct. 13098 (2011).

¹⁰⁸ *Nguyen v. New Link Genetics Corp.* 297 F. Supp. 3d 472 (S.D.N.Y. Mar. 29, 2018)

¹⁰⁹ *Id* at 478. Emphasis added.

¹¹⁰ *Weinstein v. Kirkman* No. C.13-0769-JCC, 2013 WL 12121125 (W.D. Wash. Sept. 16, 2013).

criticized any such inference as ‘not reasonable because it fundamentally misunderstands the purpose of an independent interim review of an ongoing clinical trial.’¹¹¹ It went on to state that

The Court cannot reasonably infer that ... trial data was disclosed to the board based solely on the importance of L-BLP25 to [the sponsor’s] financial prospects because such a disclosure would defeat the purpose of an independent committee and potentially undermine the usefulness of the ... trial in obtaining regulatory approval to market L-BLP25.

Notably, the trial at issue in this litigation—the Cancer Vaccine Study for Unresectable Stage III Non-small Cell Lung Cancer (START) trial—adopted one of the most rigorous stopping boundaries for interim analyses, being the O’Brien Fleming group sequential design.¹¹² Under this approach, the stopping boundaries for the two interim analyses would be $P < 0.006$ and $P < 0.0151$ for the first and second analysis respectively. While this gives weight to the argument that information was kept siloed from sponsor company representatives, it raises other questions about study design, including decisions about thresholds for disclosure.

A similar judicial focus on the siloed nature of trial information arose with respect to allegations of non-disclosure of safety events in the case of *Fortunato v Akebia Therapeutics, Inc.*¹¹³ At issue was an alleged sponsor violation of the Securities Act of 1933 by issuing a registration statement that failed to disclose information about adverse events occurring in phase 2b clinical trials. The plaintiffs argued that Akebia as the trial sponsor should have been aware of SAEs in trial participants, including that a greater proportion of safety events were occurring in treatment group as compared with control group participants.¹¹⁴ The Court accepted that trial sponsors had duties to assess safety events, including, in certain circumstances, unblinding events to determine whether they met the criteria for FDA reporting. However, in the absence of clear and particularized evidence of unblinding, the Court was unwilling to infer sponsor company knowledge of differences in safety events between trial arms.¹¹⁵ The United States District Court for the District of Massachusetts also declined to infer that a sponsor company had access to unblinded safety information in the case of in *Erste-Sparinvest Kapitalanlagegesellschaft MBH v Seres Therapeutics*, noting:

Sponsors receive notice of SAEs that occur in their trials, ..., but such notice does not ‘unblind’ the patient, by revealing whether they were in the SER-109 or placebo groups, to report these SAEs to the FDA unless, in relevant part, the event relates to an endpoint of the study ... and there is a ‘causal relationship between the drug and the

¹¹¹ *Id* at 3.

¹¹² Charles Butts et al., *Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial*, 15 LANCET ONCOL. 59, 68 (2014).

¹¹³ *Fortunato v. Akebia Therapeutics, Inc.* 34 Mass.L.Rptr. 78 (Mass. Super. Feb. 21, 2017).

¹¹⁴ According to the plaintiff complaint, 23.9 per cent of participants in the treatment group reported a SAE, compared with 15.3 per cent in the control group. Renal-related SAEs occurred in 13 participants in the treatment group as compared with 2 in the control group: First Amended Class Action Complaint and Jury Trial Demand, *Fortunato v. Akebia Therapeutics, Inc.*, No. SUCV20152665 (Mass. Super., Aug 15, 2016).

¹¹⁵ *Id.*

event,' Because none of the SAEs were found to be drug-related, even taking the allegations in the amended complaint as true, the high number of SAEs did not have any relationship to SER-109, and thus did not on its own diminish the probability of the phase 2 study's success. Accordingly, the SAEs do not create an inference that Defendants' statements were false or misleading, and here do not support a claim for securities fraud.¹¹⁶

4.2.3 Particularised Information on When Unblinding Occurred

To the extent that sponsor companies have gained *some* level of information about interim trial data, courts have required close particularization of *when* that information has been gained in order to substantiate allegations of securities fraud. Illustrative is the United States District Court for the Southern District of Indiana decision in *Vallabhaneni v Endocyte, Inc.*¹¹⁷ Plaintiffs asserted that the sponsor company knew about the investigational drug's lack of efficacy prior to the DSMB recommendation that the trial terminate based on an interim futility analysis. The plaintiffs argued that new imaging protocols, introduced more than one year before trial termination made it 'readily apparent' that the drug was not demonstrably effective in treating ovarian cancer. In dismissing the action, the Court emphasized the need for details about when and how the sponsor company could have gained knowledge about the drug's lack of efficacy. It stated that, 'Without more detail, it is impossible to determine how [the sponsor] knew that efficacy was not demonstrated at such an early stage of the phase 3 study given the double-blinded nature of the study'.¹¹⁸ The Court further questioned why the FDA would allow the study to continue if the study's data and design were as flawed as the plaintiffs' asserted.

Specificity about the timing of access to interim trial information was equally important in the case of *In re Intrabiotics Pharm., Inc. Sec. Litig.*, which stemmed from the early termination of trials involving a drug designed to reduce the risk of ventilator-assisted pneumonia. Trial termination followed a DSMB recommendation based on higher levels of morbidity and mortality in the investigational arm as compared with the control arm of the trial.¹¹⁹ Plaintiffs alleged that sponsor press releases made two months before trial termination that claimed that in experiences to date there had been 'no differences in adverse events between the active and placebo groups observed consistently among the trials' were materially false and misleading.¹²⁰ The Court accepted the possibility that, at some point before the decision to terminate was announced, the sponsor and the DSMB may have had access to information suggesting the investigational drug was unsafe. However, it was unable to determine any basis for determining when such information might have been available. In the subsequent order granting the Defendants' motion to dismiss, the District Judge dismissed the potential for review of unblinded case report forms to have provided enough information to substantiate sponsor

¹¹⁶ *Erste-Sparinvest Kapitalanlagegesellschaft MBH v. Seres Therapeutics, Inc.*, No. CV 16-11943, 2018 WL 1567614, 5 (D. Mass. Mar. 30, 2018). Internal citations omitted.

¹¹⁷ *Vallabhaneni v. Endocyte, Inc.*, No. 1:14-cv-01048-TWP-MJD, 2016 WL 51260 (S.D. Ind., Jan. 4, 2016).

¹¹⁸ *Id* at *10.

¹¹⁹ *In re Intrabiotics Pharm., Inc. Sec. Litig.*, No. C 04-02675 JSW, 2006 WL 708594 (N.D. Cal., Jan. 23, 2006), motion to dismiss second consolidated complaint granted on Aug. 1, 2006.

¹²⁰ *Id* at *5.

knowledge of the emerging adverse event profile, given that *overall* rates of adverse events and mortality were less than what would have been expected.¹²¹

4.2.4 Incompleteness of Disclosed Information

Several cases disputed the accuracy of sponsor disclosures about interim trial data, including an alleged obligation on sponsors to contextualize or interpret information for shareholders. Courts disputed any such obligation. In *City of Bristol Pension Fund v Vertex Pharm Inc.*, plaintiff shareholders alleged that a sponsor company statement had misled the market by touting interim efficacy results as being ‘highly statistically significant, with a p of 0.002’.¹²² Plaintiff shareholders alleged that the defendant should have known that the results were ‘too good to be true’.¹²³ The Court noted that the information the company presented was *factually* correct, given previous judgments in which a *P* value of 0.05 or less was an accepted measure of statistical significance. Although the company had used the information to paint an optimistic or positive picture, this did not cross the line into misleading. Other judgments have concurred that sponsor companies do not have a duty to ‘connect the dots’ for shareholders or spell out any doubts that interim data may have raised.¹²⁴

5 DISCUSSION

Clinical trial practices increasingly include the siloing of interim trial data into independent DSMBs. This is an important development in balancing the need to keep the study blind among sponsors, investigators, and others with ongoing monitoring of potential efficacy and safety signals. However, the requisite standards for trial monitoring are somewhat elusive. In particular, the point at which emerging trial information needs to be disclosed to trial participants or otherwise acted upon remains unclear. This is further complicated by the wide spectrum of pre-specified stopping boundaries incorporated into clinical trial protocols—including some set at a level of ‘proof beyond reasonable doubt’—and DSMB discretion in acting upon these pre-specified boundaries.

Courts of law provide one avenue for oversight of trial disclosure practices. Potential legal obligations include duties on sponsors and investigators to obtain and maintain an adequate informed consent from trial participants, negligent trial conduct that might stem from a failure to use or disclose emerging trial information, and other actions in tort grounded in obligations to warn of potential dangers, such as fraud and product liability. Publicly listed sponsor companies also have duties to disclose information that might have a material impact on their sales or revenue to shareholders. The question for this paper was the manner in which U.S. courts were assessing allegations that clinical trial actors had a duty to use or disclose emerging trial information, and how any such duties interacted with the siloing of information within independent DSMBs.

¹²¹ *In re Intrabiotics Pharm., Inc. Sec. Litig.* No. C 04-02675 JSW. Aug. 1, 2006.

¹²² *City of Bristol Pension Fund v Vertex Pharm Inc.* 12 F.Supp.3d 225 (Mar. 31, 2014).

¹²³ Amended Complaint for Violations of the Federal Securities Laws, 54, *City of Bristol Pension Fund v Vertex Pharm Inc.*, No. 1:12-cv-11654-FDS (D. Mass, Feb. 11, 2013).

¹²⁴ *Huang v Avalanche Biotechnologies, Inc.*, No. 15-cv-03185-JD, 2016 WL 6524401 (N.D. Cal. Nov. 3, 2016); *Shah v GenVec, Inc.* No. DKC 12-0341., 2013 WL 5348133 (D. Md, Sept, 20, 2013); *Sec. Police 7 Fire Professionals of Am. Ret. Fund v Pfizer* No. 10-cv-3105, 2013 WL 1750010 (D.N.J., Apr. 22, 2013) and appeal in *City of Edinburgh Council v Pfizer Inc*, 754 F.3d 159.

The cases present a marked picture of judicial willingness to accept the stated needs of clinical trial practices, including those that might severely limit the availability of potentially relevant information to participants, shareholders, and others. Three key constraints on legal oversight of the disclosure and use of interim trial data can be distilled.

- (1) ***An uncritical acceptance of the blinding process.*** The available cases almost uniformly accept the need for the blinded nature of much emerging clinical trial data without a deeper analysis of the role of clinical trial actors such as trial sponsors in setting the parameters for the blind, for example, through crafting the available stopping rules. The double-blinded study design was relied upon in *White v KKI*¹²⁵ to distinguish from the facts from the ‘special duties’ that researchers were held to owe participants in *Grimes v KKI* to disclose of emerging information.¹²⁶

Judicial acceptance of the blinded nature of trial information was the case even for trial protocols that imposed highly stringent stopping rules, such as the START trial at issue in *Weinstein v Kirkman*,¹²⁷ and for those in which DSMBs had almost unlimited discretion in interpreting criteria for unblinding such as the IRIS trial at issue in *Kinkaid v Inzucchi*,¹²⁸ the protocol for which allowed the DSMB to recommend unblinding at such time as there was ‘convincing evidence of the treatment effect’.¹²⁹ Similarly, the lack of disclosure to shareholders of almost certain futility in the case of *Nguyen v New Link Genetics Company* was argued and decided on the basis of lack of sponsor knowledge.¹³⁰ There was no judicial scrutiny over the sponsor role in designing the circumstances under which knowledge will be imparted; in this case, including the lack of a futility analysis in the data monitoring plan—a fact that was noted in reports on the failed trial¹³¹—or other provisions for alerting the sponsor of an ongoing negative trend.

- (1) ***Reliance on the FDA in setting the parameters for acceptable trial practices.*** In a number of the cases identified, decisions about acceptable trial disclosure practices were justified through express or implied FDA guidance. Most overt in this regard was the application of the FDA pre-emption doctrine to preclude tort liability for medical device trials, as adjudicated in *Parks v HOC*.¹³² The extent to which pre-emption applies to potential tort actions stemming from clinical

¹²⁵ *White v. Kennedy Krieger Institute* 221 Md.App. 601 (Md. Feb. 26, 2015).

¹²⁶ *Grimes v. Kennedy Krieger Institute* 782 A.2d 807 (Md. Aug. 16, 2001).

¹²⁷ *Weinstein v. Kirkman* No. C13-0769-JCC, 2013 WL 12121125 (W.D. Wash. Sept. 16, 2013).

¹²⁸ *Kinkaid v. Inzucchi* No NNHCV126035005S, 2013 WL 5496537 (Conn. Super. Ct., Sept. 16, 2013).

¹²⁹ Kernan et al., *supra* note 92.

¹³⁰ *Nguyen v. New Link Genetics Corp.* 297 F.Supp.3d 472 (S.D.N.Y. Mar. 29, 2018).

¹³¹ This was discussed in an article published soon after trial results were published: ‘Newlink has never explained why it didn’t allow independent data monitors to conduct a futility analysis of the algenpantucel-L phase III study, but the absence of one has been profitable for NewLink CEO Charles Link Jr.’: Adam Feuerstein, NEWLINK PANCREATIC CANCER VACCINE FAILS, MAY BE HARMFUL THE STREET (2016), <https://www.thestreet.com/story/13564107/1/newlink-pancreatic-cancer-vaccine-fails-and-maybe-even-harms-patients.html> (accessed Feb 1, 2019).

¹³² *Parks v. Howmedica Osteonics Corp.* No. 8:15-cv-75, 2015 WL 3581714 (M.D.Fla. Feb. 27, 2015).

drug trials operating under an Investigational New Drug application is unclear but warrants further consideration.¹³³

In situations outside of the constitutional doctrine of pre-emption, courts still relied on FDA actions to indicate reasonable or appropriate sponsor actions. For example, in assessing the materiality of interim data in *Sanders v Aveo Pharm, Inc.*,¹³⁴ the court was guided by FDA signals about the reliability of six months' versus twelve months' of trial data.

(3) **Requirements on plaintiffs to particularize when information was available to clinical trial actors.** To the extent that courts have accepted that sponsor companies or other clinical trial actors have had access to interim trial data, legal obligations to act on such information have been contingent on specific information about *when* information was obtained. This degree of particularization might be very hard for plaintiffs to satisfy, particularly given precedent for interpreting DSMB monitoring activities as falling within the definition of a 'medical review committee', and consequently privileged from discovery.¹³⁵

Several implications flow from the limitations in imposing legal obligations on clinical trial actors to disclose or otherwise use interim trial data. One is the need to be far more transparent with trial participants and others about the circumstances, if any, in which they will be informed about interim trial data. Given the double-blinded nature of the vast majority of clinical trials and the siloing of information within DSMBs, Participant Information Sheets promising that participants will be told about 'significant new findings developed during the course of research which may relate to a subject's willingness to continue participation'¹³⁶ will often be misleading. Instead, the likelihood of confidentiality until trial completion or termination should be clearly disclosed to avoid potential deception.¹³⁷

This raises the question whether participant information sheets should specify more precisely the circumstances in which a trial might be terminated for efficacy, safety, or futility. In other words, should participants be told that sponsors and investigators will only have access to emerging trial information in the event that it reaches a pre-specified stopping rule, and otherwise the information will be siloed in an independent and confidential DSMB?¹³⁸ This would alleviate concerns about participant deception, and potentially could protect the sponsor and investigators from informed consent claims. However, specifying the exact circumstances of information disclosure in any meaningful way would be incredibly challenging. For one, data monitoring charters provide DSMBs with considerable discretion, to accommodate the vast permutations of

¹³³ The Supreme Court has upheld state tort actions based on defective labelling of marketed drugs: *Wyeth v. Levine* 129 S.Ct. 1187 (2009). This suggests that in the absence of an express legislative pre-emption clause, such as applies under the MDA, state tort actions based on failure to use or disclose emerging trial information may be feasible.

¹³⁴ *In re Ariad Pharm. Inc* 98 F.Supp 3d 147 (D. Mass. Mar. 24, 2015).

¹³⁵ *KD ex rel. Dieffenbach v. United States*, 715 F. Supp. 2d 587 (D. Del. 2010).

¹³⁶ 45 CFR 46.116(b)(5).

¹³⁷ F. G. Miller & D. Wendler, *Is it ethical to keep interim findings of randomised controlled trials confidential?*, 34 J. MED. ETHICS 198, 201 (2008).

¹³⁸ The author wishes to thank the two anonymous reviewers of this article for raising this suggestion.

potential emerging information. Committing in advance to the circumstances of disclosure could actually *increase* litigation concerns in the event that a DSMB, for potentially valid reasons, determines, for example, that a trial should continue despite having reached a pre-specified stopping rule. Moreover, stopping rules are technically complex. Given well-identified challenges in helping participants to understand far less involved scientific concepts, such as randomization,¹³⁹ it seems an undue burden on them to understand and accept various stopping rules. While the provision of information—and the non-provision of misleading information—is an important start for improving trial monitoring practices, more substantive changes are needed.

Most pressingly, it is incumbent on clinical trial actors to work together with the FDA to build a more extensive ethic of data monitoring. At present, there is little consensus on the range of acceptable stopping boundaries in clinical trials, nor on the circumstances in which DSMBs may recommend to continue a trial beyond the point at which a trial reaches such a stopping boundary. As discussed in part two, at least some clinical trials have adopted highly stringent stopping boundaries, including through the use of quasi-legal terms such as ‘proof beyond reasonable doubt’. Given the apparent judicial reluctance to intervene in decisions related to trial design, self-regulation regarding acceptable parameters will be necessary. As a first step, it will be helpful simply to know the range of currently adopted stopping boundaries in order to assess the circumstances in which a trial’s design might be considered an outlier.

Another strategy for building up a shared ethic of data monitoring is establishing opportunities for liaison between DSMBs and IRBs. One possibility is a greater degree of systematic sharing of emerging trial data with the reviewing IRB contingent on IRB members entering into confidentiality agreements similar to those of DSMB members. Given IRB members are privy to considerable amount of information about ongoing trials; this should not pose an undue risk to trial validity. However, unfettered disclosure would add a potentially large additional responsibility on boards that already have high workloads.¹⁴⁰ Perhaps a more feasible means of developing a shared ethic of data monitoring would be a requirement for a DSMB to consult with the reviewing IRB only in the event of a trial reaching a decision-making milestone—most clearly, on reaching or approaching a pre-specified stopping boundary.¹⁴¹ Other circumstances that might warrant consultation include clear evidence of differences in secondary endpoints, or to accommodate evidence of an intervention’s efficacy or harm reported from another clinical trial. Collaborative discussions between the DSMB and IRB in these instances provides opportunities to deliberate on the relevant ethical trade-offs, and possible strategies for mitigating possible risks—for example, by allowing a trial to continue but requiring emerging information to be provided to participants and/or investigators. Here, DSMB members would be able to advise the IRB on potential risks that such a disclosure might have for ongoing scientific validity and the trial’s ability to answer long-term research questions, while IRB members could advise the DSMB on the risks

¹³⁹ For example, M. Stead et al., ‘Hello, hello—it’s English I speak!’: a qualitative exploration of patients’ understanding of the science of clinical trials, 31 J. MED. ETHICS 664, 669 (2005).

¹⁴⁰ Joseph A. Catania et al., *Survey of U.S. Human Research Protection Organizations: Workload and Membership*, 3 J. EMPIR. RES. HUM. RES. ETHICS 57, 69 (2008); Phoebe Friesen, Barbara Redman & Arthur Caplan, *Of Straws, Camels, Research Regulation, and IRBs*, THER. INNOV. REGUL. SCI. 2168479018783740 (2018).

¹⁴¹ Eckstein, *supra* note 13.

of non-disclosure for the ethical principle of respect for participants. While there are no ‘right’ answers, the deep and deliberative discussions required to assess these courses of action potentially provides the best opportunity for a thoughtful response.

Greater transparency about DSMB decisions after a trial concludes also could help to shape agreed data monitoring practices going forward. While some pivotal publications for clinical trials advise that the trial continued beyond a pre-specified stopping point, there is variable information on the justification for continuing the trial and the deliberative processes employed in making such a determination. For example, in one publication explaining the early termination for efficacy of a treatment for familial adenomatous polyposis, the authors state that:

The data and safety monitoring board (DSMB) reviewed the study at the first interim analysis of 33 participants. *Although the prespecified interim stopping rule had been met at that point, the DSMB recommended continuation of the study.* Study investigators were not made aware of the results of the interim analysis. The study was stopped after the second interim analysis of 67 participants by the DSMB because the prespecified stopping rule for the primary end point was met. (Emphasis added.)

This can be compared with the far more detailed justification by *Patel et al* for a DSMB recommendation to continue a trial after it had reached a stopping boundary for efficacy, which advised:

Early stopping for efficacy was predetermined at a P value $< .001$ for rejection of the null hypothesis to declare that the helmet strategy was superior to face mask. At the first interim analysis, the results met criteria for early stoppage of the trial for efficacy; however, the DSMB determined that the trial should continue because the helmet was not available for use outside the trial; therefore, non-study patients would not be deprived of the benefit. In addition, the DSMB determined that there were no safety concerns and that the study had not met other secondary end points that (e.g., intensive care unit length of stay) could have been reached with further enrollment. Subsequent to this, the DSMB evaluated work ... that reported increased mortality among patients treated with face mask NIV compared with high-flow nasal cannula. The DSMB determined that the face mask group could have been exposed to increased risk of mortality and because the study already had met the pre-established criteria for early stoppage, the DSMB recommended that the study be stopped for both efficacy and safety after the enrollment of 83 patients.¹⁴²

Clearly, this deeper explanation of the monitoring process provides a much greater opportunity to build a shared ethic of data monitoring going forward.

DSMBs are an important innovation in trial design. As clinical trials continue to increase in number and complexity, clarity about the legal and ethical status of interim information will be essential. Obligations on clinical trial actors to use or disclose emerging trial data will need to be consistent with good scientific practice, while also respecting the rights of current trial participants, patients, and shareholders. This is by no means intended as a ‘call to arms’ when it comes to litigation against DSMBs—the potential for which is clearly of concern for existing and future members.¹⁴³ Rather, a huge step forward will be transparency about when information will be disclosed, along

¹⁴² Patel et al., *supra* note 41.

¹⁴³ DeMets et al., *supra* note 59.

with a clear and justifiable framework for assessing the circumstances in which disclosure is justifiable, will be a huge step forward in this regard. In the absence of such work, prima facie disclosure obligations—including those articulated in many participant informed consent forms—fail to reflect the current reality of judicial willingness to accept the siloing of information in independent, but largely inscrutable, DSMBs.

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