HOW TO ELIMINATE RESEARCH FRAUD AND BIAS IN RESEARCH CONDUCTED BY CONTRACT RESEARCH ORGANIZATIONS

I. INTRODUCTION

Contract Research Organizations, or CROs,[1] are hired by pharmaceutical companies to research pharmaceuticals.[2] CROs are held to high standards, and their reputation and future business relies on the quality of work they do. However, because pharmaceutical companies expect both good results and good science, two expectations that can be at odds with each other, CROs may sometimes have an incentive for fraud. CROs and pharmaceutical companies need to minimize the conflicts of interest that can potentially lead to fraud, and CROs need to take steps to ensure that their employees are not engaging in fraud.

Traditionally, the FDA has viewed criminal fraud as a communication that includes "intent to deceive."[3] However, CROs have incentives to subtly alter data, and much of this may be unintentional and not fit under the definition of criminal fraud. In their quest to eliminate fraud, CROs and pharmaceutical companies should also find ways to eliminate this unintentional bias.

Part II of this article will discuss the history and responsibilities of CROs, and the role of the FDA in monitoring CROs. Part III will discuss examples of fraud in pharmaceutical

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[1] Although this paper focuses on CROs, much of the information here is also applicable to other pharmaceutical research entities.
[2] The same issues exist with the research of medical devices, and this paper, although focused on drug research, applies to medical device research also.
[3] James T. O'Reilly, FOOD AND DRUG ADMINISTRATION, Volume 1, 8-78 - 8-79 (2007).

research, and a CRO's incentives and disincentives for fraud. Part IV will discuss how to decrease fraud and bias in research done by CROs. Part V will then conclude.

II. CONTRACT RESEARCH ORGANIZATIONS AND THE FDA

a. Contract Research Organizations

1. History of Contract Research Organizations

CROs have largely replaced other avenues of pharmaceutical research in the last twenty years. Between 1992 and 2001, the market size of CROs grew from one billion dollars to almost eight billion dollars.[4]

Before 1980, most pharmaceutical research was done either by doctors at universities or by pharmaceutical companies directly.[5] Starting work on a project was expensive; obtaining equipment, recruiting, and training all took considerable time and money.[6] Since delay meant less time on the market, it was doubly important that the research be done quickly.[7]

CROs stepped in as the solution. Because CROs usually engage in multiple pharmaceutical research studies, they often already have needed equipment, and they have no

[4] Philip Mirowski & Robert Van Horn, *The Contract Research Organization and the Commercialization of Scientific Research*, 35 SOC. STUD. SCI. 503, 506 (2005).
[5] *Id.*
[6] *Id.*
[7] *Id.* at 509-10.

need to recruit and train workers when a new research study begins; this both speeds things up and contains costs.[8] Employees at a CRO may work longer hours when the workload is heavy, and work fewer hours when the workload is light, but since a CRO typically does several studies at the same time, the loss or gain of one study does not usually have a huge impact on a CRO.[9]

2. A Contract Research Organization's Responsibilities

CROs are responsible to many groups, including a CRO's sponsor, a CRO's research subjects and employees, and the general public.

A CRO has a responsibility towards its sponsor, usually the pharmaceutical company the CRO signed a contract with.[10] This includes both moral and scientific responsibilities; the CRO has a duty to conduct high-quality, honest, science,[11] so the pharmaceutical company will have accurate results and know whether or not a drug is safe and effective. A CRO has a duty to keep a drug's sponsor on the FDA's good side.[12] The quality of research may be compromised if a CRO take on more work than it can adequately handle,[13] or if a CRO engages in fraud. Poor quality work will not necessarily take the form of outright fraud, but may still result in danger to research subjects or patients, and in liability for the drug sponsor. Fraudulent or poor research can result in a number of punishments, including an FDA mandate against future research. Since all CROs do is conduct research studies, a CRO's livelihood depends on conducting adequate

[8] *Id.* at 511.
[9] *Id.*
[10] Charles J. Minnich, *Protecting Human Test Subjects and the Public: A View From the Testing Laboratory*, 35 FOOD DRUG COSM. L.J. 511, 517 (1980).
[11] *Id.*
[12] *Id.*
[13] Robert N. Endries, *The Regulation of Clinical Investigators*, 35 FOOD DRUG COSM. L.J. 415, 419 (1980).

studies.[14] A CRO may also feel that it has an obligation to give the pharmaceutical company positive results.[15]

A CRO also has a duty towards those it works closely with--human research subjects and a CRO's employees. If a drug is falsely deemed safe at the animal research level, human research subjects could be unfairly harmed.[16] Those hired by CROs as investigators have a right to be informed about the product being tested, as well as a right to adequate supervision, constructive criticism, and timely payment.[17]

CROs have a duty towards the public, especially those who end up using the product the CRO is testing; protection of the consumer is the primary reason CROs exists—to test the safety of a potential new drug.[18] CROs have an obligation to the pharmaceutical industry to share negative information about a product being tested, so that, if the product is dangerous, it will not be released and cause damage to the reputation of the pharmaceutical industry.[19] CROs have a duty to protect the reputation of their competitors; when one CRO is found to have fraudulent or inaccurate results, the pharmaceutical industry may tend to view other CROs with suspicion, and decide to either do the research itself or find someone else (a non-CRO entity) to do it.[20] CROs have a duty towards the scientific community, to protect the reputation of science.[21]

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[14] Minnich, *supra* note 10, at 525; see http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/default.htm (current as of 12/7/2009) for a list of firms and individuals who are debarred from certain pharmaceutical research.
[15] Jeanne Lenzer, *Contract Research Organisations: Truly independent research?* BMJ 2008;337:a1332.
[16] Minnich, *supra* note 10, at 517-18.
[17] *Id.*
[18] *Id.* at 516.
[19] *Id.*
[20] *Id.* at 517.
[21] *Id.*

Unfortunately, as evident in the anti-vaccine movement, much of the public already has a skeptical view of science.[22] If a CRO does bad science, either through fraud or incompetence, the reputation of science is harmed, and consumers will question sound science even more.[23]

b. The Role of the FDA

The FDA has the authority to inspect and copy the research records of drug investigators.[24] Recently, Congress ordered the FDA to make the clinical trial registry data bank, which includes certain information about a study, open to the public via the internet.[25] The data bank includes details of how many patients dropped out of a study, how many were excluded from the analysis, and so forth.[26] The data bank also includes disclosure of agreements between sponsors and investigators that restrict investigators from discussing or publishing information concerning the results of the trial.[27] The FDA also requires drug sponsors to submit a disclosure stating their financial arrangements, including information on compensation made to clinical investigators, (the value of which could be affected by the study outcome), as well as other financial ties between investigators and sponsors (equity in the sponsoring company, grant

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[22] See, for example, Amy Wallace, *An Epidemic of Fear: How Panicked Parents Skipping Shots Endangers Us All*, Wired Issue 17.11, Oct. 19, 2009. Available at www.wired.com/magazine/2009/10/ff_waronscience/all/1 as of 12/7/09.
[23] Susan M. Kuzma, *Criminal Liability for Misconduct in Scientific Research*, 25 U. MICH. J.L. REFORM 357, 399 (1992).
[24] John R. Fleder, *Administrative Inspections by the Food and Drug Administration: The Role of the Department of Justice*, 44 FOOD DRUG COSM. L.J. 297, 303 (1989).
[25] 42 U.S.C. 282(j)(3).
[26] *Id.*
[27] 42 U.S.C. 282(j)(3)(C).

money, etc.).[28] Drug sponsors are required to submit procedures for quality control, to ensure that data is not false or misleading.[29] In addition, adverse events must be reported to the FDA.[30]

III. FRAUD: EXAMPLES, INCENTIVES, AND DISINCENTIVES

Many incidents of fraud in pharmaceutical research studies are never discovered, and of those that are, many are settled.[31] However, some have received major publicity and in a few cases the FDA has actively gone after the perpetrators of fraud.

Below are examples of falsified research data, and the incentives and disincentives for falsifying data.

a. Examples of how Data is Falsified

1. Blatant Examples of Fraud

Although most pharmaceutical research is not audited by the FDA, some research is audited; an investigator may be accused of fraud if the FDA finds inadequate research records, a lack of informed consent documents from research subjects, or a failure to follow research

[28] Karine Morin, Herbert Rakatansky, Frank A Riddick, Jr, *Managing Conflicts of Interest in the Conduct of Clinical Trials*, 287(1) JAMA 78, 81 (2002).
[29] 42 USC 282 (j)(3)(D)(v)(III).
[30] Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 801, 121 Stat. 823, 824 (2007).
[31] *See* Jonas Ranstam et al., *Fraud in Medical Research: An International Survey of Biostatisticians*, 21 CONTROLLED CLINICAL TRIALS 415 (2000).

protocols.[32] Below are some examples of pharmaceutical research fraud discovered by the FDA and others.

In *United States v. Smith*, research investigators sent a pharmaceutical company research results involving non-existent research subjects.[33] The research investigators were charged with submitting false statements to the government, as the research investigators caused the pharmaceutical company to submit false FDA reports; the research investigators were also charged with failure to maintain accurate records.[34] The charge of false statements was dismissed due to a running of the statute of limitations.[35] The failure to maintain accurate records charge was dismissed due to inadequate laws; the court found that current laws applied to pharmaceutical companies and sponsors, but not to research companies.[36] The court stated, "If the FDA discovers that an investigator has falsified information in forms submitted to the sponsor, the FDA, pursuant to the regulations, may conduct an administrative hearing and revoke the investigator's entitlement to work with investigational drugs."[37] None of the defendants were given criminal convictions.[38]

Later cases punished perpetrators of research fraud more soundly. In *United States v. Keplinger*, research investigators at a research laboratory were charged with mail fraud, wire fraud, and making false statements, for engaging in fraudulent pharmaceutical research at the

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[32] James T. O'Reilly, *Elders, Surgeons, Regulators, Jurors: Are Medical Experimentation's Mistakes Too Easily Buried?*, 31 Loy. U. Chi. L.J. 317, 345 (2000).
[33] United States of America v. Smith, 740 F.2d 734 (9th Cir. 1984).
[34] *Id.* at 735.
[35] *Id.* at 736.
[36] *Id.* at 737.
[37] *Id.* at 739.
[38] *Id.*

animal testing level.[39] The alleged fraud included, among other things, underreported mortality rates, omission of histopathological data of research animals, and failure to report opinions and reports of researchers.[40]

In *United States v. Garfinkel*, an investigator received criminal charges for failing to establish and maintain drug-protocol records.[41] Garfinkel was the principal investigator of a clinical trial involving the drug Anafranil,[42] which was tested on children and adolescents to measure its effect on obsessive-compulsive disorder.[43] Garfinkel ordered an unqualified study coordinator to engage in fraudulent acts, including entering false data and secretly giving research subjects prohibited medication; the study coordinator filed a complaint about Garfinkel to her university, and the university alerted the FDA and the pharmaceutical company of the fraud.[44] The lower court followed the ruling in *Smith* by stating that the FDA could not criminally prosecute a research investigator for fraud; the Eight Circuit reversed.[45] Garfinkel was found guilty of making false statements and of mail fraud.[46] Garfinkel was sentenced to six months in prison, followed by six months of home detention with work release, 400 hours of community service, and $214,000 in fines;[47] he was also permanently debarred by the FDA.[48]

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[39] United States v. Keplinger, 776 F.2d 678, 683 (7th Cir. 1985).
[40] *Id.* at 684.
[41] United States v. Garfinkel, 29 F.3d 451, 453 (8th Cir. 1994).
[42] *Id.*
[43] United States v. Garfinkel, 29 F.3d 1253, 1254 (8th Cir. 1994).
[44] *Id.* at 1255.
[45] *Garfinkel,* 29 F.3d at 459.
[46] *Garfinkel*, 29 F.3d at 1261.
[47] John Henkel, *Psychiatrist sentenced for research fraud—University of Minnesota child psychiatrist Barry Garfinkel*, FDA CONSUMER, Apr. 2009. Available at http://findarticles.com/p/articles/mi_m1370/is_n3_v28/ai_15330335/.
[48] Barry D. Garfinkel, 62 Fed. Reg. 15713 (FDA Apr. 2, 1997).

The following research fraud incident is taken from a newspaper article[49] and the FDA's records in the Federal Register.[50] In 1997, after years of engaging in research fraud in multiple pharmaceutical research studies, Robert Fiddes was charged with fraud.[51] Fiddes had made a great deal of money from pharmaceutical companies by engaging in fraudulent research.[52] Fiddes invented research subjects, intentionally mislabeled blood and urine samples, enrolled employees and relatives of employees in studies (and changed their names in the studies to avoid detection), tore out pages from medical records to hide evidence, intentionally misinterpreted x-rays, and hid patient records.[53] In one case, a research subject's blood pressure rose dangerously when she took the experimental drug, and Fiddes, instead of taking the subject out of the study, gave her additional drugs in order to reduce her blood pressure.[54] Those drugs caused additional problems, and the subject was hospitalized; she eventually recovered.[55]

The study coordinators were aware of the fraud, but few other employees knew of it.[56] A few of the study coordinators quit because of the fraud; those that did not quit knew they would be risking their jobs if they complained to the FDA or to the research sponsors.[57]

Government auditors and pharmaceutical company monitors were reluctant to challenge Fiddes because of his prominence in the drug-testing business.[58] A former employee telephoned FDA investigators about some of the fraud she had observed, but the FDA ignored the

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[49] Kurt Eichenwald and Gina Kolata, *A Doctor's Drug Studies Turn Into Fraud*, N.Y. TIMES, May 17, 1999.
[50] Robert Fiddes, 67 Fed. Reg. 67,628 (FDA Nov. 6, 2002).
[51] Eichenwald, *supra* note 49.
[52] *Id.*
[53] *Id.*
[54] *Id.*
[55] *Id.*
[56] *Id.*
[57] *Id.*
[58] *Id.*

information.[59] Seventeen months later, a manager of a neighboring doctor's office informed an FDA auditor of rumors of fraud, and gave the auditor the name of a former employee who could provide additional information.[60] The FDA finally closed in, and Fiddes and three employees agreed to plead guilty.[61] Fiddes was given a 15-month sentence,[62] was found guilty of conspiring to make false statements to a government agency (a felony), and, along with three of his employees, was temporarily debarred from further research.[63]

Other forms of fraud, detailed elsewhere, include bribing employees of the FDA[64] and using false medical licenses.[65]

When the FDA is not involved in a research study--for example, in pharmaceutical research done purely for marketing purposes—there is more opportunity for fraud.[66] One example of this is the suppression of unfavorable studies; suppression of a study sometimes occurs when a CRO performs a negative study, and a pharmaceutical manufacturer chooses to not publicize the results.[67] The pharmaceutical company may even run additional research studies to try to obtain positive results, and then publicize just the positive results and keep the negative results secret.[68]

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[59] *Id.*
[60] *Id.*
[61] *Id.*
[62] *Id.*
[63] Robert Fiddes, 67 Fed. Reg. 67,628 (FDA Nov. 6, 2002).
[64] Rajaram K. Matkari, 65 Fed. Reg. 37,154 (FDA June 13, 2000).
[65] Mary E. Sawaya, 74 Fed. Reg. 28,049 (FDA June 12, 2009).
[66] *See* http://www.cbsnews.com/stories/2004/06/03/health/main620815.shtml (current as of 12/7/09).
[67] *Id.*
[68] *Id.*

For example, in 2004, the Attorney General of New York claimed that the drug manufacturer GlaxoSmithKline PLC had suppressed studies showing that the antidepressant drug Paxil was ineffective among minors, and might even increase the suicide rate in that group.[69] The Attorney General claimed that the only study the drug manufacturer released was one that showed mixed results on its effectiveness.[70] New York sued, GlaxoSmithKline PLC agreed to a 2.5 million dollar settlement, and the drug manufacturer agreed to release the negative studies.[71]

2. Examples of Subtle Fraud and Unintentional Bias

Fraud is not always obvious. Subtle forms of fraud and bias, harder to detect and almost impossible to prosecute,[72] remain a problem. This fraud and bias is often linked to financial interests; Professor Lisa Bero, from the Schools of Pharmacy and Medicine at UC San Francisco, says that financial interests may consciously or unconsciously affect research outcomes.[73] Studies have shown that industry funding is highly correlated with favorable studies; if a pharmaceutical company is sponsoring research about the safety or efficacy of one of its drugs, the chances that the study will be favorable is much higher than if a neutral, non-sponsored party were doing the research.[74]

Drug makers control clinical research at a far greater level than the public, and even the research community, realizes; one way in which they do this is by limiting what is disclosed in a

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[69] *Id.*
[70] *Id.*
[71] *Id.*
[72] Kuzma, *supra* note 23, at 407.
[73] Lenzer, *supra* note 15.
[74] Mirowski, *supra* note 4 at 518-19.

clinical trial process.[75] While some of these discrepancies are due to large-scale fraud, most of them are not.[76] When a researcher is invested in how well a drug does, the fraud tends to be so subtle that even the researchers may not be aware of it, and so pervasive that it penetrates almost every sponsored study.[77]

Several studies have shown that the pharmaceutical industry supports trial designs that favor positive results, such as using a placebo as a control, instead of using another drug as a control.[78] A drug that may be unimpressive when compared to already-existing drugs may look very impressive when compared to a placebo.[79]

Some studies may even be unscientific in nature.[80] Examples include studies of Prozac where the adolescents receiving the drug knew whether they were getting the actual drug or the placebo (known as an unblinded study); the results were positive.[81] In similar blinded studies, no difference was seen between those taking Prozac and those taking the placebo, indicating that Prozac had little or no impact on the adolescents.[82] In other words, except for its placebo effect, the drug is useless to adolescents.[83] Gullible mainstream media heralded the unblinded studies,

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[75] *Id.*
[76] *Id.*
[77] *Id.*
[78] *See* Justin E. Bekelman, Yan Li, Cary P. Gross, *Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review*, 289(4) JAMA 459 (2003).
[79] *Id.*
[80] *See* Lenzer, *supra* note 15.
[81] *Id.*
[82] *Id.*
[83] *Id.*

which were largely performed for marketing purposes.[84] Robert Temple, the director of medical policy at the FDA, described the use of unblinded studies in this research as "bizarre."[85]

b. Incentives for Fraud

Conflicts of interest sometimes lead to fraud. One definition of conflict of interest is "a set of conditions in which professional judgment concerning a primary interest (such as. . . .the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain).[86]

For example, Quintiles Transnational, a major CRO, at one point promised that it could deliver research designs that will "help customers prove the value of their products to patients, physicians, and regulators."[87] But promising to deliver positive results when dealing with an unknown drug is dishonest—if the study is not positive, the CRO will either fudge details to make it positive, or they will fail on their promise to deliver positive results.[88] And since negative results would mean risking future business with the client, a CRO has a financial incentive to fudge details instead.[89] Dr. Steve Wing, an associate professor at the Gillings School of Global Public Health at UNC, remarked, "This sort of advertising tells drug companies, 'We know how to get the answer you want.'"[90]

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[84] *Id.*
[85] *Id.*
[86] Richard Smith, *Beyond conflict of interest*, BMJ Vol. 317, 1 August 1998.
[87] Lenzer, *supra* note 15. The quote, perhaps as a result of Lenzer's article, seems to have disappeared from Quintiles' website.
[88] *Id.*
[89] *Id.*
[90] *Id.*

1. Stock Options and Other Direct Financial Incentives

As Robert Fiddes demonstrated,[91] it is often more lucrative to make up data than to discover data through research. Like Fiddes, most research investigators have an incentive to save money by cutting corners, but they also have financial incentives to create positive results for pharmaceutical companies.

Some CROs receive stock options or royalties for favorable results from the drug sponsors.[92] These bonuses can give a CRO an incentive to make a drug look safer or more effective than it really is. Numerous studies demonstrate that when pharmaceutical companies sponsor research, that research is significantly more likely to be favorable towards the investigational drug than when a study is sponsored by someone else.[93] In fact, one study shows that unfavorable conclusions are reached in just 5% of studies run by pharmaceutical companies (compared to 38% when run by nonprofit sponsors).[94] The difference is not just due to fraud or bias—pharmaceutical companies often stop unpromising studies early on, and so one would expect less unfavorable results.[95] And negative results sponsored by pharmaceutical companies are less likely to be submitted for peer review and published.[96] But unconscious bias, perhaps

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[91] *See* Eichenwald, *supra* note 49.
[92] James T. O'Reilly, *More Gold and More Fleece: Improving the Legal Sanctions Against Medical Research Fraud*, 42 ADMIN. L. REV. 393, 400 (1990).
[93] *See* Bekelman, *supra* note 78.
[94] Mark Friedberg, Bernard Saffran, Tammy J. Stinson, *Evaluation of Conflict of Interest in Economic Analyses of New Drugs Used in Oncology*, 282(15) JAMA 1455 (1999).
[95] *Id.* at 1455-56.
[96] *Id.*

when qualitatively interpreting results, or perhaps elsewhere, may also influence study conclusions.[97]

2. Reputation

Some believe because CROs are not beholden to any one client, research conducted by CROs is independent, and if a CRO does not provide high quality research, that CRO cannot survive.[98] However, a CRO's reputation, and thus its survival, is not just dependent on high quality research; a CRO's reputation is also dependent on whether or not the CRO produces positive results.[99] A CRO that does not produce positive results for its sponsor, despite practicing good science, meeting deadlines, and so forth, is unlikely to receive additional work from pharmaceutical companies.[100] A CRO may be willing to take extra, perhaps fraudulent, steps in order to achieve positive results so it can continue to get business from pharmaceutical companies.[101] CROs face considerable conflicts of interest because the pharmaceutical company that pays them depends on positive results.[102] The financial viability of a CRO may be pitted against the integrity of its research.[103]

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[97] *Id.*
[98] Lenzer, *supra* note 15.
[99] Morin, *supra* note 28.
[100] *Id.*
[101] *Id.*
[102] *Id.*
[103] *Id.*

Jerome Hoffman, a professor of medicine at UCLA, said "It's hard to imagine that such organisations. . . .can be completely independent when they are so fundamentally dependent on industry money for their continued existence."[104]

3. Avoidance of Lawsuits

Pharmaceutical companies sometimes use legal threats to silence CRO researchers.[105] These legal threats may be without merit, and the CRO may win in court, but the CRO will lose considerable time and money.[106]

For example, a researcher who conducted two studies for the drug company Apotex signed a confidentiality agreement for the first study, and the research results appeared positive.[107] The second study, comparing the drug with another existing drug, indicated that the drug might be ineffective or even toxic in some patients.[108] The researcher had not signed a confidentiality agreement for the second study, and decided it was her responsibility to publish the results.[109] Apotex threatened to sue if the results were published; the researcher published the results despite the threat.[110] Apotex sued, and the researcher underwent years of serious harassment.[111] The New England Journal of Medicine published this story, and stated, "The

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[104] Lenzer, *supra* note 15.
[105] Steve Morgan, Morris Barer, and Robert Evans, *Health Economists Meet the Fourth Tempter: Drug Dependency and Scientific Discourse*, 9 HEALTH ECON. 659, 662 (2000).
[106] *Id.*
[107] David G. Nathan & David J. Weatherall, *Academic Freedom in Clinical Research*, 347 NEW ENG. J. MED. 1368, 1368-70 (2002).
[108] *Id.*
[109] *Id.*
[110] *Id.*
[111] *Id.*

enormous legal and financial power of the pharmaceutical industry puts clinical investigators in a very difficult position if there is a major controversy about the outcome of a particular study."[112] The safety of patients is at stake. This extreme example shows the great lengths some drug manufacturers will go to in order to suppress unfavorable studies.[113] It is important to note that this example is that of a university researcher, who, one would think, would have more independence than a CRO would.[114]

A pharmaceutical company is unlikely to sue a CRO that gives the pharmaceutical company a positive result, unless the CRO engages in blatant, easily discoverable fraud. But if a CRO produces negative results on an investigational drug, the pharmaceutical company may not be so friendly. The pharmaceutical company will certainly have greater motivation to look for sloppy work if the CRO's results are negative.

c. Disincentives for Fraud

1. Criminal Liabilities

Criminal prosecution for research fraud is quite rare, but it does occur.[115] Mail or wire fraud and submission of false reports to the government are the primary criminal charges in

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[112] *Id.*
[113] *Id.*
[114] *Id.*
[115] James T. O'Reilly, *Elders, Surgeons, Regulators, Jurors: Are Medical Experimentation's Mistakes Too Easily Buried?*, 31 LOY. U. CHI. L.J. 317, 345 (2000).

research fraud cases.[116] These crimes are felonies and seem to result in relatively short prison terms.[117] Liability for death and injuries, although perhaps not always recorded as study-related, [118] is also a disincentive; I have found one case involving criminally negligent homicide in pharmaceutical research fraud (combined with other incidents of fraud), with a prison term of about six years.[119]

2. Debarment from Research

The FDA has the authority to debar people and corporations that engage in fraudulent acts from engaging in future research.[120] The FDA has placed a publicly-accessible debarment list online; no corporations are currently on the list.[121] Over one-third of the debarments on the list occurred in 1993; in the last six years, there has been an average of less than two debarments per year.[122] Debarments may be as short as five years, or they may be permanent.[123] A quick

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[116] O'Reilly, *supra* note 92, at 401.
[117] *See, for example,* Eichenwald *supra* note 49. The defendant received a fifteen month sentence for numerous acts of serious fraud spanning several years.
[118] O'Reilly, *supra* note 115.
[119] Paul H Kornak, 71 Fed. Reg. 9555 (FDA Feb. 24, 2006). This is possibly the largest sentence ever received for pharmaceutical research fraud.
[120] *See* 21 USC *§* 335a.
[121] *See* http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/default.htm (current as of 12/7/2009).
[122] *Id.*
[123] *Id.*

look at the debarment list reveals that most of the debarments occurred for reasons other than research fraud.[124]

The government views the punitive effects of debarment as incidental to the main purposes of debarment, which is to protect public health and protect the integrity of the pharmaceutical industry.[125]

The FDA can terminate debarments if, for example, the debarred party assists the FDA in investigations or prosecutions, and if the termination of the debarment "serves the interest of justice and does not threaten the integrity of the drug approval process."[126]

3. Civil Liability

CROs may suffer civil liabilities for fraud. The Attorney General of New York, for example, sued a pharmaceutical company for releasing some research while hiding additional research.[127] It is certainly possible for parties to sue a CRO for fraud if a research subject is harmed by a research investigator's fraud, as one research subject was harmed by Robert Fiddes.[128] Members of the public who took an unsafe drug that had fraudulently been shown to be safe, and who were injured by the drug, may have standing to sue (and the CRO could be named as a defendant in the initial complaint or be brought in by another party, such as the

[124] Click on the Volume Page links for more information on specific debarments. Many of the debarments occurred due to illegal sales of pharmaceuticals.
[125] Constantine I. Kostas, 63 Fed. Reg. 34,652, 34,653 (FDA June 25, 1998).
[126] Padam C. Bansal, 62 Fed. Reg. 11,212 (FDA Mar. 11, 1997).
[127] http://www.cbsnews.com/stories/2004/06/03/health/main620815.shtml (current as of 12/7/09).
[128] Eichenwald, *supra* note 49.

pharmaceutical company). And a pharmaceutical company that sponsors a CRO would be able to sue a CRO if that CRO engaged in fraud that resulted in incorrect study results.

IV. HOW TO REDUCE FRAUD AND BIAS IN CONTRACT RESEARCH ORGANIZATION RESEARCH

If fraudulent research is not discovered, pharmaceutical companies may submit that fraudulent research to the FDA, and a drug, possibly either less effective or more dangerous than the research shows, is introduced to the public. The public's health can suffer as a result. For that reason, a discussion is warranted on how to reduce research fraud.

I have six suggestions for decreasing fraud in pharmaceutical research performed by CROs. First, reduce financial incentives for fraud. Second, increase the understanding of lower-level researchers. Third, require optimal trial designs for all drug research. Fourth, increase transparency in pharmaceutical research. Fifth, provide adequate funding for the FDA field investigation staff. Sixth, provide stricter punishments for research fraud. Each of these points will be discussed in the order given above.

a. Reduce Financial Incentives for Fraud

It may not always be possible to determine when judgment is tainted due to conflicts of interest,[129] and so it is important to set up safeguards to minimize fraud. Better enforcement and

[129] Morin, *supra* note 28, at 83.

larger punishments would also reduce the financial incentive for fraud; those two points will be discussed later.

The financial incentives of the business world don't work well in the world of science.[130] As long as fraudulent behavior is punished with enough frequency and severity, CROs will stay away from that fraudulent behavior.[131] But when undetected or insufficiently penalized, fraudulent behavior can be good business.[132] As long as they can get away with it, successful pharmaceutical companies and CROs "will choose favorable results over scientific integrity."[133] Scientists should be skeptics.[134] Yet CROs have every reason to not be skeptics; they have every reason to root for the success of the drug they are studying.

The Association of American Medical Colleges has addressed the issue of conflicts of interest; conflicts of interest in science are "situations in which financial or other personal considerations may compromise, or have the appearance of compromising, an investigator's professional judgment in conduct or reporting."[135]

Current laws require pharmaceutical companies to disclose financial ties between sponsors and research investigators.[136] This is an important step towards eliminating fraud in bias, but it is not enough.

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[130] Morgan, *supra* note 105, at 660.
[131] *Id.*
[132] *Id.*
[133] *Id.* at 661.
[134] *Biology*, 4th Edition, Campbell, p. 15 (1996).
[135] Catherine D. DeAngelis, Phil B. Fontanarosa, & Annette Flanagin, *Reporting Financial Conflicts of Interest and Relationships Between Investigators and Research Sponsors*, 286 JAMA 89, 89-91 (2001).
[136] Morin, *supra* note 28.

The only way to rid pharmaceutical research of bias and subtle fraud is to eliminate conflicts of interest. CROs should not have a financial incentive to provide positive results for a drug. Stock options, which can increase or decrease according to results of research, should not be provided as an incentive for fraud. CROs should not improve in reputation based on how many positive studies they produce. If pharmaceutical companies were truly interested in eliminating fraud from their drug studies, they would hire CROs with a reputation for honesty and good science. This might mean that pharmaceutical companies would have fewer positive results, but it would improve the public's perception of pharmaceutical companies, and it would reduce the number of lawsuits pharmaceutical companies face when a drug ends up being less effective or less safe than originally thought.

b. Increase Employee Understanding of Research

Because CRO employees are reduced to machines that play their role, they are probably not able to recognize subtle fraud practiced by their supervisors.[137] If they don't understand the protocol of a study, they can't act as a whistleblower when the CRO is fraudulent.[138]

Investigators are more likely to adhere to the details demanded by the study, and are more helpful at reporting fraud or mistakes, if they actually understand the study; lab technologists, for example, may sometimes see behavior by their superiors that they do not understand, but without a better understanding of the study, are unsure of whether that behavior is valid or fraudulent.[139]

[137] *See* Mirowski, *supra* note 4, at 519.
[138] *Id.*
[139] *Id.*; also Eichenwald, *supra* note 49 (many of the employees were not aware of the research fraud).

Employees at CROs are focused on narrow, specific tasks.[140] Turnover rates in the industry have been estimated at 25% to 30 % per year.[141] Focus is placed on speed instead of accuracy.[142]

Employees at CROs may be less attached to the products they are researching than a researcher at a pharmaceutical company, and may have less bias than an employee at a pharmaceutical company might have.[143] But those actually running the studies at CROs have a huge incentive to make sure the study is favorable towards the drug, because if a CRO doesn't produce favorable results, the CRO doesn't get work.[144] Educating lower-level employees on the research they are performing will allow them to better detect both subtle and blatant fraud.[145] The FDA and pharmaceutical companies should demand that employees involved with pharmaceutical research understand the research, so that those employees can recognize fraud when it occurs.

The medical profession should emphasize "the need for investigators to be trained in the conduct of clinical trials, as well as in the ethics of research." Investigators should only participate in clinical trials when the trials relate to the investigator's area of expertise. CROs should educate their employees in the ethics of research, and research investigators should be aware of the potential conflicts of interest that may bias them.[146]

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[140] Pierre Azoulay, *Agents of Embeddedness*, NAT'L BUREAU ECON. RES., Working Paper 10142, p. 20. Available at http://www.nber.org/papers/w10142 (current as of 12/7/2009).
[141] *Id.* at 22
[142] *Id.* at 23.
[143] *Id.*
[144] *Id.*
[145] *Id.*
[146] Morin, *supra* note 28, at 83.

c. Require Optimal Trial Designs

Pharmaceutical manufacturers have a great deal of control over the trial designs of clinic research; the manufacturer can control the selection of patients, what product the investigational drug is being compared with, how drop-outs are reported, how side-effects are reported and analyzed, what information is made public, and so forth.[147]

Given that the pharmaceutical industry prefers trial designs that favor positive results, such as using placebos as a comparison instead of an existing drug,[148] the FDA should create new requirements for the industry; the FDA should require that all testing, regardless of whether the testing is for a new drug application or for marketing purposes, should be tested against the best possible alternative, and that the drugs be an appropriate dose and appropriately administered.

The FDA should also require that appropriate subjects be selected and that investigators be qualified for the specific research they engage in.[149]

d. Increase Transparency in Pharmaceutical Research

CROs are almost always obligated to keep their research hidden from everyone but the pharmaceutical company that sponsored the research, and, to some extent, the FDA. But "secrecy. . . .is the antithesis of good, transparent science."[150]

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[147] Morgan, *supra* note 105, at 661.
[148] Bekelman, *supra* note 78, at 463.
[149] O'Reilly, *supra* note 115, at 354-55.
[150] Morgan, *supra* note 105, at 662.

Traditional scientific research, which includes peer review (examination and approval by experts in the particular field), and publication in scientific journals, places science into the public domain.[151] CROs are among the most secretive of drug researchers; unlike universities, CROs usually don't have any incentive to publish their work,[152] and research done by CROs in order to obtain a New Drug Application for a pharmaceutical company is kept secret.[153] Besides potential safety issues and the stunting of scientific progress,[154] keeping drug research secret from the public can also help hide fraud.[155] It is difficult to determine if the FDA is doing a sufficient job detecting fraud when the vast majority of research is kept secret.[156]

Fortunately, recent changes in FDA rules, the Food and Drug Administration Amendments Act of 2007, requires additional reporting of clinical research results and additional reporting of some adverse events.[157] This is a positive step forward.

However, even with the 2007 Amendment, CROs can still hide fraud. To make drug research more apparent, the FDA should require that research findings be published in a scientific journal before the FDA approves a New Drug Application. Currently, the only peer review most drug research receives is from the FDA.[158] Other experts, then, would be able to examine the data and look for faults and potential fraud. Pharmaceutical companies would

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[151] Morin, *supra* note 28, at 82.
[152] Mirowski, *supra* note 4, at 513.
[153] O'Reilly, *supra* note 115, at 322-23.
[154] *See* Public Citizen Health Research Group v. FDA, 185 F.3d 898 (DC Cir. 1999). Both the majority and the concurring opinion discuss patient safety and secrecy in pharmaceutical research.
[155] Morin, *supra* note 28, at 82.
[156] *Id.*
[157] 42 U.S.C. 28 2(j)(3)(I)(ii)-(iii)
[158] *Public Citizen*, 185 F.3d at 901-02.

probably lose a competitive edge in publishing the research,[159] so perhaps a trade-off (extending the length of patents, for example) could accompany the publication requirement.

In addition, research investigators that do research not submitted to the FDA, such as research done purely for marketing purposes, are able to hide their research, to a great extent, even from the FDA.[160] The research done on antidepressant drug Paxil, discussed earlier, shows how this is done; negative results are hidden while positive results are published.[161]

CROs are hired to research pharmaceuticals, not to publish research results. But perhaps CROs should be given the responsibility to publish the results of every drug study they perform, as suppressing study results can be just as harmful as falsifying them.[162] Investigators should be required to timely publish results, regardless of whether or not those results are positive; otherwise, the integrity of science is compromised.[163]

The pharmaceutical research performed by CROs should be analyzed by the same academic review processes other scientific research undergoes—namely, publication and peer review.[164]

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[159] *Id.* at 905.
[160] O'Reilly, *supra* note 115, at 335-36.
[161] *See* http://www.cbsnews.com/stories/2004/06/03/health/main620815.shtml (current as of 12/7/09).
[162] Examples of researchers publishing negative results do exist, but pharmaceutical companies place considerable pressure on research investigators to keep them from doing so; *see* Nathan, *supra* note 107.
[163] Morin, *supra* note 28, at 82.
[164] Morgan, *supra* note 105, at 663.

e. Provide the FDA Adequate Funding for Field Investigations

The FDA only has funding to conduct audits on a small percentage of drug research studies.[165] As more and more of these studies are being conducted outside of the US, the ability of the FDA to conduct audits for fraud diminishes.[166] Even within the United States, the FDA seems to lack the resources to follow up on reports of fraud.[167]

An increase in funding for the FDA to conduct field investigations, followed by an increase in investigations, would result in more discovery of fraud. An increase in the discovery of fraud would not only decrease fraud by eliminating fraudulent pharmaceutical research directly; it would also create an additional incentive for CROs to avoid research fraud.

f. Provide Stricter Punishments for Individuals and CROs that Engage in Fraud

Very few researchers are debarred or imprisoned for research fraud; those that are debarred or imprisoned often receive temporary debarments or short prison terms.[168] Fines for fraudulent research should be increased.

Prison terms, even for multiple frauds committed against multiple parties for years at a time, are relatively short; Fiddes, for example, was given a fifteen month sentence, even though he had engaged in massive fraud in several pharmaceutical research studies, and even though his

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[165] O'Reilly, *supra* note 115, at 345.
[166] *Id.*
[167] Eichenwald, *supra* note 49; an ex-employee's report of pharmaceutical research fraud was ignored for over 17 months, until additional sources also reported fraud.
[168] *See* http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/default.htm (current as of 12/7/2009).

fraudulent research practices hospitalized at least one research subject.[169] It seems that the only way to get much more than a year for fraudulent research is when that fraudulent research results in death.[170] Court and juries should understand the seriousness of research fraud, and assist the FDA in providing longer prison sentences for those who engage in research fraud.

Congress should enact a federal criminal statute to deal directly with scientific misconduct.[171] A scientific misconduct criminal statute would indicate public intolerance of scientific fraud, and would be better suited to prosecute research investigators who engage in fraud.[172] The statute could be tailored to meet the needs of the scientific research community (an extended statute of limitations to allow for pharmaceutical companies, universities, and CROs to investigate fraud before the FDA does, a mens rea of "knowingly," etc.).[173]

FDA does not permanently debar many researchers. Between 2004 and 2009, a total of eleven people had been permanently debarred from pharmaceutical research, less than half the number permanently debarred in 1993 alone.[174] Most of those debarred were debarred for reasons other than research fraud.[175] The number of permanent debarments has decreased significantly since 1993,[176] perhaps due to under-enforcement or perhaps due to lesser punishments such as fines or warnings. Even Fiddes, who engaged in massive research fraud,

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[169] Eichenwald, *supra* note 49.
[170] *See* Paul H Kornak, 71 Fed. Reg. 9555 (FDA Feb. 24, 2006).
[171] Kuzma, *supra* note 23, at 414. This article goes into additional depth on what a scientific misconduct criminal statute would look like, and the advantages of such a statute.
[172] *Id.*
[173] *Id.* at 415.
[174] *See* http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/default.htm (current as of 12/7/2009).
[175] *Id.*
[176] *Id.*

did not receive permanent debarment.[177] The FDA should be willing to hand out more, longer-lasting debarments to those who engage in research fraud.

Fines should also be increased, and pharmaceutical companies, CROs, and universities that are responsible for preventing fraud should be fined for failure to do so. Currently, pharmaceutical companies may look the other way when they suspect fraud. The Fiddes case details how this can occur.[178]

An independent study monitor who worked with Pfizer challenged Dr. Fiddes about discrepancies in his research.[179] Fiddes complained to Pfizer and had that monitor taken off the job.[180] A spokeswoman for Pfizer stated that, in case of a conflict with a researcher and a monitor, "In order to insure the most objective and best monitoring, we generally recommend that if there is personal conflict, and no certainty of irregularities, that a new neutral person is assigned to review all of the data."[181] In other words, unless there is a "certainty of irregularities," pharmaceutical companies like Pfizer will ignore all suspicious behavior and continue utilizing fraudulent research.

Pharmaceutical companies should be fined for this irresponsible behavior; significant fines could produce an incentive for pharmaceutical companies to search for and eliminate fraud in research done by entities the pharmaceutical company sponsors.

Longer prison sentences, more debarments, and larger fines would provide an additional disincentive for research fraud.

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[177] Robert Fiddes, 67 Fed. Reg. 67,628 (FDA Nov. 6, 2002).
[178] Eichenwald, *supra* note 49.
[179] *Id.*
[180] *Id.*
[181] *Id.*

V. CONCLUSION

In an ideal world, decisions about pharmaceutical research would be made based on hard scientific evidence about safety and efficacy.[182] Unfortunately, ours is not an ideal world.

While CROs may face liabilities when they engage in fraudulent research, those liabilities will do little to stop the more subtle forms of fraud that infiltrate through CROs. In order to stop research fraud effectively, CROs and pharmaceuticals must find a way to eliminate conflicts of interest. When a CRO's success is primarily based not off the quality of the research done, but on whether the research shows the drug is safe and effective—in other words, when a CRO's success is based off the results of the research instead of the quality of the research—a CRO will have every incentive to engage in minor forms of research fraud in order to create more favorable results.

Congress, pharmaceutical companies, CROs, and the FDA should act to decrease the amount of fraud and bias that occurs in pharmaceutical research.

[182] Morgan, *supra* note 105, at 660.