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Legislative Issues in Disclosing Financial Conflicts of Interest to Participants in Biomedical Research: Effectiveness and Methodology

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This research focuses on the analysis regarding disclosure of financial conflicts of interest (FCOI) after Gelsinger v. University of Pennsylvania (Penn). The main legal issue was that the participants did not have enough opportunity to make an autonomous decision about participating in the research because he was not informed about the researchers' and the institution's substantial FCOI. The disclosure system was adopted by the Code of Federal Regulations. Under the regulation, researchers and institutions need to report FCOI over $5,000 to the institution, and the internal review boards have to report to the federal authority if needed. In case of human research, the disclosure to Food and Drug Administration is mandatory. FCOI disclosure system would help participants to make an autonomous decision, and increase trust to the research process and researchers. Moreover, the system would let researchers keep fiduciary duty while (possibly) lowering legal liability in case of a lawsuit. There were discussions about the disclosure methodology in the United States. However, there have not been a lot of discussions in Korea even after the "Humidifier Disinfectant" case. Therefore, new legislations need to be considered. First, the system requires disclosure funded by not only government but also private institutions. Second, like California Supreme Court, the subject would be reviewed under the reasonable person standard by participants, including patents, equity, and stock. Third, the disclosure needs to include simple or brief explanation to the FCOI to be better understood by the participants. Fourth, the disclosure should be in the informed consent process.

Keywords: FCOI; Legislation; Biomedical Research; FDA; Regulation

INTRODUCTION

Should research participants be told about the financial conflicts of interest (FCOI) of researchers or institutions? Until 1999, legal issues in the human research disclosure process had been focused on the disclosure of the potential risks and its management (1). However, when Dr. James M. Wilson conducted research without disclosing important FCOI information and resulted in a young human subject's death, critical opinions had emerged regarding whether the FCOI should be disclosed, and if so, how the process needs to be established in detail (2,3).

CASE STUDY: WILSON CASE (GELSINGER V. UNIVERSITY OF PENNSYLVANIA [Penn])

An 18-year-old participant named Jesse Gelsinger, died in one "human gene transfer study" conducted at the Penn in 1999. His death occurred after 4 days of infusion with a geno-vector. After the Food and Drug Administration (FDA)'s investigation, the government concluded that the subject's death was caused by two improper research procedures (4).

First, the risk of Jesse's participation should have been reviewed under strict procedure regulation before the research, and Jesse, because of his rare disease, should not have been involved in the research (5). Jesse had ornithine transcarbamylase deficiency (OTCD), which makes it difficult for the liver to process proteins (4). Because of it, Jesse's "ammonia levels fell outside the protocol's safety limit" (4). Under FDA regulation, a study was supposed to stop if "patients (had) suffered serious side effects … to be reported to the FDA" (5). The FDA later concluded that Jesse's high ammonia level, which indicated high risks, is one of the important facts that should have been reported to the FDA, and Jesse's participation should have been prohibited.

Second, information provided by the researchers was not enough, so called "misleading disclosure" (4). FDA's investigation revealed that Jesse and his parents were not informed of

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the "result of the prior animal (monkey) studies" (5). Not only that, they did not know about "Dr. Wilson's potential gains" and the institution's interests related to the study (5). Prior to the research, Jesse had signed an OTCD gene therapy consent form, which provides that, "Dr. James M. Wilson... and Genovo Inc... have a financial interest in a success outcome from the research involved in the study" (6). However, Jesse's parents argue that they "should have been told more about the financial relationships." They added that they thought that Jesse "was dealing with physicians, not entrepreneurs" (7).

FCOI had been related with the two sides, Dr. Wilson as a researcher and Penn as an institution. First, Dr. Wilson, a director of the Institute for Human Gene Therapy (IHGT) at Penn, was a founder and one of the CEOs of Genovo, a pharmaceutical company. Wilson's stake was estimated to be around "28.5–33 million dollars" following the internal document of Penn (4). Not only that, following the Wall Street Journal's article, his expected gain from the trial was 13.5 million dollars (4). Dr. Wilson was allowed "to control up to 30 percent of Genovo's stock," which was uncommon in comparison to the fact that professors were allowed to hold only up to 5% of the company that they were employed in. It was discovered later that the internal committees to oversee the research "were dominated by Penn Faculty" (7). Second, Penn was another potential beneficiary of the study. In 1995, Penn waived part of "conflict-of-interest guidelines," which had provided "exclusive rights to license patent from Wilson's lab at Penn to Genovo" (7); and Genovo "provide(d) nearly a quarter of the budget" to the IHGT (7). After Jesse's death, Penn has changed its policies, and has discontinued all human gene-transfer experimentation at IHGT. The principal investigator, Dr. Wilson, stepped down from the president of IHGT (8).

The lawsuits between Jesse Gelsinger's parents and Penn had been ended with settlement. Since no public document was released from the court or both parties, the detailed arguments between the parties were not disclosed. However, without released official documentations, the case has become a landmark case in regulating FCOI in the process of biomedical research with human subjects.

FCOI ISSUES FROM WILSON CASE

Issue 1. Whether FCOI affects scientific research results: "maybe"

The tragic case had induced significant results, while the issue ("Whether FCOI affects on professional research result") had not been importantly recognized before the accident.

Regarding this, there were debates among scholars. One group of scholars had opinions that the correlation between FCOI and research results in scientific areas is unclear. For instance, Mildred Cho, a bioethicist at Stanford University and formerly at Penn, said "It is almost impossible to find a smoking gun... Gelsinger's death may or may not have been a function of the commercial ties. In all likelihood, it was not" (7).

However, lots of researchers seem to admit the possibility of conflicts of interests (COIs). For instance, Arthur Beaudet, "a member of the Recombinant DNA Advisory Committee of the National Institutes of Health (NIH)," said that "There are so many potential conflicts. The investigators may be perceived to have conflicts in their desire to be successful. The company stock changes price depending on the academic announcement" (7). Dr. Wilson, ten years later, also said that, "I'm more knowledgeable about who was responsible for the overselling of gene therapy. It was all the stakeholders: the investigators, because there's funding... The need of those groups and the desire to move forward is very compelling to anyone involved in the research, and leads to the investigator pushing too hard or overstating the potential of the therapy" (8).

One research study conducted by Dr. Friedman indicates the correlation between the FCOI and research results. Dr. Friedman compared two groups in drug treatment studies; one having FCOI, while the other having none (9). As a result, the former shows higher positive results (85%) than the latter (40.7%). Moreover, the former had lower negative results (1.7%) than the latter (35.6%). It was similar when they performed researches for "all treatment studies" (9). The authors said that "We observed a strong association between positive results and COI among all treatment studies... The odds are extremely small that negative results would be published by authors with COI" (9).

Inspired by the perspective above, this article presumes that FCOI may be able to influence the research conclusion.

Issue 2. How to regulate FCOI: "mandatory disclosure"

The second legal issue is how to regulate FCOI. One possible way is to prohibit the investigator with FCOI from participating in human research (10). For instance, American Society for Gene Therapy articulated that "all investigators directly responsible for patient selection, the informed consent process and/or clinical management in a trial must not have equity, stock options or comparable arrangements in companies sponsoring the trial" (11). However, the policy had been criticized as it might discourage clinical trials; thereby prohibition may be "recommend(ed), not required" in most institutions (12).

Another regulatory tool is to let the researchers or institutions disclose FCOI to potential participants in the "informed consent process" (13). After participants are informed of FCOI, they may have a chance to consider potential effects of the FCOI and make a decision to participate or not (12). Disclosing relevant information could be a way of balancing rights between the researchers and the participants in human subject research; thereby, it may be more acceptable than prohibiting the researchers from conducting the research.

Issue 3. Disclosing FCOI to participants: "effectiveness and methodology"

Regarding mandatory disclosure requirements in regulatory FCOI, more specific legal questions are the effectiveness of the regulation and methodology of it.

First, effectiveness is reviewed under two perspectives. The first issue is whether disclosure of FCOI helps participants' autonomous decision. The second issue is whether the FCOI disclosure system increases participants' trust in the researchers and research results. From the researchers' or institutions' perspective, the issue is whether it lowers the researchers' legal liability in court.

Second, methodology issues include more specific questions in the process. For instance, disclosure subject (patent, equity, per capita payments etc.), disclosure method (with explanation or not), or disclosure timing (consent process) are discussed.

Frameworks

Among the issues from the case, this paper focuses on specific issues: "Disclosing FCOI to participants." In reviewing the "Disclosing FCOI to participants: Effectiveness and Methodology", the regulatory frameworks and legal issues may follow. To be specific, part II of this paper looks at history and current legal frameworks including general regulations (i.e., Department of Health and Human Service (HHS) Guidelines); part III explores effectiveness and methodology of the disclosing system; and part IV suggests a better and detailed disclosure system.

HISTORY AND LEGAL FRAMEWORKS

History

The U.S. Congress had addressed FCOI research in 1980 as part of the "Bayh-Dole Act" (14). The act was the first one that required investigators to disclose FCOI to interested parties including regulators, institutional officials, and funding agencies. In 1995, NIH started to discuss the need for review programs (15), proposing an investigator's obligation to report Significant Financial Interests (SFI) ($5,000–$10,000) to the institution employed.

As the requests for regulation on disclosing FCOI have increased, after Jesse's death in 1999, legal issues have focused on more detailed "effectiveness and methodology." Finally, in 2004, the HHS guideline provided that FCOI is required to be managed by a "separate committee" (16). In 2009, government officials began to require FCOI review for research funded by the FDA, the National Science Foundation (NSF), or the Public Health Service (PHS) (12).

Legal Frameworks under Charter of Fundamental Rights (C.F.R.) § 50, 94

Procedure

Though current law does not require all investigators to disclose FCOI to participants, most researchers are obligated to disclose FCOI in research. The main reason is that most research funded by agencies in the PHS are governed by the PHS regulations, which require investigators to disclose FCOI to the "institution's designated official(s)" all their SFIs before the application "for PHS-funded research" or thirty days after they "discovered or acquired a new SFI" (15). Following the PHS regulations, most research institutes, affiliated to the university or not, have internal regulations and review systems requiring the researchers to reveal FCOI before initiating the research.

After FCOI is disclosed, the "designated institutional official(s)" within the institution would review it (15). If the internal review board "reasonably determines" that SFI "directly and significantly affect(s)" the research, the institution shall implement "a management plan" (15).

Under the regulation, a general management plan includes mandatory public disclosure at the time when publishing the result, monitoring, reducing, separating between FCOI responsibilities and research conclusion, "elimination of FCOI," etc. (15). However, when the research involves human subjects, the institution is required to disclose FCOI directly to participants and "PHS Award Components" (i.e., FDA, NIH, Center for Disease Control and Prevention [CDC]) (15).

Disclosure subjects

The SFI includes "anything of monetary value" (15). Under C.F.R. § 94, the report shall include any kind of valuable assets (17). "Consulting fees, honoraria, paid authorship, equity interests, intellectual property (patents, copyrights)" above $5K or statements (if the value is not "readily determined") would be included (17).

However, some of assets may be excluded. First, "salary, royalties, or other remuneration" provided by the institution where he is currently employed would not be SFI. Second, reimbursed travel for education or academic purpose would not be included according to the determination by "institutional officials(s)" under each internal policy (17).

The specific standards, at which investigators are required to disclose FCOIs to the institution, was changed in 2011. Before 2011, the minimum threshold was $10,000 and did not include "equity interest in non-publically traded entities" (18). Revised regulation lowered the minimum threshold to $5,000, and expanded the scope to include "any equity interest in non-publically traded entities" (18). Moreover, the new regulation expanded the disclosure requirement from "only SFI that investigators deem related to the research" to "all SFI related to investigators' institutional responsibilities" (18). The responsibility to determine the "relationship" remains with the institution (18). The reimbursements from sponsored travel or employment standards are defined more in detail (Table 1).

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Table 1. Change of SFI standard from 1995 to 2011 (18)

Characteristics	1995 regulation	2011 regulation
Disclosure standard	$10,000	$5,000 (including any equity)
Disclosure decision	Only if investigators deem related to PHS-funded research	All SFI related to the research
Types excluded	All forms of remuneration	Income from investment method (i.e., mutual funds, retirement accounts, if investigators do not directly control)
Sponsored travel	Not mentioned explicitly	The institution determines

SFI = Significant Financial Interests, PHS = Public Health Service.

Disclosure with informed consent requirement

Under common law, researchers need to disclose eight minimum requirements in the informed consent process (19). The list includes a description of "any reasonably foreseeable risks or discomforts to the subject" and "any benefits to the subject or to others which may reasonably be expected from the research" (17). The consent form must be approved by the Institutional Review Boards (IRBs) and signed by the participants (or legally authorized representation) (17). IRBs shall review the consent form regarding "the extent financial interest" (16), for instance, "the source of funding" or "financial arrangement of an institution or an investigator" and "how it being managed" (17).

Moreover, the 2011 Advanced Notice of Proposed Rulemaking (ANPRM) provides that informed consent should include plain-language description within the limited lengths form (19). Under the ANPRM, IRB requires the consent form to be written "at a 6–8th grade reading level" (20). For instance, Johns Hopkins Medicine IRB recommends that the informed consent form should be "no higher than an 8th grade level" (21). It also suggests description including loud reading for participants and use of "word processing tool" (21). The consent form allows participants to "fully understand the implications of participation" (22). One IRB member provides that the "science, medical and technical" shall be avoided, if necessary, they should be "clearly defined in simple language" (22).

EFFECTIVENESS AND METHODOLOGY

Effectiveness

FCOI disclosure may affect participants and researchers. From participants' perspectives, it provides a valuable chance for participants to make a decision autonomously, and increase participants' trust regarding the research process and results. From researchers' view, this process provides them the chance to keep the fiduciary duty (possibly) lowering legal liability. Detailed discussions are as the following.

Autonomous decision making

FCOI disclosure allows participants to make an autonomous decision as it provides a chance for the participants to reach a conclusion after he "ha(d) gained substantial understanding of the potential risk and benefits" (12). Substantial understanding is not easy to define because of the variations in participants' ability or background of understanding, the nature and implications of different FCOI. For instance, some participants may misunderstand or overestimate the influence of FCOI. Or others may understand the value or implications of FCOI involving stocks, equity, etc. differently. To help participants understand FCOI better, some researchers argue that additional explanation of FCOI consent form is needed, which will be discussed in part III-2-2) (13).

Even when participants substantially understand FCOI, the information will not necessarily influence participants' decision making. In one study, generally 60%–70% of participants answered that they wanted to know FCOI, and about 60%–80% said the information would not affect (their) decision (23). The most common reasons for their unwillingness to know are: the FCOI information was not as significant as other sources of information; the belief that such conflicts are unavoidable; and that the information is covered by the investigators' privacy interests (13).

However, in another research study, investigators or IRB chairs (around 70%–90%) answered that the prominent reason of disclosing FCOI is to "enable potential participants to make better informed decisions" (investigators 88%, IRB chairs 74%) (13). The portion of "enabling informed decision making" is much larger than other reasons including "building trust" (investigators 38%, IRB chairs 30%) or "reducing the risk of legal liability" (investigators 38%, IRB chairs 35%) (13).

Those policy researches indicate that, despite the investigators and IRB chairs' expectations, disclosing FCOI might not substantially be helpful for participants' autonomous decision because "the conflicts are unavoidable" (13). However, still, 60%–80% of the participants want to know FCOI, and 80% of researchers believe that disclosing would be helpful to the autonomous decision. Therefore, although the correlation between the autonomous decision and disclosing FCOI is not substantial or clear, the main purpose of the regulation ("disclosure of FCOI to participants") would be to help participants' autonomous decision making.

Trust

Disclosing FCOI may increase participants' trust regarding the research process and the results in relation to the "investigators,

institutions, and research enterprises" (13). Trust in relationship is defined as "a willingness by one to allow another to take care of something the truster cares about, where such care for involves some exercise of discretionary powers" (2). Trust has an important meaning in research because participants have "expectation of fidelity" and "loyalty" to investigators regarding their safety (2). Likewise, Dr. Francis, a director of NIH, stressed the importance of trust saying, "the public trust in what we do is just essential" (24).

Following the study above, about 30% of respondents had answered that disclosing FCOI would be helpful in "building trust" (13). On the other hand, another study shows that disclosing FCOI has different effect in trust according to the character and materiality of disclosed information (12). For instance, disclosing "per capita payment" helps to increase the trust "in slight range," while equity relationship slightly decrease the trust (12).

Legal liability

Finally, disclosing FCOI may lower investigator's legal liability in case of a lawsuit. To be specific, by disclosing FCOI, researchers are presumed that they had acted in good faith in protecting the participants, and participants had consented to participate in the trial with the knowledge of FCOI (25).

There could be arguments whether disclosure could lower the legal liability after the trial at court. One opinion argues that sufficient FCOI disclosure to participants is required to exempt researchers from fiduciary obligation (12). However, in general, researchers may not be free from fiduciary duty even after they had disclosed FCOIs (26). Like this remark from one researcher, the disclosure would not be "a moral carte blanche" to investigators (27). Even though, like Moore v. Regents of University of California, failure to disclose FCOI may be a "cause of action" under the "lack of informed consent" or "breach of fiduciary duty" (26).

Methodology

Disclosure subject: reasonable person standard

Subjects to disclosure would be determined by the reasonable person standard. Under the current regulation, the institution (i.e., IRB) "reasonably determines that the FCOI (SFI) could directly and significantly affect... the research" (15,28). Reasonableness is determined where "reasonably prudent subjects understand that investigators will seek both payments as well as recognition for their services" (28,29). Courts also would review the FCOI under the reasonable person standard. The California Supreme Court held that "a physician... must disclose personal interests unrelated to the patients' health, whether research or economic, that may affect his medical judgment" (26).

Reviewing from the reasonableness standard, FCOI could be divided into two parts. First, substantial FCOI would include "patent, equity, stock," etc. (23). Second, payments for actual cost of the research and modest amount of the indirect cost of the institution will not be required to be disclosed to participants (29).

Disclosure method: just information or information with explanation

When investigators or institutions disclose FCOI to participants, two methods are discussed. One is to disclose only FCOI; while the other is to let the participants know more in detail with explanation regarding the meaning or potential consequence of the FCOI. Since participants are not experts in the research field, they "(m) ay not know how to evaluate" the information; or "(l) ikely to underestimate the degree of (FCOI) influence" (23,30). For instance, where there is equity interest between the investigators and sponsors, some participants may not understand the information not only because they are unfamiliar with it but also because the information (and potential risk itself) is ambiguous.

Providing only information is one way to let participants decide by themselves (13). Some opinions prefer this as it is more neutral and unbiased "informed decision making" (13). Supporters of this opinion argue that the explanation written by investigators may not be neutral; or may not reflect the potential risks or influences precisely (13). Supporters also point out that unclear or complex explanation may decrease the participants' trust or researchers' transparency, and incur confusion to the participants (28).

However, according to the other method, information with explanation including potential consequences of relationship would help participants to understand better (13). According to one study, an IBR chair suggests that the explanation of FCOI is needed, saying that, "participants need to understand that investigators may potentially alter or affect or influence the result" (13). It also would increase trust as it is a way of providing information to better understand.

Moreover, if explanation is added to the FCOI, it needs to be "brief and simple" with a plain language (6–8th grade reading) to help participants understand (31). The consent process also needs to be performed by the trained coordinators, with highlights if needed (13).

Disclosure timing: in the informed consent process

The final issue is the timing of FCOI disclosure (13). The timing is significant because it gives participants an opportunity to make an autonomous decision, building trust about the research. According to a study, some respondents explained that the informed decision means that parties "let them fully understand (aware)" all issues related to that particular study (13). Therefore, to provide a chance to fully understand FCOI and decide, the disclosure needs to be at the beginning of the process, during the informed consent procedures (13).

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CONCLUSION

As discussed above, after 2011 revision of the federal regulation, there were suggestions and discussions regarding how to articulate the disclosure system in the United States, while there had not been much discussion in Korea. However, recently, cases similar to Wilson had been incurred in Korea. For instance, after "Humidifier Disinfectant" case in 2016 and Hwang Woo-Suk's case in 2005, researchers' and participants' concerns are more closely related to FCOI (32).

Like aforementioned, as FCOI becomes more significant, a detailed FCOI disclosure system that would be adaptable in Korea's legal system needs to be discussed. The legislative approach should include agreements among researchers, participants, and scholars; and the detailed methodology needs to be designed after balancing interests between interested parties. Moreover, in order to induce gradual changes to avoid confusion in practice, the disclosure system may be adopted from specific areas such as trials in gene medicine including human subjects, etc.

Legal suggestions including FCOI disclosure system are as follows. First, the FCOI disclosure system needs to be applied not only to researches funded by government but also studies funded by private institutions. The reason is that, like Jesse's case, FCOI issues could take place more frequently in privately funded research.

Second, the disclosure threshold needs to be determined after the interested parties had reached an agreement. Following current federal regulation and guideline, investigators need to disclose FCOI above $5,000. However, the research and opinions had indicated less clear relationship with the effectiveness of FCOI disclosing. Therefore, the regulations may provide more burdens in institutions or investigators without significant effectiveness regarding participants. However, the threshold amounts and specific forms may be set in Korea in different ways. For instance, the amount standard including patent, stocks or equity might be higher than $20,000 or more. The per capita payments or consulting fees would be set aside from mandatory disclosure as long as they are reviewed by internal board (i.e., IRB).

Third, the institutions may decide whether they provide explanation about FCOIs or not, because it could be different according to each researcher and participant. If needed, the explanation should be written in plain language.

Fourth, FCOI disclosure needs to be performed in the process of informed consent and other requirements of consent may be applied. This is because the effectiveness of disclosing is based on the policy reasons of encouraging autonomous decisions, increasing trust, and lowering the legal burden of proof of participants. Later disclosure after the informed consent process may not be effective for the purpose of disclosure system.

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