PSYCHIATRIA ET NEUROLOGIA JAPONICA



**Review Article**

# What Physicians Need to Understand about a Conflict of Interest

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## Abstract

A conflict of interest (COI) is a set of conditions in which professional judgment concerning a primary interest may be influenced by a secondary interest. A COI should be considered to exist if the influence of the secondary interest appears to exist, even if it does not.

Primary interests of a physician may be, depending on the situation, the welfare of the patients, research validity, and education of medical students. A secondary interest is not always financial gain (financial COI), but a non—financial interest, such as reputation, promotion, competition, and even an inquiring mind, may interfere with the primary interest (non-financial COI).

After the Gelsinger case was reported in 1999, financial COI of researchers first drew attention in the international community. In this context, the primary interest is research validity, including the safety of participants, and the secondary interest is financial gain. There have been several famous cases of research misconduct overseas, which were likely affected by financial COI. Japan is no exception; research misconduct involving a pharmaceutical company and researchers in several medical schools led to a strict management policy of financial COI in clinical research, and enactment of the Clinical Trial Act in 2017. It is difficult to ensure research integrity by managing financial COI. However, research integrity may be threatened by researchers who seek more impactful research results and papers.

COI is not only an issue in the context of research. Management of financial COI is becoming more important in clinical practice. Indeed, coverage of the relationship between physicians and pharmaceutical companies is increasing. The Japanese media recently reported on the free meals provided at new drug briefings by pharmaceutical companies in addition to funding physicians. COI management is not just required in research or clinical practice. In the field of medical education, the guidelines for managing COI were published in 2019 in Japan.

Primary interests of a physician can conflict with each other. The relationship between physicians and patients in clinical practice cannot directly translate into the relationship between researchers and subjects in research or between teachers and materials in medical education. It should be noted that patient participation in clinical research and medical education may undermine their best interests in clinical practice.

**Keywords**: conflict of interest, conflict of primary interest, primary interest of physicians

## Introduction.

When explaining ethics, Toshio Sato is often quoted as saying, "Interest in ethics increases when ethics is in disrepair, confusion, or crisis, or rather, when it becomes anti-ethical" 16). In other words, when something that had been in order is disrupted or lacking, it attracts attention.

In recent years, there has been a great deal of interest in conflicts of interest and their management. All speakers are now required to disclose conflicts of interest in presentations at many conferences, including this one. With regard to conflicts of interest, it seems that rather than a disruption of what had been in place, the current situation is that practices that had been taken for granted for a long time are now being questioned as to whether they are really acceptable.

This paper reviews conflicts of interest of physicians, focusing on the mission of physicians, and discusses how we should deal with conflicts of interest.

## I. What is a conflict of interest?

A conflict of interest is defined by Dennis Thompson as "a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)" 21). In the case of

research, where physicians are most likely to be asked to disclose conflicts of interest, this means situations in which the validity of the research (i.e., research fairness and protection of research subjects), which is the primary interest of the research, may be compromised by secondary interests such as economic interests. In fact, economic interests are the main subject of conflict-of-interest disclosures in this Society.

The primary interest in the definition of conflict of interest depends on the mission of the physician. First, physicians have a mission as healers to do their best for the patients in front of them. In addition, they have a mission as researchers to pursue new medical knowledge, and a mission as educators to the next generation of would-be medical professionals 20). Research and education are not for the benefit of the patient in front of us, but for the benefit of future patients. The primary interest of the physician is the mission, and the physician is expected to pursue a different primary interest. If a physician simultaneously assumes the roles of healer, researcher, and educator, he will be working for different primary interests in each context of practice, research, and education (Table 1). Economic benefits are the most common secondary interest, but recognition from others, promotion, and academic inquiry can also be secondary interest.

Although it is often misunderstood, the existence of secondary interests in itself is not the problem with conflict of interest. It is essential to raise research funds in order to conduct research, and it is not reprehensible to work hard in one's practice in order to gain recognition from others, or to work vigorously in medical education in order to be promoted. What must be avoided is the distortion of judgments about primary interests for the sake of secondary interests.

Is there a problem, then, if the primary interest is not unduly influenced by the secondary interest? The answer is "No". If we go back to Thompson's definition, when there is a primary interest and a secondary interest, a "condition" in which the secondary interest can unfairly influence the primary interest is a problem 21). The "Guidelines for the Management of Conflict of Interest (COI) in Health and Labour Sciences Research" (MHLW Guidelines), one of the most important guidelines for conflict of interest management in Japan, defines conflict of interest as "a situation in which fair and appropriate judgment required in public research is impaired or concerns may be expressed by a third party that it is impaired due to financial interests with an external party". This does not mean that there is no problem as long as no inappropriate

judgment is made, but that the "visibility" of how it is seen by those around is being questioned 8).

## II. Contrary interests and responsibilities

The MHLW guidelines further subdivide and define conflicts of interest in the broad sense as defined by Thompson (Fig. a) 8). It categorizes "conflict of interest in a narrow sense" when the secondary interest is economic gain, and further categorizes it into "conflict of interest as an individual" and "conflict of interest as an organization", such as a university or research institution. Conflicts that arise as a result of the responsibilities or roles of one's main work and one's concurrent activities are referred to as "conflict of responsibility". The classification of the MHLW guidelines may be easier to understand for researchers at universities and other institutions.

As for physicians' conflicts of interest, it would be easier to understand if the definitions of conflicts of interest and conflicts of responsibility were considered differently from the MHLW guidelines (Fig. b). That is, conflicts of responsibility are regarded as non-economic conflicts of interest, and if the problem is actually a conflict of economic interests, even if externally it appears to be a conflict of roles, it is regarded as an economic conflict of interest. Specifically, a situation in which a person spends so much time on dual-career activities that he or she neglects university duties is classified as a conflict of responsibility under the MHLW guidelines. However, if a person spends a lot of time in dual-career activities for economic gain, it is reasonable to consider that this as an economic conflict of interest. On the other hand, if a physician who works as an industrial physician for a company as part of his or her concurrent activities also treats employees of that company as an attending physician at the hospital where he or she has his or her main job, a situation in which the primary interests of the roles of the physician at the hospital and the industrial physician at the company may conflict with each other over the sharing of medical information, for example, is considered to be a conflict of duty for the physician.

In fact, if we define conflict of duty as "a situation in which judgments about the primary interests of multiple roles affect each other", it becomes easier to understand the ethical conflicts faced by physicians with multiple roles. Physicians often take on the roles of so-called healers, researchers, and educators (Table 1). Therefore, conflicts of responsibility from multiple roles may arise even in their main duties, and it is not important whether the roles are

those of their main duties or those of their concurrent activities. For example, a physician who is a researcher often recruits patients whom he sees as their therapist into his clinical research. If there is no direct benefit or is risk to the patient in participating in the clinical research, the primary interests of the therapist, who seeks the well-being of the patient, and the researcher, whose primary interest is to conduct the research, are fundamentally incompatible. Thus, the duties of a healer and those of a researcher are often in conflict.

## III. Conflict of interest in research and its management

Among medical treatment, research, and education, conflicts of interest in research have received the most attention, and since a long time ago, rules have thus been formulated. This is because there is a history of researchers' conflicts of interest resulting in damage to the safety of research subjects and research fairness, which are the primary interests of research, leading to the research being denounced or questioned by society (Table 2). The Gelsinger case, which resulted in the death of a research subject, was particularly shocking 5) and is said to have led to the revision of the Declaration of Helsinki in 2000, which stipulates the disclosure of conflicts of interest. The Paxil case 15)24) and the Vioxx case 10)22) led to a pre-registration system for clinical trials, and the Diovan case 7) in Japan triggered the enactment of the Clinical Research Law.

It is known that conflicts of interest can cause bias in the various processes of planning, conducting, and publishing research 1). From the standpoint of a pharmaceutical company, it is a rational decision not to fund a clinical study if the results are expected to be unfavorable to its drug. As a result, no research is conducted (interventional research bias). Or, if a clinical study is conducted and the results are unfavorable to the company's sales strategy, the company may not publish the paper (publication bias). In addition, it is easy to overstate results favorable to the company, i.e., the effect, and to understate adverse events (outcome reporting bias). It has also been pointed out that if the results are not as expected, sub-analyses of outcomes that were not considered in the study design are often attempted to produce favorable results.

Now, what does it mean to manage conflicts of interest? The principles for managing conflicts of interest in the MHLW guidelines are shown in Table 3. In addition to ensuring research fairness, protection of research participants, and transparency, it is

clearly stated that researchers and their institutions are responsible for managing conflicts. In addition, it is important to note that "management should be conducted so as not to give the impression to society that objectivity and fairness are impaired". In other words, the level of control will vary depending on how people in society perceive it.

We tend to think that disclosing the status of conflicts of interest and, in the case of research, explaining it to the research subjects and obtaining their consent (disclosure rules) is sufficient. In Japan, the "Ethical Guidelines for Clinical Research" formulated in 2003 included disclosure rules for the first time, but it was unclear what else should be done to manage conflicts of interest, and it was necessary for the institutions to which researchers belonged to make their own decisions. In this regard, the "Guidance on the Management of Conflicts of Interest under the Clinical Research Act", compiled in conjunction with the Clinical Research Act, clearly describes the management of conflicts of interest, and should be referred to in addition to specific clinical research (Table 4) 9). In addition to stipulating the rules of disclosure and consent in Criterion 1, Criterion 4 stipulates in detail the management of conflicts of interest for principal investigators, and states that, in principle, a person cannot become a principal investigator if he or she has certain financial relationships. If a person becomes a principal investigator, he or she must not be involved in data management, monitoring, or statistical analysis, and must be subject to audits during the research period. The management of conflicts of interest also includes spouses and first-degree relatives who share the same livelihood as the principal investigator, and subcontracting physicians are also required not to be involved in data management, monitoring, and statistical analysis in accordance with Criterion 4. Furthermore, if researchers belonging to related companies participate in the research, they are not to be involved in the recruitment of subjects, data management, monitoring, or statistical analysis, in principle. In exceptional cases where their involvement in data management and statistical analysis is necessary, they are required to undergo an audit during the research period.

After the enactment of the Clinical Research Law, the MHLW guidelines were also partially revised, and it was stated that research other than specified clinical research should adopt the same standards as those set forth in the Clinical Research Law, or that if it is difficult for researchers to solve conflict of interest problems, they

should consider withdrawing from participation in research or waiving economic benefits 8). The "COI Management Guidelines of the Japan Medical Association" lists the following as things that should be uniformly avoided: being induced to accumulate cases for money, receiving funding for participation in academic conferences unrelated to research, and receiving extra-contractual success fees based on research results 12).

## IV. Conflict of interest in medical practice

The primary interest in practice is the health and well-being of the patient. However, there are no clear norms regarding conflicts of interest in medical practice. The World Medical Association's "WMA Manual of Medical Ethics" (translated by the Japan Medical Association) explains that "The primary ethical principle underlying these guidelines is that physicians should resolve any conflict between their own interests and those of their patients in their patients' favour", and states the principle that primary interests take precedence over secondary interests is also stated 6). However, as mentioned earlier, it is only natural that primary interests take precedence over secondary interests, and it is necessary to find a way to prevent primary interests from being perceived as being unduly influenced by secondary interests.

The relationship between medical treatment activities and pharmaceutical companies has been reviewed mainly at the initiative of pharmaceutical companies. The turning point came in April 2012, when the Japan Pharmaceutical Manufacturers Association (JPMA) began to implement the "Guidelines for Transparency in Relationships between Corporate Activities and Medical Institutions", which discloses information on money paid to medical institutions and physicians. Additionally, the Fair Trade Council of Ethical Drug Manufacturers and Distributors also strengthened its self-regulation on entertainment for physicians 25). In recent years, the Waseda Chronicle, a non-profit organization, has published a database of lecture fees paid to physicians published by pharmaceutical companies based on these transparency guidelines, which can be searched by individual physician's name 23). With regard to the disclosure of conflicts of interest centered on funding from pharmaceutical companies, the outer moat of physicians is being filled in.

Recently, it should be noted that reports on the relationship between physicians and pharmaceutical companies regarding profit sharing other than research expenses and

honorarium for lecturers have become more prominent. Specifically, there have been reports on the free lunches provided by pharmaceutical companies at so-called product briefings 11)26). A cross-sectional study of pharmaceutical company profit-sharing data and physician prescribing history suggests that free meals worth less than $20 may increase the frequency of physician prescribing 4). A survey of resident physicians in the U.S. showed that many physicians believe that other physicians are influenced by pharmaceutical company promotions, but that they themselves are not 18). As mentioned earlier, "how others see it" is important for conflicts of interest, so if there is a situation where "other doctors may be influenced", it is probably a matter that should be managed in the future. For example, if a for-profit company holds a briefing session in a government office and provides free lunches to civil servants, it is likely that few people would be convinced by the explanation that "eating lunches will not affect policy or ordering decisions".

When it is argued that physicians should stop receiving free lunches from pharmaceutical companies, there is a counterargument that there is weak evidence to show that physicians' prescriptions are affected. Do we really need evidence such as a randomized controlled trial that assigns physicians to a group with free lunches or a group without free lunches and examines changes in the frequency of prescriptions? If so, we have to laugh at the wonderful spread use of Evidence-Based Medicine in Japan.

Conflicts of interest in practice are not limited to relationships with pharmaceutical companies. The interests of one's institution and the incentives that a physician receives from his or her institution for the number of hospitalizations and surgeries may also be in conflict with the primary interest of patient welfare. In addition, the number of procedures and surgeries required to apply for certification as a specialist may be a secondary, non-economic interest.

## V. Conflict of Interest in Education

The primary interest in education is the acquisition of knowledge and skills by learners. Regarding conflicts of interest in education, the Japanese Society for Medical Education published "Conflict of Interest (COI) in Health Professions Education" on January 8, 2019 19). According to these guidelines, for example, it is inappropriate to force students to purchase the teacher's own book when there are other appropriate textbooks available, and a transparent rationale for pedagogical effectiveness and necessity is required when introducing educational materials. The

authors also call attention to ethical considerations in educational research with learners. For medical research involving human subjects, detailed rules are clearly defined in the Clinical Research Act and the Ethical Guidelines for Medical Research Involving Human Subjects, but there are no official rules for research involving human subjects other than medical research. Therefore, there is understandable concern that research on educational methods may be conducted without sufficient ethical consideration and without awareness of the conflicts of responsibility between educators and researchers.

"Conflict of Interest (COI) in Health Professions Education" also refers to the management of conflicts of interest by physicians as healers, stating that "some health professionals may believe that they have fulfilled all their moral obligations by disclosing conflicts of interest, but that alone does not address the issue of conflicts of interest". These guidelines also prohibit the provision of gifts, food and beverages, and labor from pharmaceutical companies, the personal use of samples of pharmaceutical products, and the receipt of travel expenses for company-sponsored seminars. It is expected that these guidelines will become a model for the management of conflicts of interest in medical practice in the future.

## VI. Contrary to the responsibilities of medical treatment, research, and education

Although the management of so-called conflicts of interest is extremely important, the author would like to emphasize that the primary interests of the three roles of physicians - practice, research, and education - can be in conflict. In other words, there is a potential conflict in the mission of physicians, which becomes even more apparent when reviewed from the perspective of the patient rather than the physician. In the practice of medicine, the patient is offered the best medical treatment for himself/herself by the physician as a healer. Of course, the patient's wishes are respected, but the physician has a certain amount of discretion. For example, even if the treatment proposed by the doctor and the patient's intentions do not match at first, the doctor is expected to consult with the patient to find out what is best for the patient, and in some cases, the doctor may even persuade the patient. The process of building consensus through repeated dialogue about medical indications and the patient's intentions and values is called shared decision making. On the other hand, in research, the doctor-patient relationship becomes a relationship between the researcher and the

research subject. In research, there is basically no expectation of a definite medical benefit to the patient, and participation in research is a form of self-sacrifice. Therefore, voluntary informed consent in the strictest sense of the word is required for this self-sacrifice. Some research ethics committees have even prohibited the use of the title "Request for Research Cooperation" in explanatory documents so as not to undermine patients' voluntariness.

Patients are rarely aware of the difference between the roles of treatment and research, and often misunderstand that there is a therapeutic benefit to participating in research [therapeutic misconception]. For researchers who want to increase the number of research participants, it is important to be aware of the difference between the roles of healer and researcher, because it is difficult for them to have incentives to clear up the misunderstanding between treatment and research. It is important for both the physician as researcher and the patient as research subject to understand that research is not treatment, and if the research has therapeutic benefit, to fully explain the extent to which it is treatment and the extent to which it is research, so as to obtain a firm understanding. This is especially important in the field of neuropsychiatry, where some form of support is often required for decision-making.

I would like to point out the problem of case reports in terms of conflicts of responsibility that involve medical treatment, research, and, in some cases, education. Case reports are thought to be an important opportunity for young physicians to learn first how to present at conferences and write papers. In general, the "Ethical Guidelines for Medical Research Involving Human Subjects" do not apply to case reports, so no ethical review is required. Ethical considerations are often emphasized, such as whether informed consent has been obtained for the case report and the protection of personal information. However, there is an augument that if excessive examinations are performed for case reports that would not be performed in normal medical practice, that is exactly the kind of research that needs to be reviewed. There is also a concern that co-authors and co-presenters may have been determined without meeting authorship requirements. If case reports are to be the first opportunity for young researchers and physicians to present papers at conferences, they should also be an opportunity to learn about ethical considerations and authorship issues.

In education, the physician is the educator, and the patient is the

"teaching material" for the learner. In the case of medical student training, consent is often obtained from the patient, but how this should be done when the training is for physicians including residents, is something that needs to be examined in the future.

In the case of research involving learners in educational settings, conflicts of responsibility between researchers and educators become an issue. The study of the effects of new educational methods or materials is an intervention study. While the "Ethical Guidelines for Medical Research Involving Human Subjects" apply to medical research involving human subjects, there are no official guidelines for non-medical research such as education, and this is an issue for the future.

## Conclusion.

From 2018 to 2019, universities, where the issue of inappropriate entrance examinations for medical schools was pointed out, were criticized for their "attitude of prioritizing the university's business convenience and neglecting the fairness of entrance examinations for that purpose" 17). This can be understood as a case of inadequate management of conflicts of responsibility between the roles of manager of a university hospital and educator of a university medical school.

Another important issue, the reform of work styles, can also be understood in the context of conflicts of responsibility. I think that we have placed too much emphasis on the fact that we are doctors, and have neglected the perspective as ordinary living people. Through reform of the way we work, we may be asked how to maintain a balance between the nature of a clergyman and that of a worker, or how to manage the position and responsibilities of a doctor as a professional and as a consumer or family man.

Editor's note: This is a review article based on the educational lecture given at the 115th Annual Meeting of the Japanese Society of Psychiatry and Neurology.

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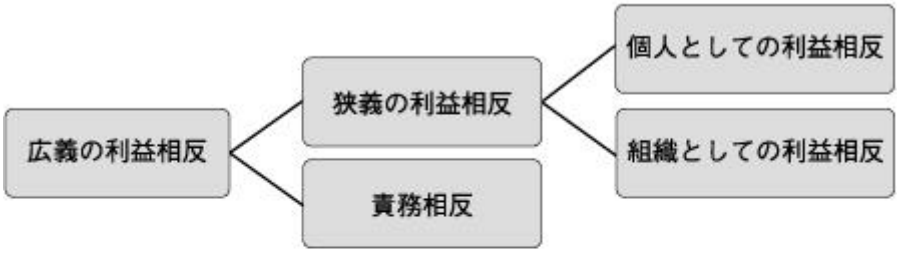
表1　診療，研究，教育における「医師-患者」関係

| | 診療 | 研究 | 教育 |
|---|---|---|---|
| 関係 | 治療者と患者 | 研究者と研究対象者 | 教育者と「教材」 |
| 第一義的な利益 | 患者の健康・福利 | 普遍化可能な知識の獲得（研究公正を含む）・研究対象者の保護 | 学習者（医学生，研修医など）の知識や技能の獲得 |
| インフォームド・コンセント | 患者は自分にとって最善かどうかを判断，医師にも一定の裁量権がある（シェアド・ディシジョン・メイキング） | 他者の利益のために自己犠牲を引き受けるかを判断，研究者に裁量権はない（同意には自発性が求められる） | 医学生の場合には，自発的な同意が必要 |

Table 1 Doctor-patient Relationship in Medical Care, Research, and Education

Treatment / Research / Education
Relationship / Healer and patient/ Researcher and research subject/ Educator and "teaching material"
Primary interest
Health and well-being of patients
Acquisition of universally applicable knowledge (including research fairness)/protection of research subjects
Acquisition of knowledge and skills of learners (medical students, residents)
Informed consent
Patients decide what best for them; physicians have some discretion (Shared decision making)
Patients decide whether they are willing to sacrifice themselves for the benefit of others; researchers do not have discretionary authority. (Voluntary consent is required)
Voluntary consent is required for medical students

a. 厚生労働科学研究における利益相反(Conflict of Interest：COI)の管理に関する指針[8)]




b. 医師の利益相反と責務相反に関する概念図

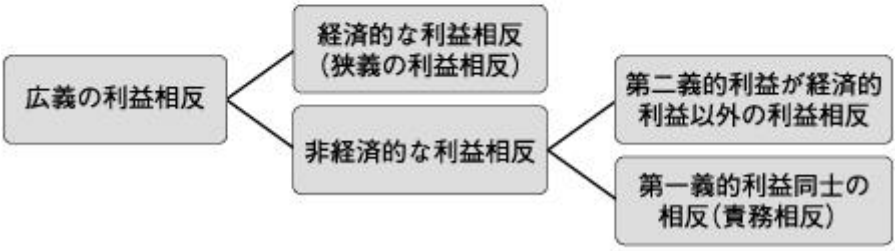



図　利益相反と責務相反

Figure Conflict of Interest and Conflict of Duty

a. Guidelines for the Management of Conflict of Interest (COI) in Health and Labour Sciences Research 8)
Conflict of interest in the broad sense
Conflict of interest in the narrow sense
Conflict of responsibility
Conflict of interest as an individual
Conflicts of interest as an organization
b. Conceptual Diagram of Physicians' Conflict of Interest and Responsibility
Conflict of interest in the broad sense
Economic Conflict of interest (Conflict of interest in the narrow sense)
Non-economic Conflict of interest
Conflict of interest where the secondary interest is other than economic interest
Conflic of primary interest (conflict of responsibility)

表2　主な利益相反事件

| | | 事件の概要 | 参考文献 |
|---|---|---|---|
| 国外 | ウェイクフィールド事件 | ・筆頭著者（ウェイクフィールド）は，自閉症などの行動障害と腸管の炎症病変を合併する小児の病態を報告し，MMR ワクチンとの関連を示唆した論文を 1998 年に Lancet に発表した（すでに撤回）<br>・論文掲載直後に記者会見を行い，MMR ワクチンと自閉症の関連に言及し，単独型のワクチンのほうが安全だと主張した<br>・多くの国におけるワクチン接種率の低下につながった<br>・筆頭著者は，論文発表前年に単独型麻疹ワクチンの特許を申請していた<br>・反ワクチン団体の弁護士に顧問として雇われ，総額約 7,000 万円を得ていた<br>・論文の研究対象となった患者は反ワクチン団体のつてで集められた患者で，患者データや病歴が大幅に書き換えられていた | 2, 3) |
| | ゲルシンガー事件 | ・先天性代謝異常症に対する臨床試験で，本来は組入基準から外れていたゲルシンガー少年に研究薬が投与され，死亡した（1999 年）<br>・有害事象や動物実験段階での問題が規制当局に報告されていなかったことが後日判明した<br>・この研究責任者は，試験薬を提供したベンチャー企業の設立者で，未公開株を 30% 所有し，その企業が研究資金を提供していた．さらに大学の理事会も未公開株を 50% 保有していた | 5) |
| | パキシル事件 | ・小児・若年者のうつに対するパキシルの効果を検討した複数の臨床試験のうち，positive な結果の試験を選択的に出版（2001 年）していたことが明らかになった<br>・出版されていないデータも含めて解析したところ risk＞benefit である可能性が示された | 15, 24) |
| | バイオックス事件 | ・慢性関節リウマチ患者に対するバイオックスとナプロキセンの比較試験（VIGOR 試験）で，心血管リスクの上昇のデータが過少に報告された（2000 年）<br>・心血管リスクの上昇の可能性が指摘されてからも製薬会社は安全性を強調する「教育活動」を継続するなど，適切に対応しなかったことが判明した | 10, 22) |
| 日本国内 | 未公開株報道事案 | ・大学発ベンチャー企業として初めて東証マザーズに上場した企業が開発を進めている遺伝子治療薬について，臨床試験を担当した大学教授らが，2002 年の上場前に同社の未公開株を取得して利益を得ていたと 2004 年に報道された<br>・2002 年当時，日本には利益相反に関した公的なルールはなかったが，扇情的に報道された | 13) |
| | ディオバン事件 | ・製薬企業が資金を提供し，日本国内の 5 つの大学で 2002 年から 2010 年にかけて実施された同社の主力商品である降圧薬ディオバンの大規模臨床試験において，研究不正が行われた<br>・降圧効果に対照薬との差はなかったが，脳血管障害や狭心症などの発生が有意に少なかったなどとする論文が，相次いで著名な医学雑誌に掲載されて，広告資材として活用された<br>・複数の大学に 1 億円以上の奨学寄付金が提供されていた<br>・5 大学すべての研究に企業の社員が，社員であるということを少なくとも論文上は隠して，別大学の非常勤講師の肩書で関与していたこと，うち 2 大学ではその大学の調査委員会で，血圧や合併症件数などのデータ操作があったことなどが明らかになり，すべての論文が撤回された | 7) |
| | イグザレルト事件 | ・ある診療所でイグザレルトを服用中の患者にアンケート調査をした論文で，2012 年から 2013 年にかけて，製薬企業の社員がカルテを患者に無断で閲覧し論文の下書きをしていたこと，社員の関与を論文に記載しなかったことが発覚し，論文は撤回された | 14) |

Table 2 Major Conflict of Interest Cases

Summary of the case / References

Overseas

Wakefield case

The first author (Wakefield) published a paper in the Lancet in 1998 (already retracted) that reported a condition in children with behavioral disorders such as autism and inflammatory lesions of the intestinal tract, and suggested an association with the MMR vaccine. Immediately after the publication of the article, he held a press conference, referring to the association between the MMR vaccine and autism, and claimed that the monotype vaccine was safer. This led to lower vaccination rates in many countries. The first author had applied for a patent for a monovaccine measles vaccine the year before publication. The first author was employed as a legal advisor to an anti-vaccine group and received a total of approximately 70 million yen. The patients studied in the paper were recruited through an anti-vaccine group, and their data and medical histories were substantially falsified 2,3).

Gelsinger case

In a clinical trial for inborn errors of metabolism, a boy whose name is Gelsinger who was not originally included in the study, was given the drug and died (1999).

It was later discovered that no adverse events or problems in the animal testing phase had been reported to regulatory authorities.

The principal investigator was the founder of the venture company that provided the study drug and research funding, and owned 30% of the company's private equity. In addition, the university's board of directors also owned 50% of the private equity 5).

Paxil case

It was revealed that out of several clinical trials examining the effects of Paxil on depression in children and young adults, the trials with positive results were selectively published (in 2001).

The analysis including unpublished data showed the possibility that risk > benefit 15,24).

Vioxx case

In the VIGOR study of Vioxx versus naproxen in patients with chronic rheumatoid arthritis, data on increased cardiovascular risk were underreported (2000).

Even after the possibility of increased cardiovascular risk was pointed out, the pharmaceutical company was found to have failed to take appropriate action, such as continuing "educational activities" emphasizing safety 10,22).

Japan

Case of reported private equity

In 2004, it was reported that university professors who were in charge of clinical trials of a gene therapy drug being developed by a company that was the first

university-launched venture company to be listed on the Mothers market of the Tokyo Stock Exchange, had acquired private shares of the company prior to its listing in 2002 and profited from them.

Although there were no official rules on conflicts of interest in Japan in 2002, the story was sensationalized 13).

Diovan case

A pharmaceutical company funded a large-scale clinical trial of Diovan, the company's mainstay antihypertensive drug, conducted at five universities in Japan between 2002 and 2010, in which research fraud occurred.

The papers, which claimed that the antihypertensive effect of Diovan was not different from that of the control drug, but that the incidence of cerebrovascular disease and angina pectoris was significantly reduced, were published in a series of prominent medical journals and used as advertising materials.

More than 100 million yen in scholarship donations were provided to several universities that performed the studies.

In all five universities, an employee of the company was involved in the studies under the title of "adjunct lecturers" at another university, hiding the fact that he was an employee, at least in the papers. In two of the five universities, the investigative committees of the universities revealed that data on blood pressure and the number of complications had been manipulated, and all the papers were retracted 7).

Ixarelto case

A paper on a survey of patients taking Ixarelto at a clinic was retracted after it was discovered that a pharmaceutical company employee had accessed medical records without the patients' permission and drafted the paper between 2012 and 2013, and that the employee's involvement was not noted in the paper 14).

表3 「厚生労働科学研究における利益相反（COI）の管理に関する指針」に掲げられた「原則」

| |
|---|
| ・研究をバイアスから保護すること |
| ・ヒトを対象とした研究においては，被験者が不当な不利益を被らないようにすること |
| ・外部委員をCOI委員会等に参加させる等，外部の意見を取り入れるシステムを取り入れること |
| ・法律問題ではなく，社会的規範による問題提起となることに留意し，個人情報の保護を図りつつ，透明性の確保を管理の基本とすること |
| ・研究者はCOIの管理に協力する責任があり，所属機関はCOIの管理責任と説明責任があることを認識し，管理を行うこと |
| ・客観性，公平性を損なうという印象を社会に与えることがないように管理を行うこと |

（文献8より引用）

Table 3 "Principles" set forth in the "Guidelines for the Management of Conflict of Interest (COI) in Health and Labor Sciences Research"

Protect research from bias.
In research involving human subjects, ensure that subjects do not suffer undue disadvantage.
Incorporate a system for incorporating outside opinions, such as having outside members participate in COI committees.
Pay attention to the fact that this is not a legal issue, but an issue raised by social norms, and make ensuring transparency the basis of management while protecting personal information.
The researcher is responsible for cooperating in the management of COI, and the institution to which the researcher belongs is responsible for the management of COI and is accountable for its explanation. Management should be carried out in recognition of this.
Management should be conducted in a manner that does not give society the impression that objectivity and impartiality have been compromised.
(Quoted from Reference 8)

表4　臨床研究法における利益相反管理ガイダンス利益相反管理基準（様式A）の概要

| |
|---|
| ・基準1：研究計画書・説明文書に記載し，成果公表時に開示 |
| ・基準2：研究資金等の提供を受ける場合は契約を締結する |
| ・基準3：研究開始後に新たに発生した利益相反も管理の対象となる |
| ・基準4：次の場合は原則として研究責任医師から外れる<br>①寄附講座に所属し給与を受給，②年間250万円以上の個人的利益（給与，講演，贈答，接遇など），③役員就任，④一定以上の株式保有，⑤特許を保有・出願 |
| ・基準5：基準4の①から⑤に該当するにもかかわらず研究責任医師となる場合，データ管理，モニタリング，統計解析に関与せず，かつ研究期間中に監査を受ける |
| ・基準6：研究責任医師と生計を同じくする配偶者や一親等の親族が基準4の②から⑤に該当する場合，データ管理，モニタリング，統計解析に関与しない |
| ・基準7：研究分担医師が基準4の①～⑤に該当する場合，データ管理，モニタリング，統計解析に関与しない |
| ・基準8：関係企業等の研究者は，原則として被験者のリクルート，データ管理，モニタリング，統計解析に関与しない．例外的にデータ管理，統計解析に関与させる必要がある場合，研究期間中に監査を受ける |

（文献9より作成）

Table 4: Guidance on the Management of Conflicts of Interest in the Clinical Research Act Summary of Conflict of Interest Management Standards (Form A)

Criterion 1: Described in the research protocol and informed concent form, and disclosed when the results are published.
Criterion 2: Conclude a contract when research funds are provided.
Criterion 3: Conflict of interest that newly arise after the start of the study shall also be subject to the management.
Criterion 4: In principle, a person who is associated with particular company should be excluded from being a principal investigator in the following cases: (1) belonging to an endowed chair and receiving a salary, (2) receiving personal benefits of 2.5 million yen or more per year (salary, lectures, gifts, hospitality), (3) becoming an officer, (4) owning more than a certain amount of stock, and (5) owning or applying for a patent.

Criterion 5: If a person becomes a principal investigator in spite of any of criterion (1) through (5) of 4, he or she will not be involved in data management, monitoring, or statistical analysis and will be subject to audit during the research period.
Criterion 6: If a spouse or first-degree relative who shares the same livelihood as the principal investigator falls under criterion (2) to (5) of 4, they will not be involved in data management, monitoring, or statistical analysis.
Criterion 7: If a subcontracting physician falls under criterion (1) through (5) of 4, he or she will not be involved in data management, monitoring, or statistical analysis.
Criterion 8: In principle, researchers from related companies will not be involved in the recruitment of subjects, data management, monitoring, or statistical analysis. In exceptional cases where it is necessary to involve them in data management or statistical analysis, they will be audited during the research period.
(Prepared from Reference 9).