中國醫藥大學附設醫院
China Medical University Hodpital

人體研究的利益衝突

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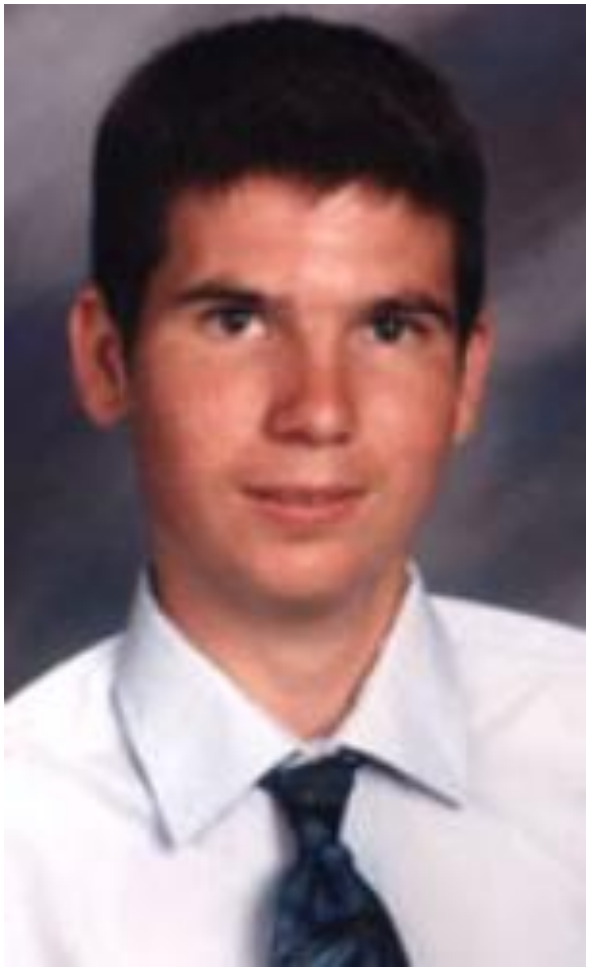
The Case of Jesse Gelsinger

- **Jesse Gelsinger** (June 18, 1981 – September 17, 1999) was the first person publicly identified as having died in a clinical trial for gene therapy. Gelsinger suffered from **ornithine transcarbamylase (OTC) deficiency**, an **X-linked genetic disease of the liver**, the symptoms of which include **an inability to metabolize ammonia**. The disease is usually fatal at birth, but Gelsinger had a milder form of the disease. As his deficiency was partial, Gelsinger managed to survive on a restricted diet and special medications.



https://en.wikipedia.org/wiki/Jesse_Gelsinger

The Case of Jesse Gelsinger

- Gelsinger joined a clinical trial run by **the University of Pennsylvania** that aimed at developing **a treatment for infants born with the severe form of the disease**.
- On September 13, 1999, Gelsinger was injected with **an adenoviral (腺病毒) vector** carrying a corrected gene to test the safety of the procedure. He died four days later at the age of 18, on September 17 at 2:30 pm, apparently having suffered **a massive immune response** triggered by the use of the viral vector to transport the gene into his cells, leading to **multiple organ failure** and **brain death**.

https://en.wikipedia.org/wiki/Jesse_Gelsinger

The Case of Jesse Gelsinger

- A FDA investigation concluded that the scientists involved in the trial, including the co-investigator **Dr. James M. Wilson** (Director of the Institute for Human Gene Therapy), broke several rules of conduct:

- Inclusion of Gelsinger as a substitute for another volunteer who dropped out, despite **Gelsinger's having high ammonia levels** that should have led to **his exclusion from the trial**.
- Failure by the university to report that **two patients had experienced serious side effects from the gene therapy**.
- Failure to disclose, in the informed-consent documentation, **the deaths of monkeys** given a similar treatment.

https://en.wikipedia.org/wiki/Jesse_Gelsinger

The Case of Jesse Gelsinger

- **Financial Conflict of Interest**

- Dr. Wilson 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**," and **his expected gain from the trial was 13.5 million dollars**.
- 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.
- 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**"; and **Genovo "provided nearly a quarter of the budget" to the Institute for Human Gene Therapy at Penn**.

Kim (2017)

The Definition of Conflict of Interest

- A set of conditions in which an investigator's judgment concerning **a primary interest** (e.g., **subject welfare**, **integrity of research**) could be biased by **a secondary interest** (e.g. **personal or financial gain**)
- A conflict exists **whether or not decisions are affected by the personal interest**; a conflict of interest implies only **the potential for bias or wrongdoing**, not a certainty or likelihood.

Nelson (2006a)

Evolution of the Clinical Research Enterprise

- Once upon a time, most biomedical research was **funded by the government** and **conducted in academic centers**. The rewards were primarily related to **advancement of knowledge**. Clinical studies tended to be **small in scale**, **observational**, **investigator initiated** and **relatively inexpensive**.
- This began to change in the decades after World War II as both federal and industrial funding of research increased. The nature of clinical research also evolved, **with large-scale, multicenter, randomized trials** providing the safety and efficacy testing before new products were brought to market.

Nelson (2006a)

Evolution of the Clinical Research Enterprise

- During 1980-2000, **investments in research and development** by pharmaceutical companies increasing **from $2 to $30 billion**. **The return on this investment** is also considerable, with many drug exceeded **$1 billion** per year in sales.
- **Total spending on clinical trials** by government and industry reached **$4.5 billion** in 2000 in the US alone, and rapid expansion occurred in the international arena. Of this amount, **only 20% was funded by the government, with 80% coming from industry**.

Nelson (2006a)

Evolution of the Clinical Research Enterprise

- In the 1990s, **managed care(管理式照護)** influenced the clinical trial environment. At the corporate level, the economics of drug development changed such that companies could no longer increase their prices to recoup costs and generate profits.
- These pressures forced sponsors **to avoid academic centers** that were viewed as inefficient and expensive when selecting sites to conduct their trials. **Independent sites**, **private-practice or hospital-based physicians** not affiliated with academic centers were chosen instead, perhaps gathered into networks by site management organizations.
- **Contract research organizations (CRO)** became a major force, allowing companies to outsource much of the work of managing their trials.

Nelson (2006a)

Evolution of the Clinical Research Enterprise

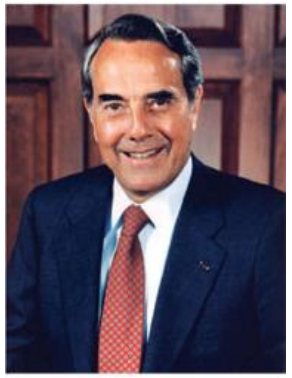
- During the mid-1990s, the number of **private-practice physicians** involved in drug studies increased by **60%** over a 5-years span. Conversely, the proportion of trials conducted in academic medical centers **dropped from 80% to 40%** over the same period of time.
- Noticing that this migration of clinical trials away from academic centers, a growing number have established **clinical trials offices** to centralize administrative processes, streamline IRB submissions and contract negotiations, and facilitate interaction with industrial sponsors. Fewer than 10% of academic centers had such centralized structures in 1997. Within 1 year, that number had increased to over **50%**. The revenue of academic centers from industry grants were increased again.

Nelson (2006a)

Evolution of the Clinical Research Enterprise

- In 1980, the US Congress passed **the Bayh-Dole Act**, which provided universities with incentives to move research results into commercial applications.
- Before Bayh-Dole, the government retained the intellectual property rights to technology developed through federal support. It was observed, however, that only a tiny fraction of publicly funded technology ever made it to the marketplace.
- The 1980 legislation encouraged academic institutions to **patent new products**, **to license these products to industry**, and **to share royalties with their faculty**.


Birch Bayh


Bob Dole

- This technology transfer paved the way for productive joint ventures between nonprofit and for-profit sectors. It also, however, created **new and unanticipated opportunities for conflict of interest**.

Nelson (2006a)

Sources of Conflict of Interest in Research

- **Non-monetary rewards**: **respect of peers**, **appointments**, **promotions**, **tenure**, **grants**, **fame**, **prizes**, and the **publications** that support all of these.
- **Financial conflict of interest in clinical research**
- **Equity holdings** in commercial sponsors, **consulting fees**, **royalties**, **patent rights**, and **honoraria** for serving on advisory boards or for giving lectures
- Faculty may **assign students or trainees to work on projects** from which the investigator stands to benefit
- Even **the negotiated budgets to compensate investigators and institutions for conducting research** may represent sizable conflict of interest, depending on how they are structured and how the resulting revenues are handled.

Nelson (2006a)

Sources of Conflict of Interest in Research

- Investigators might be inclined to **enroll as many subjects as possible**, **push the limits on entry criteria**, promote research participation **when other alternatives might be preferable**, or **report positive findings when results are equivocal.**
- Conflict of interest may jeopardize **the trust and confidence of the public**. It may **endanger lives** – not only those of **the immediate subjects under study**, but those of **future patients** treated on the basis of biased results.

Nelson (2006a)

Institutional Conflict of Interest

- **AAMC**: An institution may have a conflict of interest in human subjects research whenever the financial interests of **the institution**, or of **an institutional official** acting within his or her authority on behalf of the institution, might affect—or reasonably appear to affect—**institutional processes for the conduct, review, or oversight of human subjects research**.
- **AAHRPP: An organization** or **key organizational leaders** sometimes have financial interests that conflict with the organization's obligation to protect participants or preserve the integrity of the research. For example, an organization or key organizational leader might have **a proprietary or ownership interest in research that is being reviewed or conducted by the organization**.

AAMC (2008), AAHRPP (2018)

Recruitment Incentives

➢ Enrollment Bonuses

- **Bonuses that are offered outside the negotiated budget**, e.g., investigators or study coordinators may receive a letter from the CRO managing the study, urging them to find the last few subjects needed to meet the predetermined enrollment goals and offering additional payments for each subject.
- Although it can be argued that extra costs will be incurred in identifying these last few subjects, the amounts offered often exceed those costs, even if advertising is involved. Moreover, the budget negotiated to cover the actual cost of conducting the research often includes amounts for advertising or recruitment efforts. Thus, enrollment bonuses may represent something approaching pure profit for the investigator.

Nelson (2006b)

Recruitment Incentives

- Such incentives might lead an investigator or study coordinator **to influence inappropriately a potential subject's decision to participate** through:
  - **Downplaying the risks of a study**;
  - **Overselling the possible benefits**;
  - **Ignoring alternatives that might be available**;
  - **Overlooking medical history that might exclude a patient**; or
  - **Pushing the limits on entry criteria**.
- As a general rule, **IRBs should not approve a study in which investigators or their staff will receive an enrollment bonus**.

Nelson (2006b)

Recruitment Incentives

➢ Referral Fees

- Referral fees, also called "**finder's fee**" or "**bounties**," are **payments offered to physicians or other primary caregivers for identifying patients who may be eligible study subjects**.
- These might be offered at the suggestion of the sponsor or CRO but, unlike enrollment bonuses, would typically be offered indirectly, by or through the principal investigator.
- The payment of referral fees interjects an influence that may run counter to **the fiduciary obligation of a primary caregiver**. That is, the health professional may be motivated by financial interests to refer a patient **when such referral might not be of any benefit to the patient**.

Nelson (2006b)

Recruitment Incentives

- The act of referring may also influence the potential subject's decision making if participation in research is perceived to be **recommendation of a trusted caregiver**.
- **The American Medical Association's Code of Medical Ethics** Opinion 11.3.4 (2018):
  - "Payment by or to a physician or health care institution solely for referral of a patient is fee splitting and is unethical."
  - "Physicians may not accept…payment referring a patient to a research study."
- **The American College of Physicians' Ethics Manual**, 6th ed.: "Giving or accepting finder's fees for referring patients to a research study generates an unethical conflict of interest for physicians."

Nelson (2006b), AMA (2018), ACP (2012)

Recruitment Incentives

- **Poststudy Rewards**: Self-report from an investigator
- "One of the most extravagant vacations I ever took was an **all-expenses-paid trip** to Cancun (墨西哥坎昆市) as a poststudy reward for having enrolled five subjects in a rather ordinary clinical trial. In return, the sponsor flew three members of our research team and spouses to a luxury resort, where we joined similar groups from other sites that had also hit their enrollment targets. **Ostensibly at 'an investigator's meeting', we spent 30 minutes reviewing the results of the trial, and 3 days on the beach**."

Nelson (2006b)

Recruitment Incentives

- "This story illustrates **the insidious nature of this reward system** and the very human response we can expect when investigators are offered **what might be judged in hindsight to be a conflict**. For me, this personal experience confirms yet again the fundamental observation that **investigators are not always in a position to assess their own circumstances critically, despite the best of intentions**."

Nelson (2006b)

Recruitment Incentives

- **Gift Authorships**: Manuscripts are drafted by the **sponsor's medical writers**, with authorship on the final publication offered to **investigators who enrolled the most subjects**, or to prominent scientists in the field who may not have been involved in the actual research.
- **Future Participation**: Top-performing sites that **meet (or exceed) their enrollment targets in a timely manner** take on "**most-favored site**" status and will be invited to participate in future studies. Conversely, low-enrolling sites will be dropped. The linkage to number of subjects enrolled makes this an indirect form of recruitment incentive.

Nelson (2006b)

本院利益衝突申報時間：研究人員

- **研究人員**：包括計畫主持人、共/協同主持人、研究團其他成員
- 計畫主持人向**研究倫理委員會提出臨床研究計畫書**時（包括**初次申請**、**持續審查**），每位研究人員應申報**其本人**、**配偶**和**未成年子女**，是否持有相關之**財務利益/非財務關係**
- 若有**財務利益狀況/非財務關係之改變**時（自新取得財務利益之日起**回溯 12 個月**之財務利益總和達顯著利益門檻、或**新增研究人員**等）亦應於 **30日內**更新申報資料

本院利益衝突申報時間：主管、會計室

- **本院醫療、醫事、教學及研究部門之一級（含）以上主管**，應**每年1 月 15 日前**向**利益衝突審議委員會**，申報前一年度是否持有相關之**財務利益/非財務關係**
- **本院會計室**應依研究倫理委員會之要求，提出**臨床研究委託者、試驗使用之藥品或醫療器材之提供者**等，對本院**捐贈超過價值3,000,000 元以上**之資料，以審查有否機構財務利益衝突之情形

須申報之顯著財務利益

- 於**申報前12個月**期間，自本臨床研究相關之**單一臨床研究委託者**及其相關實體所收受之**報酬**（如**顧問費**、**演講費**、**出席費**、與臨床研究相關且可能受研究結果所影響的**金錢補助**等）、**捐贈**、**禮品**及**其他具金錢價值之給付**，合計達**150,000 元以上者**
- 於申報時，對**臨床研究計畫委託者**之資產**持股**利益（如**股份**、**股票選擇權**或其他與臨床研究相關且可能受研究結果所影響的**所有權利益**等）**達資本額5%以上者**或參考公開市場價值**超過 150,000 元**
- 研究人員為該臨床研究所使用之**專利或著作之所有權人**或對臨床研究所使用之專利或著作獲有**授權金**

須申報之顯著財務利益

- **計畫主持人**於**提出臨床研究計畫書**時，應申報是否**本院對該研究計畫案**持有下列各款**之財務利益**：
- 本院為該臨床研究所使用之**專利或著作之所有權**
- 本院對該臨床研究所使用之專利、著作或技術，獲有**智慧財產權授權金**或**技術移轉等利益**
- 本院醫療、醫事、教學及研究部門之**一級（含）以上主管**，為該臨床研究計畫所使用之**專利或著作之所有權人**或**獲有智慧財產權授權金**

須申報之可能構成利益衝突之非財務關係

- 研究人員/主管或其配偶擔任本計畫之臨床研究委託者及其相關實體之不支酬主管職或顧問
- 本研究納入研究人員/主管的直屬部屬、助理或學生做為研究的對象

利益衝突委員會考量重點

➢**利益衝突審議委員會**依據以下考量，決議是否有利益衝突，並做相關處置建議並通報**研究倫理委員會**，包括：

- 研究的**學術價值**
- 研究**對受試者可能產生的風險性**有多大
- 所持有之**財務利益的種類**以及**金額**或**非財務關係之性質**
- 財務利益/非財務關係**是否會影響該臨床研究的執行與其結果**，或該臨床研究**可能影響財務利益所得/非財務關係**
- **涉及利益衝突的人員**或**中國醫藥大學附設醫院本身**，是否具有**獨特的能力、經驗、設備等背景**，是執行該臨床研究之**不二人選**
- 持有顯著財務利益/非財務關係的**主管之職權與此臨床研究及相關研究人員的關係**

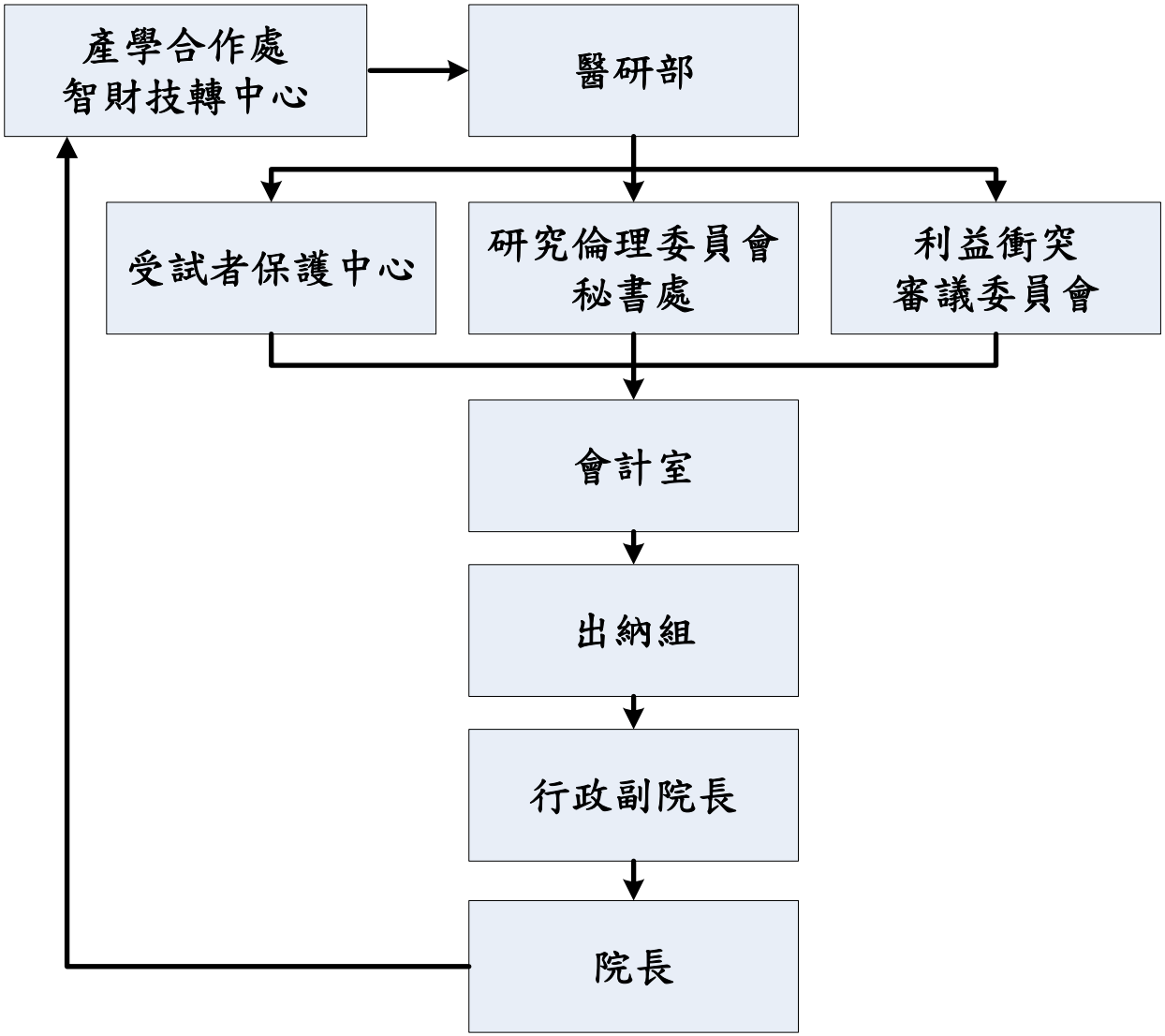
利益衝突委員會可能的處置建議

- **解除**所有的顯著財務利益/非財務關係
- **公開揭露**所持有之顯著財務利益/非財務關係
- 設置**獨立之資料安全監督機制**
- 涉及利益衝突的人員**迴避部分的研究**，例如計畫主持人避免**執行取得受試者同意**或是**資料分析**等工作
- 涉及利益衝突的**主管迴避行使職權督導**該研究計畫之執行以及其相關研究人員
- **每年向利益衝突審議委員會報告**，是否遵循建議，迴避或減免利益衝突

決定是否通過研究計畫

- **涉及潛在利益衝突的人員**需於收到研究倫理委員會的審查結果之後**兩週內回覆**，**說明是否依建議迴避、減免或解除潛在的利益衝突**
- **利益衝突審議委員會審議**涉及利益衝突的人員之**回覆**，並將審議結果通報研究倫理委員會，**研究倫理委員會決定是否通過**
- **研究倫理委員會**參考利益衝突審議委員會之決議，決定**是否通過研究計畫/核准研究計畫繼續執行**，並確認是否符合研究委託機構以及主管機關的通報規定
- **研究倫理委員會**於研究計畫審查完成後**將結果通知計畫主持人**

通報院內技轉申請案


產學合作處
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受試者保護中心
研究倫理委員會
秘書處
利益衝突
審議委員會
會計室
出納組
行政副院長
院長

案例討論

- Dr. Sellers, Assistant Professor of Medicine in the Hematology/Oncology Division at University, is a clinical investigator of ovarian cancer. She discovers **a protein in ovarian cancer cells** and shows that **a monoclonal antibody (MAB)** to it can reduce the progression of cancer in a mouse xenograft model. No biotech company has so far licensed the MAB from University, and the NIH did not fund a proposal for Phase I studies in humans for a possible proof of principle. However, Dr. Sellers is **a very effective "champion" for this technology** and has raised local venture capital money to start a small biotech company to further develop the project.

AAMC(2008)

案例討論

- According to University policy, Dr. Sellers **receives approval to start up the company**, and University **licenses the MAB technology to Dr. Sellers's start-up company**. The company proposes to sponsor a Phase I clinical trial in which Dr. Sellers will inject the MAB into human subjects with ovarian cancer to study the effect of the antibody on the progression of the cancer.

AAMC(2008)

案例討論

- Appropriately, Dr. Sellers was only minimally involved in the license negotiations between the company and University. Review of the company structure indicates that Dr. Sellers has obtained **100,000 shares of founders stock**. She is not an officer, or a member of the Board of Directors or the Chair of the Scientific Advisory Board of the company. However, she is **a member of its Advisory Board** and she receives **a payment of $30,000 a year** for her service on it.

AAMC(2008)

案例討論

- Does a specific **financial conflict of interest** exist?
- Is there an increased risk to **human subject safety**? Is there an increased risk of **failure to adhere to the inclusion/exclusion criteria of the protocol**? Is there a danger of **over-stating the potential benefits of the MAB** while soliciting consent?
- Should Dr. Sellers **be allowed to conduct this study** in light of her conflict of interest?

AAMC(2008)

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