# 臨床研究的性別議題

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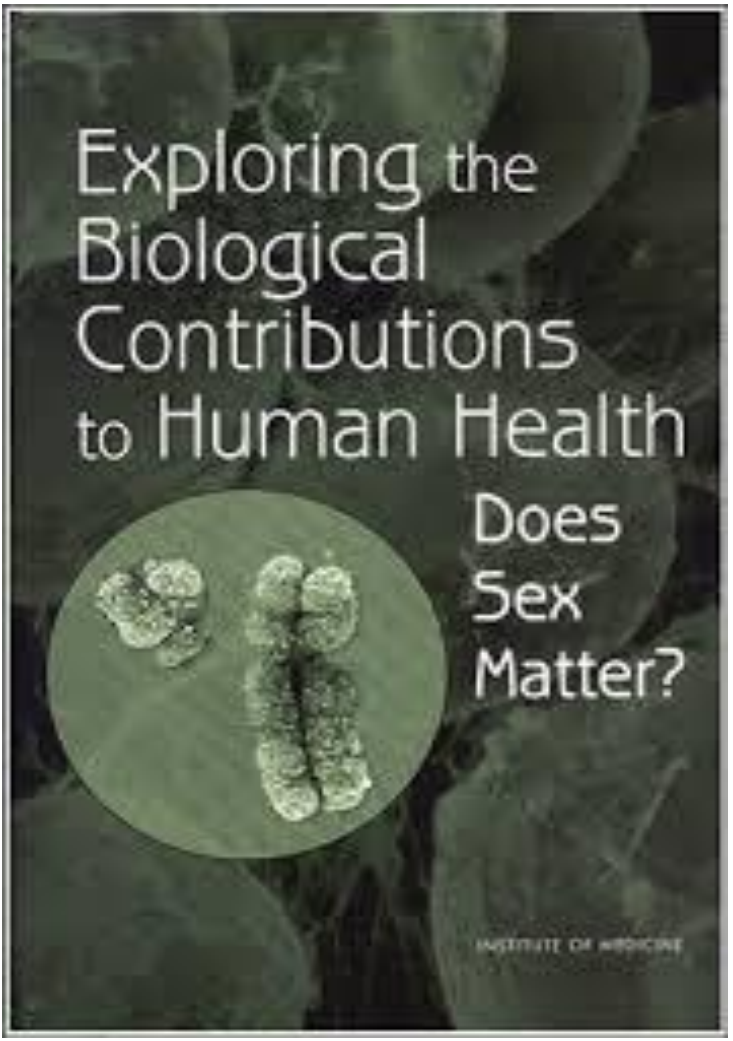
# 定義

US Institute of Medicine
2001出版




- Sex (生物性別) 由DNA編碼的特徵所定義的生物變項，如生殖器官和其他生理和功能的特徵。
- Gender (社會性別）男女的社會、文化、心理的特徵。
- 主張：生物性別、社會性別、兩者交互結果皆會影響分子和細胞過程、臨床特徵、健康、疾病結果。


**SEX** refers to a set of biological attributes in humans and animals. It is primarily associated with physical and physiological features including chromosomes, gene expression, hormone levels and reproductive/sexual anatomy. **Sex is usually categorized as female or male but there is variation in the biological attributes that comprise sex and how those attributes are expressed.**

**GENDER** refers to the socially-constructed roles, behaviors, expressions and identities of girls, women, boys, men, and gender- and sexually-diverse people. It influences how people perceive themselves and others, how they act and interact and the distribution of power and resources in society. **Gender identity is not confined to a binary (girl/woman, boy/man) nor is it static**; it exists along a continuum and can change over time. ..

**'Sex' and 'gender' are often used interchangeably, despite having different meanings**:

# 交織性（intersectionality):

性別與年齡、階級、種族、族群、城鄉等因素的交錯與相互影響造成的不平等


圖來源:性別分析 + 課程:加拿大經驗分享20211124

# EVERY CELL IS SEXED AND EVERY PERSON IS GENDERED

# Does sex/gender matter?

性別差異、醫學研究與健康不平等

# 為什麼性別對健康是個重要議題？

- 當個人或群體與既定的性別規範（包括男性或女性的概念）、角色、責任或關係不相適應時，他們往往會遇到恥辱、歧視性作法或社會排除。所有這些都會對健康產生不利影響。性別與生物自然性別相互作用，但卻與之不同。（資料來源：WHO 性別與健康「定義」）

# 健康議題上的性別差異(1)

目前被證實有性別差異疾病，包含：

- 心血管疾病cardiovascular disease,
- 肺部相關疾病pulmonary dysfunction,
- 腸道激躁症（irritable bowel syndrome）
- 內分泌、免疫系統的疾病（endocrine and autoimmune disorders）
- 精神疾病（mental illness ）

以藥物迷你寧（ **Minirin**）為例，它可以活化腎臟中的血管加壓素受體以調節水分恆定(Juul et al., 2011)。已發現女性對加壓素的抗利尿作用比男性更敏感。這可能是因為精氨酸加壓素受體的基因位於 X 染色體上，一個可能可以躲過 X去活化的區域。男性只有一個 X 染色體，因此每個細胞只有一個血管加壓素受體基因；女性則較可能有兩個副本。因此，**服用迷你寧的年長女性最有可能出現鈉濃度降低的情況，從而導致虛弱、頭暈和昏厥等副作用。為避免不必要的傷害，歐盟和加拿大都建議年長女性使用較低劑量的迷你寧。因此，該藥物在在銷售時，其標籤包裝上為女性與男性提供了不同的劑量建議。**

http://genderedinnovations.taiwan-gist.net/case-studies/drugs.html#tabs-2

Sex differences are observed in response to many drugs. Females have a **1.5- to 1.7- fold greater risk of developing an adverse drug reaction**, and several drugs have been withdrawn from the market over the last two decades for sex-based adverse events. Medical devices are particularly subject to gender bias, based on the significant physical differences between men and women

Successful Strategies for Engaging Women and Minorities in Clinical Trials , September 22-23, 2011

# 問題在哪裡？

# 生醫研究中的性別議題

醫學研究，女性受試者代表不足。

研究設計與成果少有性別分析

女性受試者代表不足。

根據美國ＮＩＨ的統計，有補助要求的臨床研究，女性受試者已接近一半。

但各類人體研究或臨床試驗中，女性受試者人數仍有落差。

A review of cardiovascular treatment trials included in Cochrane Reviews reveals that only 27 % of the total trial participants in the 258 clinical trials were women. More importantly, among trials recruiting both men and women, only **one third reported a gender-based analysis** . More than 79 % of **animal studies** published in Pain over a 10-year period **included male subjects only**, **and only 4 % studied sex differences** .

Heidari et al. Research Integrity and Peer Review (2016) 1:2 DOI 10.1186/s41073-016-0007-6

# Medical devices often approved for use without testing for safety by sex and gender

July 26, 2017

A new study finds that before the government approves medical devices for use on the public, companies applying for approval rarely determine if or how sex and gender might influence their safety or effectiveness.

The researchers examined **82 studies** filed in 2015 with the U.S. Food and Drug Administration (FDA) in support of premarket approval for original medical devices**. Of the 77 studies that included both men and women, only 17% were analyzed by sex.** Only 9% were analyzed by age and 4% by race.

資料來源:
https://medicine.yale.edu/news-article/15444/

# 女性受試者代表性不足

- 被排除於醫學研究之外
  - 賀爾蒙週期的考量
  - 生育可能性考量
  - 胎兒保護，排除懷孕女性

- 招募女性受試者上的障礙
  - 對於女性處境缺乏理解

# 女性受試者招募困難的可能原因

- Barriers to Enrollment of Women
- Lack of understanding about main obstacles to participation of women in clinical research;
- Fear of fetal consequences if a female participant becomes pregnant (e.g., effects of radiographic assessments or concomitant drug therapy);
- Inclusion/exclusion criteria potentially not needed to define the study population may unintentionally exclude women (e.g., upper age limit);
- Lack of understanding about differences in disease etiology and pathophysiology may lead to under-diagnosis and under-referral of women;
- Investigator and sponsor avoidance of female patients due to the perception that it takes more time and money to recruit them; and
- Family responsibilities limiting women's ability to commit time for study follow-up.

資料來源：Evaluation of Sex-Specific Data in Medical Device Clinical Studies ,2014

# 醫學研究缺乏性別分析

- 女性或雌性動物資料不足
- 研究成果缺乏性別（生理性別、社會性別）分析

- Cardiovascular disease
  - the leading cause of death for women in the U.S yet only one-third (35%) of clinical trial subjects in cardiovascular research are female and just 31% of studies that include women report outcomes by sex.
- Lung cancer
  - the leading cause of cancer death among women in the U.S.
  - the lack of gender-specific research findings
- Depression
  - women are 70% more likely than men to suffer from

    depression over the course of their lifetimes
  - fewer than 45 percent of animal studies on anxiety and depression use female lab animals.
- Alzheimer's Disease
  - a woman's overall lifetime risk of developing Alzheimer's disease is almost twice that of a man
  - the impact of hormonal changes at menopause and sex differences in gene expression have begun to emerge as potential explanations.


Charting the Course: A National Summit on the Future of Women's Health ,2014

# 實踐性別融入醫學研究之策進作為

- 動物實驗或臨床研究應有足夠雌性實驗動物或運用女性檢體
- 納入具有代表性數量的女性受試者
- 補足性別差異的數據缺口
- 研究設計到成果發表進行性別分析

# 其他國家的作法1：美國

➢1993年

- 制訂 The NIH Revitalization Act of 1993，要求所有申請經費補助之臨床試驗研究計畫應納入女性並對不同性別進行分析。

## 2001年，**NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research**

1.定義臨床研究及得不進行性別及族群分析之情形。
2.特別是第三期臨床試驗應檢視不同群體的差異效果

- 臨床研究（clinical research)

(1) Patient-oriented research.
(2) Epidemiologic and behavioral studies;
(3) Outcomes research and health services research

- 得不進行性別分析之情形如下：

(1)女性及少數族群擔任研究受試者對其健康不利；
(2)女性或少數族群擔任受試者對研究目的不合適(inappropriate)；
(3)已有堅實的科學證據顯示，臨床試驗結果在「女性或少數族群身上」和「未被要求加入女性或少數族群的一般研究對象」之間並無顯著差異；
(4)研究為使用無法連結至活著的個人的人體組織體外研究(in vitro studies that utilize human tissues that cannot be linked to a living individual)；
(5)其他NIH定義不需進行性別及族群分析的情形。

# Consideration of Sex as a Biological Variable in NIH-funded Research

## Notice Number: NOT-OD-15-102

## Key Dates

**Release Date:** June 9, 2015

## Related Announcements

NOT-OD-16-034
NOT-OD-16-031
NOT-OD-16-012
NOT-OD-16-011
NOT-OD-15-103

## Issued by

National Institutes of Health (NIH)

## Purpose

The National Institutes of Health (NIH) is committed to improving the health outcomes of men and women through support of rigorous science that advances fundamental knowledge about the nature and behavior of living systems. Sex and gender play a role in how health and disease processes differ across individuals1, and consideration of these factors in research studies informs the development and testing of preventive and therapeutic interventions in both sexes. This notice focuses on NIH's expectation that scientists will account for the possible role of sex as a biological variable in vertebrate animal and human studies. Clarification of these expectations is reflected in plans by NIH's Office of Extramural Research (OER) to update application instructions and review questions; once approved by the Office of Management and Budget (OMB), these updates will take effect for applications submitted for the January 25, 2016, due date and thereafter. Please refer to NOT-OD-15-103 for further consideration of NIH expectations about enhancing reproducibility through rigor and transparency.

2019年,
Guidelines for the Review of Inclusion on the Basis of Sex/Gender, Race, Ethnicity, and Age in Clinical Research

- 同儕審查專家有責任評估未納入性別及少數族群之理由是否具正當性，若無正當性，審查專家須說明計畫未被接受之原因。審查指引建議提供工作表範例予審查專家依據步驟進行對照審查，以輔助其正確判斷計畫是否符合NIH之規範要求。

the Food and Drug Administration Safety and Innovation Act (FDASIA)(2012)

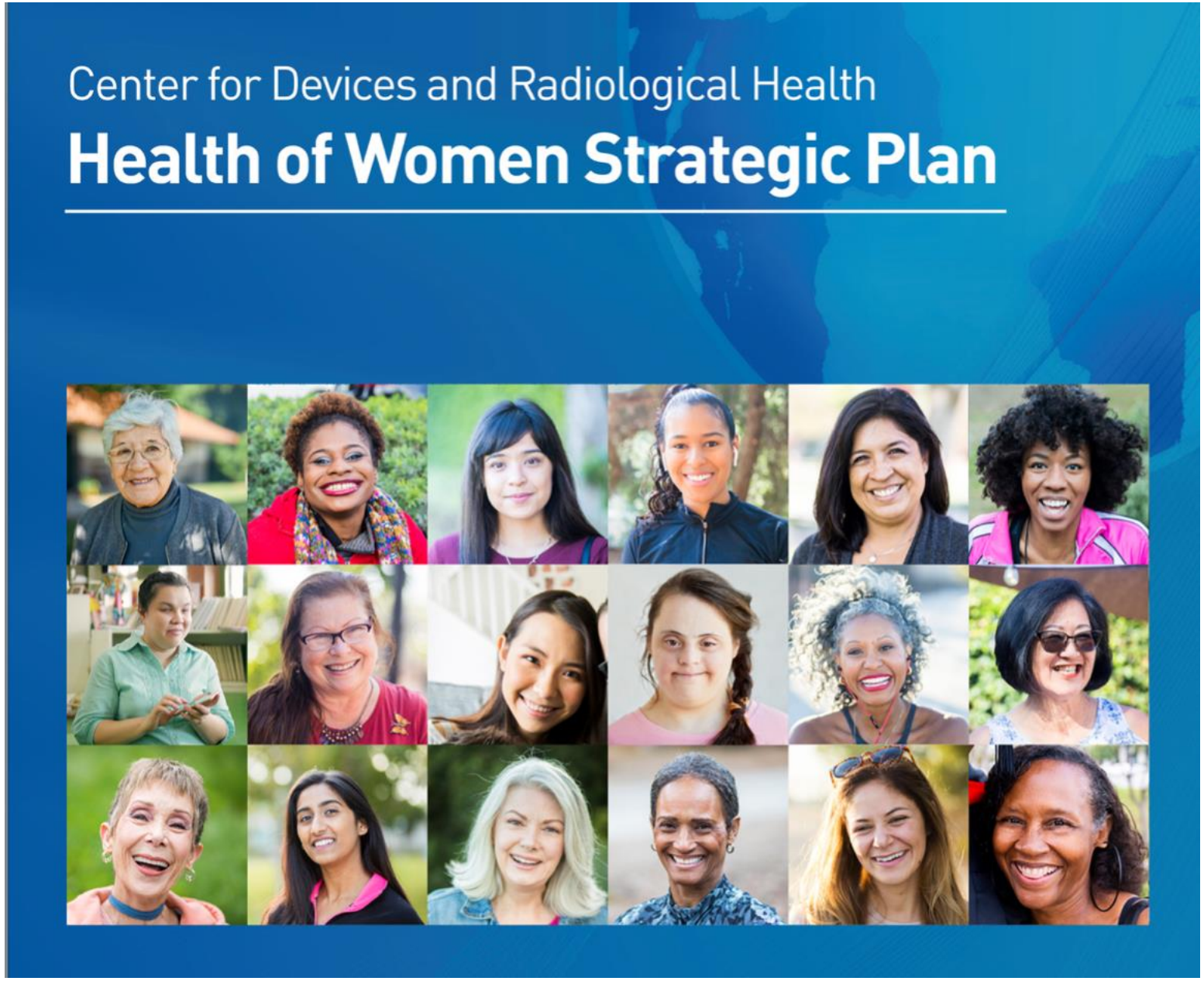
**SEC. 907. REPORTING OF INCLUSION OF DEMOGRAPHIC SUBGROUPS IN CLINICAL TRIALS AND DATA ANALYSIS IN APPLICA- TIONS FOR DRUGS, BIOLOGICS, AND DEVICES.**

- **要求自2013年起提交藥物、醫療器材等臨床試驗成果時包含性別等人口群的子群體之數據分析**
- **主管機關每年提出相關分析之報告**
- **主管機關每年提出年度策進作為**

2014 FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data

**2016  the 21st Century Cures Act**,

section 2039 Enhancing the rigor and reproducibility of scientific research
(1) **preclinical experiment design, including analysis of sex as a biological variable**;
(2) **clinical experiment design,** including—
(A) the diversity of populations studied for clinical research, with respect to biological, social, and other determinants of health that contribute to health disparities;
(B) the circumstances under which summary information regarding biological, social, and other factors that contribute to health disparities should be reported; and
(C) the circumstances under which clinical studies, **including clinical trials**, should conduct an analysis of the data collected during the study on the basis of biological, social, and other factors that contribute to health disparities;
(3) applicable levels of rigor in statistical methods, methodology, and analysis;
(4) data and information sharing in accordance with applicable privacy laws and regulations; and
(5) any other matter the working group determines relevant.




TheCDRH Health of Women Strategic Plan,issued January 2022,SilverSpring,Maryland.

**Priorities 1**
**Sex- and Gender-Specific Analysis & Reporting**

**Priorities 2**
**Integrated Approach for Current & Emerging Issues Related to the Health of Women**

# 其他國家的作法2：加拿大


# Institute of Gender and Health

- We are shaping science for a healthier world 為更健康的世界形塑科學
- 主旨：促進 sex/gender是如何影響健康的研究，並應用這些研究結果找出和處理男性/女性、女孩/男孩和多元性別等人們正面臨的較急迫性的健康議題。

資料來源:黃淑玲，性別因素在醫療研究中的趨勢

# Sex, Gender and Health Research Guide

- 不偏廢生物性別，培養生物醫學研究者的人文關懷與社會科學素養
- Sex- and Gender-Based Analysis Plus（SGBA+)強調除了性別視角之外，也應考慮收入、教育、職業、社會地位、性傾向、族群、地理位置等等因素。
- 強調重視多元性別者的健康 LGBTQI2S–（lesbian, gay, bisexual, transgender, queer and questioning, intersex and Two Spirit)

資料來源:黃淑玲，性別因素在醫療研究中的趨勢

# 如何進行性別分析？

# 就醫學研究的發展而言，為何需要進行性別分析？

- to avoid drawing incorrect conclusions.
- to report data by sex, gender, or both is to facilitate meta-analysis.
- to reduce waste in research.

JAMA. 2016;316(18):1863-1864.
doi:10.1001/jama.2016.16405

# SABV in Biomedicine Checklist （Sex as A Biological Variable, SABV ）

1.Review available literature for the influence of biological sex

2. Consider the influence of sex when formulating the research questions

3.Consider the influence of sex in study design

4. Incorporate both males and females into studies

5. Analyze data and report data disaggregated by sex

6. Consider the influence of sex in the interpretation of study results

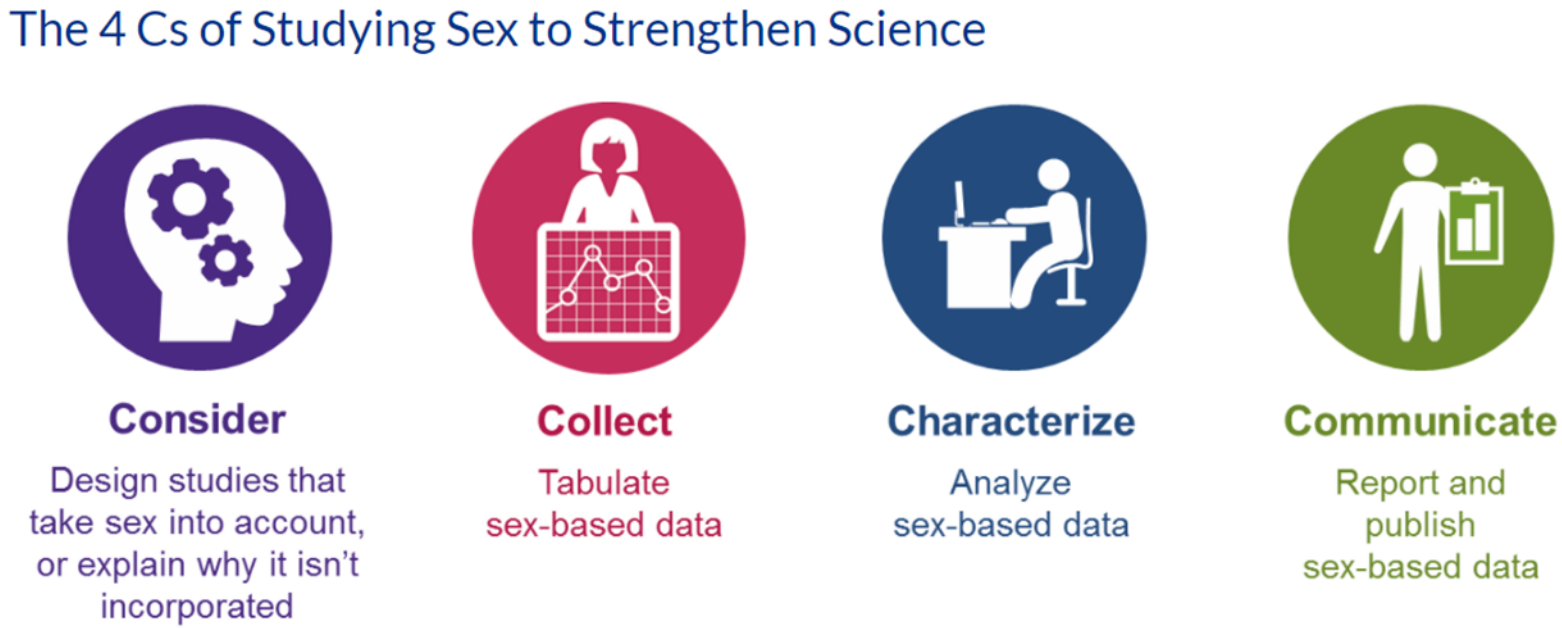
7. Articulate strong justification for a single-sex study

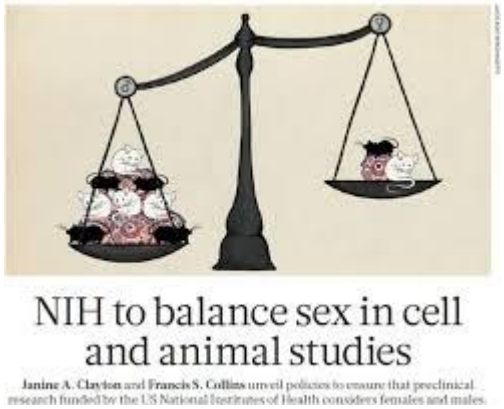
8. Appropriately generalize research findings

http://genderedinnovations.stanford.edu/methods/SABV_checklist.html

2014-2015
Consideration of Sex as a Biological Variable in NIH-funded Research

NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies.





NIH to balance sex in cell and animal studies

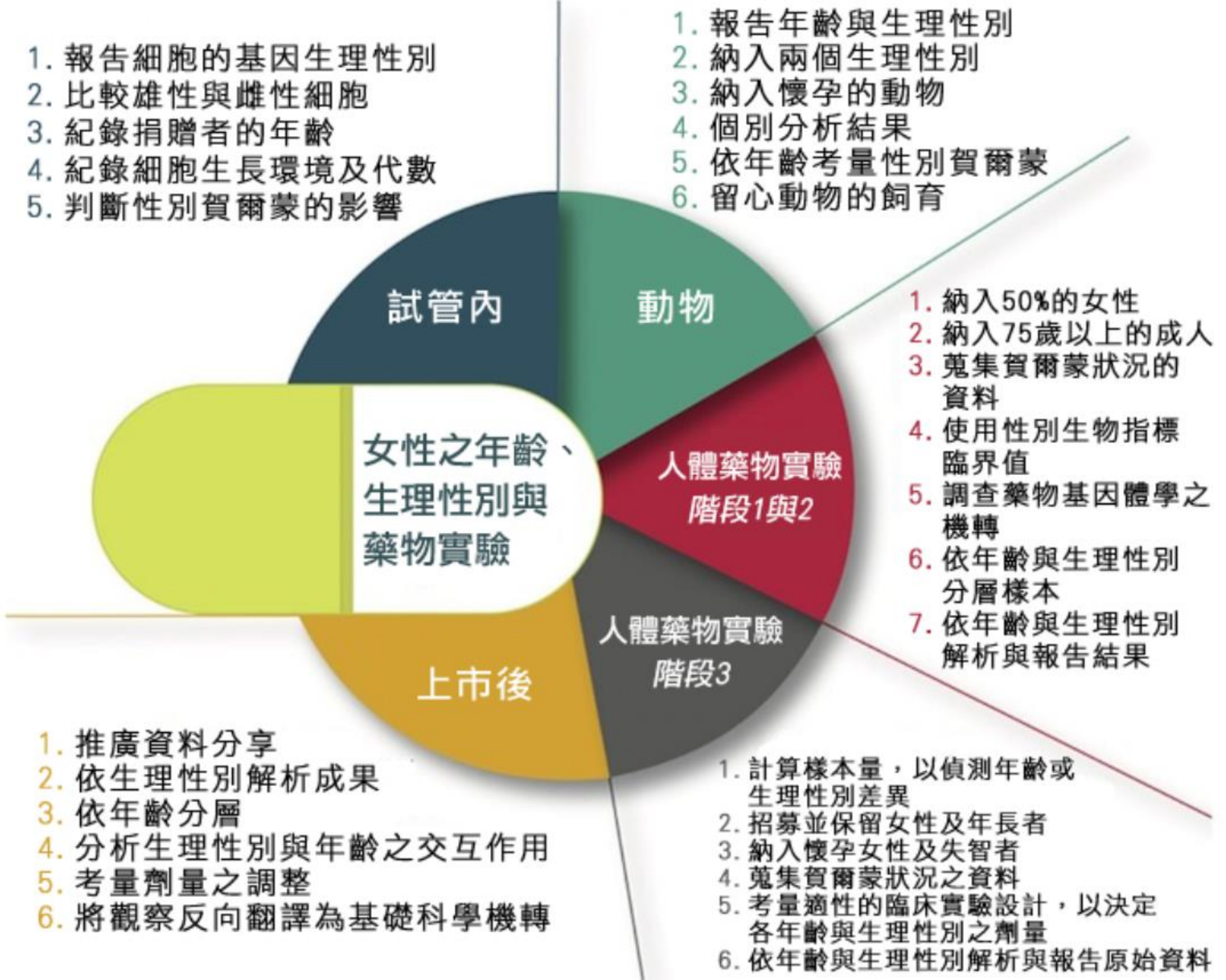
Janine A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

資料來源：
https://orwh.od.nih.gov/sex-gender/nih-policy-sex-biological-variable

# 藥物臨床試驗融入性別

- 在藥物開發的所有階段納入女（雌）性和男（雄）性。
  - 從早期的細胞和動物試驗到人體臨床試驗，所有藥物試驗都必須包括女（雌）性和男（雄）性，且數據必須按生理性別分類並單獨分析之。
- 按生理性別分列副作用報告。
- 在藥物標籤上說明生理性別差異。
- 推廣性別轉型之治療方法。
  - 社會性別與生理性別的交錯
  - 促進具性別敏感度的治療需要消除診斷問題中的性別偏見和刻板印象，以便能更準確地檢測女性、男性和多元性別族群的症狀。

http://genderedinnovations.taiwan-gist.net/case-studies/drugs.html#tabs-3




資料來源：性別化創新網站

## SAGER guidelines

## 性別資料分析的建議模式

**Table. Suggested Approach for Reporting Demographic Characteristics of Study Participants and Outcome by Sex and Gender (N = 59)**

| Demographic Characteristics | |
|---|---|
| Total No. | 59 |
| Age range, y | 18-90 |
| Sex, No.[a] | |
| Male participant | 27 |
| Female participant | 32 |
| Gender, No.[b] | |
| Men | 26 |
| Women | 33 |
| **Outcome, No. (%)**[c] | 50 (85) |
| Males | 20 (40) |
| Females | 30 (60) |
| Outcome, No. (%)[d] | |
| Male | 20 (74) |
| Female | 30 (94) |

[a] Ascertained by genotyping of blood sample.

[b] Ascertained by self-report.

[c] The number (%) occurring in males and females of the total outcomes (n = 50).

[d] Number (%) of outcomes occurring within the subgroups of males (20/27) and females (30/32).

JAMA. 2016;316(18):1863-1864. doi:10.1001/jama.2016.16405

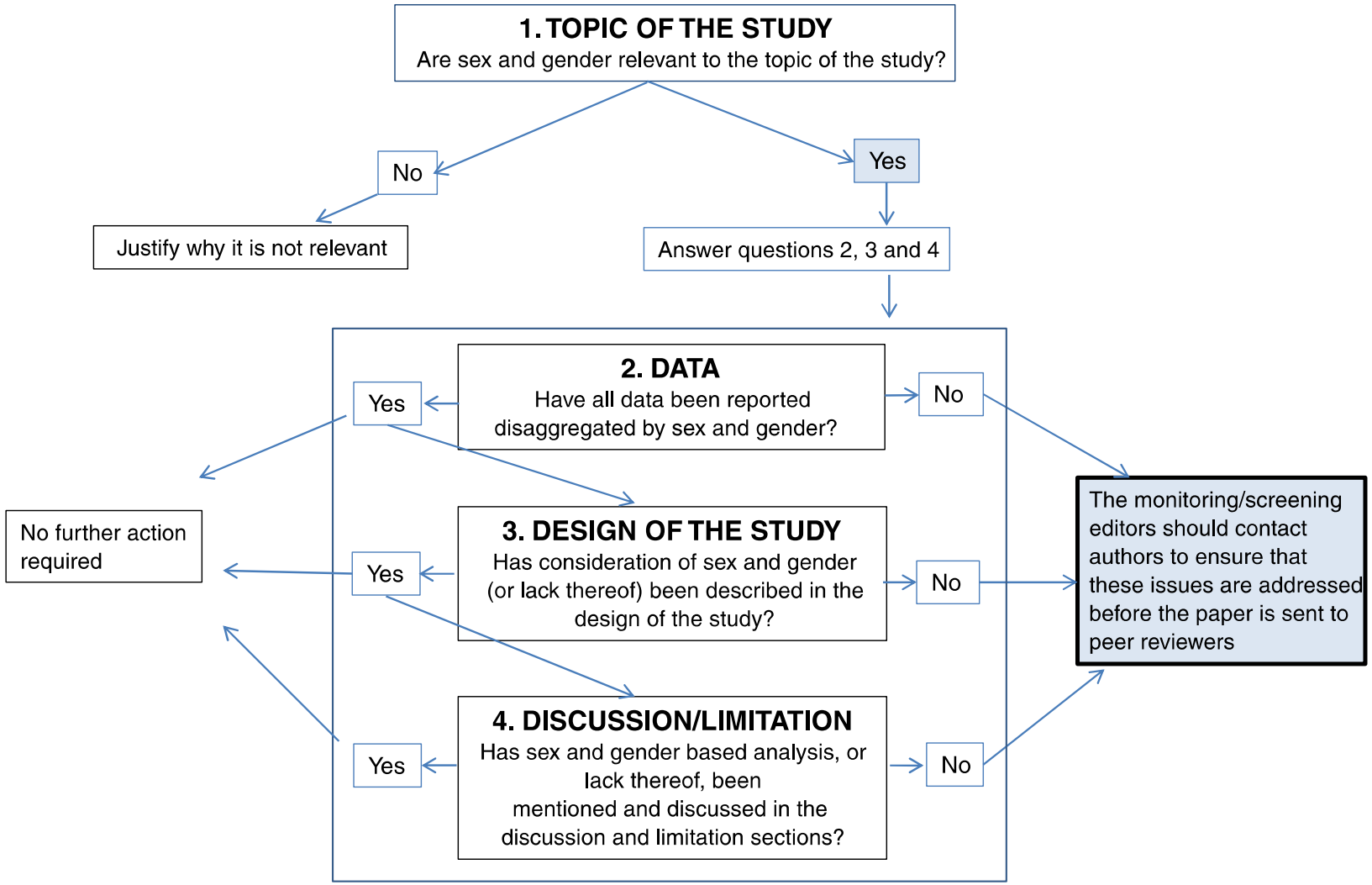
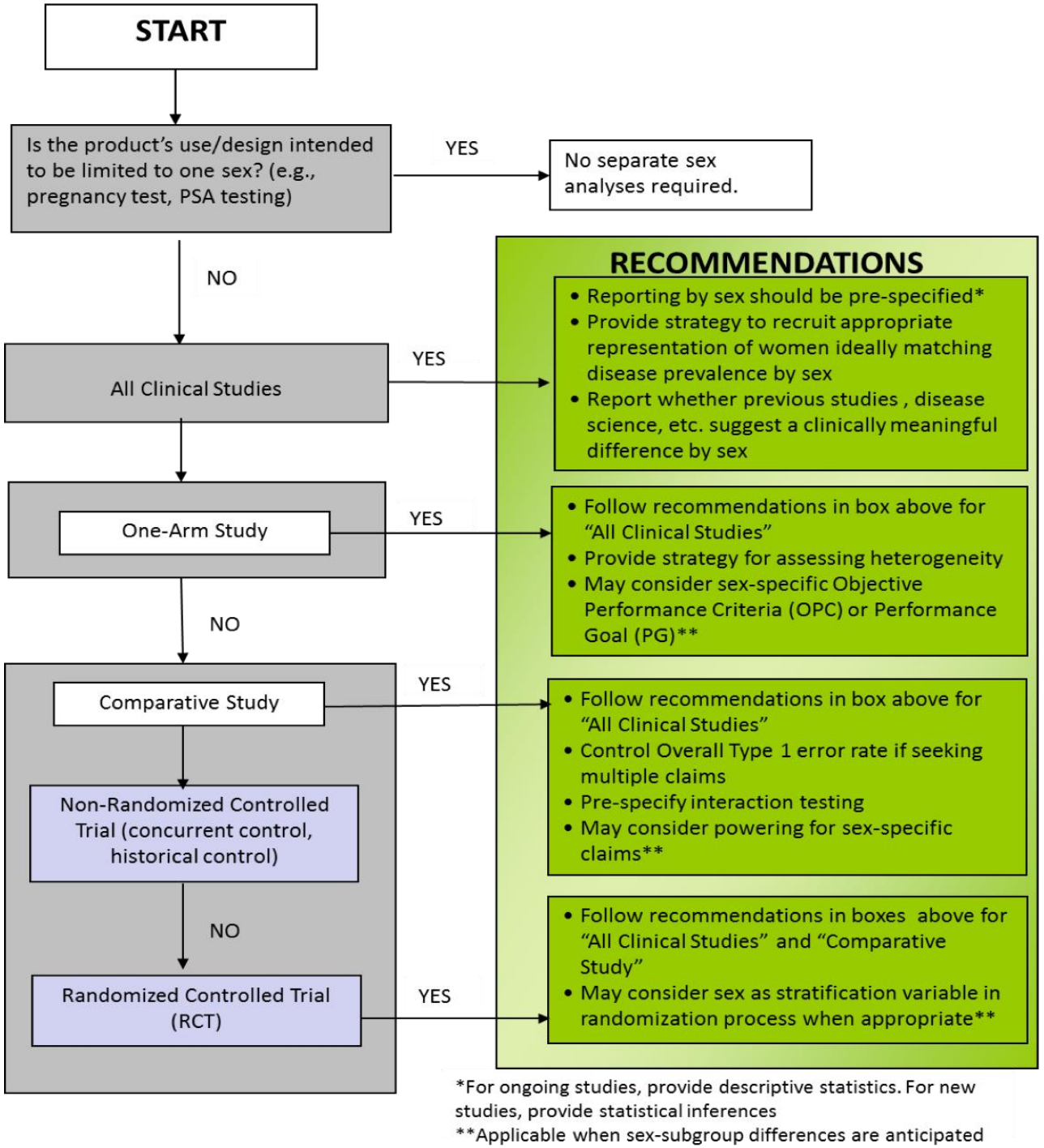



**Fig. 1** SAGER flowchart guiding editors' initial screening of submitted manuscripts




資料來源：
Evaluation of Sex-Specific Data in Medical Device Clinical Studies ,2014

# 代結語：A Better World

- 性別（sex /gender)融入生醫研究，包含納入具有代表性的女性受試者、雌性動物研究數據，以及研究成果的性別分析。
- 其目的在於，促進性別平等、縮小健康不平等，在科學上因為性別融入，促成了性別化創新的可能性。

# 性別與健康研究相關網站

台灣女人健康網

性別化創新

**http://genderedinnovations.taiwan-gist.net/**