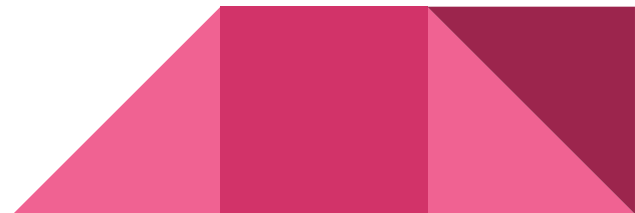


Current Topics and Best Practices in Research Ethics

UCSF Winter/Spring 2024 RCR for Basic Sciences
Postdocs

Meeting 2

Tori Sharma, PhD



How was your first discussion session meeting?



- What to do about research misconduct
- Addressing questionable research practices
- Contemporary ethical issues in biomedical research
- Social and environmental impacts of research
- Scientists as responsible members of society

How recently (if ever) have you had Responsible Conduct in Research (RCR) training?

Within the last 4 years

0%

More than 4 years ago

0%

Have not previously had RCR training

0%



Bad Publicity....

- Public disclosure of research misconduct cases at four major research centers in 1980
- Twelve serious cases of research misconduct between 1974-1981
- Reports that the National Institutes of Health (NIH), universities, and other research institutions were inadequately responding to those allegations.



William Summerlin: 1974

- Reported that he could transplant tissue from genetically unrelated animals without rejection
- Invaluable for transplant medicine
- White mice with black patches
- A technician noticed that these "transplanted patches" were actually drawn on the skin of the mice with a felt-tipped marker and could be removed with alcohol.
- Summerlin admitted the fraud



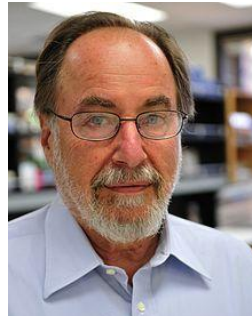
Robert A. Slutsky, 1985

- Published one paper every 10 days for years (!)
- Included names of many co-authors to mislead editors and cover up for what later was learned to be a false data.
- Reviewer noted duplicated data in two articles
- Slutsky resigned
- Investigation found that, of the 145 publications that were reviewed
 - 77 were valid
 - 55 were questionable
 - 13 were fraudulent



Thereza Imanishi-Kari, David Baltimore, and Margot O'Toole, 1991

- Postdoctoral researcher vs Nobel Prize winner
- Subject of federal investigations and congressional hearings
- Led to the establishment of regulations against research misconduct
- The case took more than 10 years to resolve.



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Post-doc Margot O'Toole

- Could not validate work soon to be published in Cell by her employer, Thereza Imanishi-Kari
- Co-author on the paper was a Nobel Prize winner, David Baltimore
- O'Toole believed Imanishi-Kari manipulated data
- Presented her evidence to committees at Tufts and MIT



The result

- Committees ruled that misconduct had not occurred
 - Imanishi-Kari had been sloppy in her research
- An NIH committee at the time also cleared Imanishi-Kari



Not enough

- Two scientists from the investigation believed the investigation was inadequate
- Chair of the Energy and Commerce Committee (which oversees the budget for the NIH) who headed the Congressional hearings also was in doubt
 - All three believed that problems existed in the way that universities handled allegations of misconduct
- Committee brought in the Secret Service
 - Determined that Imanishi-Kari had tampered with evidence provided to the committee
 - Baltimore continued to defend Imanishi- Kari



More investigation

- In 1991, the NIH's fraud division, at that time called the Office of Scientific Integrity, found that significant portions of the data were fabricated
- Thereza Imanishi-Kari was banned from receiving federal grant money for 10 years (later exonerated....)
- David Baltimore resigned from his presidency of Rockefeller University
- Margot O'Toole was ostracized and answered telephones for her brother's moving company (for five years)

Congress Reacts: 1985 – Health Research Extension Act

- Secretary of HHS must issue a regulation requiring
 - Applicant/awardee institutions to establish (Section 493 Public Health Service (PHS) Act) an administrative process to review reports of scientific fraud
 - Report to the Secretary any investigation of alleged scientific fraud which appears substantial
 - The Director of the NIH, to establish a process for receiving and responding to reports from institutions



Three Areas of Misconduct Policies

- Establish **definitions** for misconduct in research
- Outline **procedures** for reporting and investigating misconduct
- Provide **protection** for whistleblowers and persons accused of misconduct

Federal Definition of Research Misconduct

- “**Fabrication, falsification, or plagiarism (FFP)** in proposing, performing, or reviewing research, or in reporting research results”
- To be considered research misconduct
 - “significant departure from accepted practices”
 - “committed intentionally, or knowingly, or recklessly”
 - “proven by a preponderance of evidence.”



The Federal Definition

- Is a minimum standard
- Does not imply that all other behaviors are acceptable
- Does not encompass
 - criminal behavior
 - personal disputes
 - violations of grant management policies
 - ***discrimination***
 - ***harassment***



The Government Requires PHS funded Institutions to

- Have procedures for receiving and investigating reports of research misconduct, including:
 - Designated individuals authorized to receive and investigate allegations- Research Integrity Officer (RIO)
 - Provisions for an initial inquiry
 - Provisions for a formal investigation
 - A designated individual who is authorized to weigh the conclusions reached in the investigation and impose administrative action
 - Provisions for reporting findings to ORI (Office of Research Integrity)

The New Common Federal Policy

- Research institutions and researchers must not in any way retaliate against whistleblowers who report research misconduct in good faith.
 - Even if accusations are not sustained
 - And as long as they are brought in good faith
 - Informants must be protected and given support since they play a vital role in professional self-regulation
- Institutional definitions must include some version of FFP (Fabrication, falsification, and plagiarism)



Misconduct Inquiries Policy

- Proceedings of an inquiry are confidential to protect to the maximum extent possible
 - Members of the inquiry panel
 - Individual(s) filing the allegation
 - Person accused
 - Witnesses
- All individuals are asked to refrain from discussing the matter with anyone, including
 - Faculty members
 - Students
 - Family members
 - Media



Under Federal law, which of following constitutes research misconduct?

FABRICATION

0%

HARASSMENT

0%

PLAGIARISM

0%

FALSIFICATION

0%

RETALIATION

0%



SCIENCE

Years of Ethics Charges, but Star Cancer Researcher Gets a Pass

Dr. Carlo Croce was repeatedly cleared by Ohio State University, which reaped millions from his grants. Now, he faces new whistle-blower accusations.

By JAMES GLANZ and AGUSTIN ARMENDARIZ MARCH 8, 2017



The hard part of defining ethical research

- There is no one best way to undertake research
- No method applies to all scientific investigations
- Accepted practices can and do vary from discipline to discipline and even from laboratory to laboratory

Useful Links at UCSF

- [Animal Care and Use](#)
- [Use of Biological Agents](#)
- [Conflict of Interest & Conflict of Commitment](#)
- [Export Controls](#)
- [Faculty Consulting Activities](#)
- [Human Research Protection Program \(HRPP\)](#)
- [Code of Conduct and Integrity of Research](#)
- [Controlled Substances Program](#)
- [Office of Ethics and Compliance](#)



Misconduct Puts Careers at Risk

- Can result in being debarred from receiving Federal funds for a specified period of time
- Research institutions
 - may terminate a researcher's employment
 - may require supervision of future research activities
- Publicity
 - [ORI Website](#)
- Can result in a prison sentence (!)





CHARLIE NEBERGALL/AP/PA

Dong-Pyou Han (centre) confessed to fabricating and falsifying data on an HIV vaccine.

RESEARCH MISCONDUCT

http://www.nature.com/polopoly_fs/1.17660!/main/topColumns/topLeftColumn/pdf/nature.2015.17660.pdf

Uneven response to scientific fraud

The case of jailed US vaccine researcher Dong-Pyou Han shows up inconsistent nature of penalties.

BY SARA REARDON

There is the scientist who serves time on charges of research misconduct. But on 1 July, Dong-Pyou Han, a former biomedical scientist at Iowa State University in Ames, was sentenced to 57 months in prison for fabricating and falsifying data in HIV vaccine trials. Han has also been fined US\$7.2 million and will be subject to three years of supervised release after he leaves prison.

His case had a higher profile than most, attracting interest from a powerful US senator. Han's harsh sentence raises questions about how alleged research fraud is handled in the United States, from decisions about whether to prosecute to the types of punishment imposed by grant-making agencies.

In a confessional letter sent to the university just before its investigation concluded, Han said that he began the subterfuge to cover up a sample mix-up that he had made years before.

The US Office of Research Integrity (ORI), which oversees investigations into alleged misconduct involving NIH funds, barred Han from receiving federal grants for three years — the maximum penalty that it generally imposes on junior investigators. The case probably would have ended there had it not drawn the attention of Senator Charles Grassley (Republican, Iowa), who has a history of investigating misconduct in the biomedical sciences.

“This seems like a very light penalty for a doctor who purposely tampered with



How Common is Research Fraud?

- 0.01% (Nicholas Steneck) according to federal misconduct findings
 - Likely under-reported
- Average number of allegations to ORI
 - 1994 to 2000, 45 per year
 - 2001 to 2010, 85 per year
 - 2020 (only), 204
 - 2021 (only), 230
 - 2022 (only), 269
 - Increasing reporting or increasing fraud?
- According to surveys (Daniele Fanelli)
 - 2% admitted to fabrication or falsification at least once
 - 14% observed the behavior in colleagues
 - 33% admitted to questionable research practices



What are the motivations?

- Career pressure
- Belief that one already knows the right answer
- Notion that data may not be reproducible

(Goodstein)

- The “work structure” of modern science

(Sydney Brenner)



Research Misconduct

Pressure to lie

What is your first impression of this video/scenario?

Nobody has responded yet.

Hang tight! Responses are coming in.



Personal Responsibility and Problems with Rules

- Rules generally set minimum standards for behavior
- Should strive for a higher standard of conduct
- Responsible research requires more than simply following rules
- Rules will not resolve some of the personal conflicts and moral dilemmas
- Rules also cannot replace the critical reasoning skills
- Researchers will face ethical dilemmas in research



So Many Regulations, What Should I Do? The Simple Test...

- Imagine what you are preparing to do will be posted immediately on the web (IG, SnapChat, FB, google news, etc)
- If you are comfortable having colleagues, friends, and family know what you did, chances are you acted responsibly

How much damage?

Andrew Jeremy Wakefield



- Published that there was a link between the administration of the MMR vaccine and autism and bowel disease
- Other researchers were unable to reproduce the findings
- Reporter Brian Deer identified undisclosed financial conflicts of interest on Wakefield's part
- The British General Medical Council (GMC) conducted an inquiry into allegations of misconduct against Wakefield and two former colleagues
 - 4 counts of dishonesty
 - 12 counts involving the abuse of developmentally challenged children

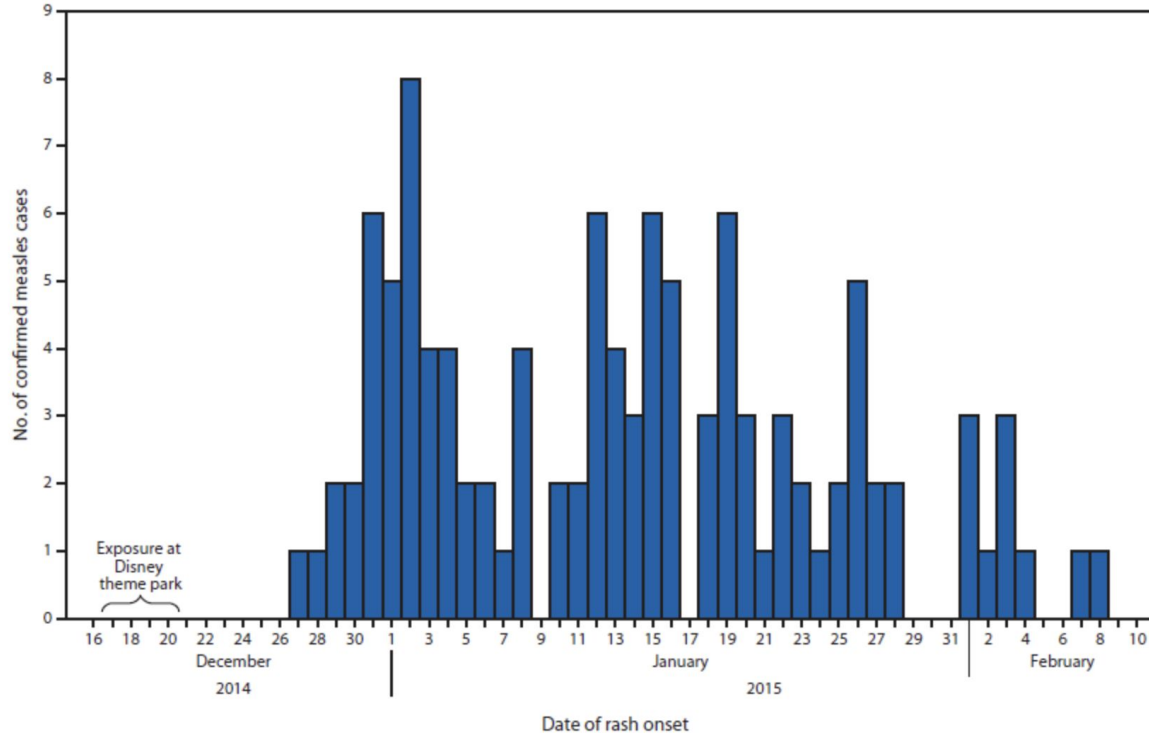
Andrew Jeremy Wakefield

- The Lancet fully retracted the 1998 publication noting that elements of the manuscript had been falsified
- The editor-in-chief said the paper was "utterly false" and that the journal had been "deceived"
- Wakefield was struck off the UK medical register and was barred from practicing medicine
- He had planned to launch a venture on the back of an MMR vaccination scare that would profit from new medical tests and "litigation driven testing"



Disneyland Measles Outbreak 2014-2015

FIGURE. Number of confirmed measles cases (N = 110),* by date of rash onset — California, December 2014–February 2015



* Reported to the California Department of Public Health as of February 11, 2015.

Measles Outbreak, Fueled by Vaccine Fear, Sends Kids to Hospital

by Shaquille Brewster and Maggie Fox / May.10.2017 / 5:46 AM ET



More recently from the CDC:

Measles cases in 2019

- From January 1 to December 31, 2019, 1,274* individual cases of measles were confirmed in 31 states.
- This is the greatest number of cases reported in the U.S. since 1992.
- The majority of cases were among people who were not vaccinated against measles.

Measles cases in 2022

- From January 1 to December 31, 2022, a total of 121 measles cases were reported by 6 jurisdictions.



HEALTH

OCT 9 2015, 5:05 PM ET

Measles Vaccine Gaps Put U.S. At Risk, Reports Show

by MAGGIE FOX

This Electron Micrograph Reveals Both A Paramyxovirus Measles Virus, And Virions Of The Polyomavirus, Simian Virus Sv40 Smaller Circles. The Envelope Of The Measles Virus Has Broken, Exposing The Nucleocapsid Filaments. Interest In Sv40 Has Increased In The Last Several Years Because The Virus Was Found In Certain Forms Of Cancer In Humans, For Instance Mesotheliomas Rare Tumors Located

LETTER

Early brain development in infants at high autism spectrum disorder

Heather Cody Hazlett^{1,2}, Hongbin Gu¹, Brent C. Munsell³, Sun Hyung Kim¹, Martin Styner¹, Jason J. Wo Meghan R. Swanson², Hongtu Zhu⁶, Kelly N. Botteron⁷, D. Louis Collins¹¹, John N. Constantino⁷, Steph Annette M. Estes^{9,10}, Alan C. Evans¹¹, Vladimir S. Fonov¹¹, Guido Gerig¹², Penelope Kostopoulos¹¹, Robe Juhi Pandey¹⁴, Sarah Paterson¹⁵, John R. Pruett Jr⁷, Robert T. Schultz¹⁴, Dennis W. Shaw^{8,9}, Lonnie Zwa Joseph Piven^{1,2} & the IBIS Network*

Brain enlargement has been observed in children with autism spectrum disorder (ASD), but the timing of this phenomenon, and the relationship between ASD and the appearance of behavioural symptoms, are unknown. Retrospective head circumference and longitudinal brain volume studies of two-year olds followed up at four years of age have provided evidence that increased brain volume may emerge early in development^{1,2}. Studies of infants at high familial risk of autism can provide insight into the early development of autism and have shown that characteristic social deficits in ASD emerge during the latter part of the first and in the second year of life^{3,4}. These observations suggest that prospective brain-imaging studies of infants at high familial risk of ASD might identify early postnatal changes in brain volume that occur before an ASD diagnosis. In this prospective neuroimaging study of 106 infants at high familial risk of ASD and 42 low-risk infants, we show that hyperexpansion of the cortical surface area between 6 and 12 months of age precedes brain volume overgrowth observed between 12 and 24 months in 15 high-risk infants who were diagnosed with autism at 24 months. Brain volume overgrowth was linked to the emergence and severity of autistic social deficits. A deep-learning algorithm that primarily uses surface area information from magnetic resonance imaging of the brain of 6–12-month-old individuals predicted the diagnosis of autism in individual high-risk children at 24 months (with a positive predictive value of 81% and a sensitivity of 88%). These findings demonstrate that early brain changes occur during the period in

(see Methods for diagnostic and exclusi were comparable in (mean) race/ethnic maternal age at birth (33 years old), infant tional age at birth (39 weeks). The HR-AS the other two groups (83% of the HR-AS 59% and 57% of the LR and HR-neg grov in the LR group had a higher education l

Infants were evaluated at 6, 12 and 24 r detailed behavioural assessments and hi nance imaging (MRI) of the brain, to p and behavioural trajectories during inf below were conducted on a subset of 10 r = 91 HR-neg) and 42 low-risk infants) were successfully obtained. On the bas: 2–4 years of age², we hypothesized that br before 24 months of age; that overgro expansion of the cortical surface area; and are temporally linked to the emergence ASD. We also investigated whether diffe brain characteristics might suggest early before the onset of the defining behavio of ASD.

We first examined group difference growth rate (Fig. 1). The growth rate of the not differ between groups from 6 to 12 r wise comparisons at 24 months showed

Autism develops much earlier than the MMR vaccine is given

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Office of the Ombuds

Use of services provided by the Office of the Ombuds is voluntary and confidential.

- All conversations with the Office of the Ombuds are confidential and off the record.
- The Office does not create or maintain records for the University.
- Any notes taken during the course of a case are routinely destroyed on a quarterly basis once the Office determines the case is closed.



Effective Collaboration

What constitutes collaboration?

- ❑ Sharing reagents, techniques, info or samples
- ❑ Small joint project
- ❑ Multi-center projects
- ❑ Not necessarily geographically close locations
- ❑ Potentially competing interests



True or False? At least one of my current projects is a collaboration

True, I'm in a collaboration with an academic partner(s)

0%

True, I'm in a collaboration with industry partner(s)

0%

False, I am not currently involved in a collaboration

0%

I am unsure at this time

0%



Effective collaboration begins with...

“a clear understanding of roles and relationships, which should begin the day the collaboration is established by discussing the details of the collaboration.”

On Being a Scientist, A Guide to Responsible Conduct in Research: Third Edition, (2009)

Details to know...

- ❑ Goals of project & anticipated outcomes
- ❑ Role of each partner in collaboration
- ❑ How data will be collected, stored & shared
- ❑ How design changes will be made
- ❑ Publication responsibilities
- ❑ Criteria for authorship
- ❑ Conflicts of interest



Details to know...(2)

- ❑ Who will submit reports & meet requirements
- ❑ Who can/will speak publicly about this work
- ❑ Intellectual property rights & ownership
- ❑ Changes to agreement & when it comes to an end
- ❑ Ownership of spin-off projects
- ❑ Check-points & kill-points
- ❑ Fate of samples/materials at end of project



Communication plans

- ❑ Establish schedule of regular meetings/visits
 - ❑ Report findings, preliminary results
 - ❑ Discuss the changing landscape of the project
 - ❑ Discuss recent developments in the field
- ❑ Establish regular discussion of financial issues
 - ❑ (particularly important if project is funded)
 - ❑ Report run-of-the-mill expenses & anticipated spending



Informal Agreements

- ❑ Unfunded
- ❑ Charter and/or Meeting Minutes
 - ❑ Shared drive document
 - ❑ Email
- ❑ Updates after meetings or new results



UCSF Office of Sponsored Research

UCSF Innovation Ventures

New Guidance on Research Security

Word Cloud: One word about your knowledge on research security

Nobody has responded yet.

Hang tight! Responses are coming in.



Recent Developments in Research Security

- JASON Report (2019)
 - Full disclosure of all potential conflicts of interest
 - Recommends violations be investigated and adjudicated as research misconduct
- NSPM-33 (2021)
 - Requires digital persistent identifiers
 - Mandates Research Security Programs
 - Guidance on consequences for breaches
- CHIPS and Science Act (2022)
 - Establishes a clearing house for research security and integrity
 - Mandates research security training as part of RCR
 - Certification of grant applicants that they are not participating in malign foreign recruitment programs
- Research Security Programs Standard Requirements (2023)
 - Requires an institutional research security program (registered in SAM.gov)
 - Research security, cyber security, foreign travel, and export control



Encourages Appropriate Use of Funds



Prevents Deceptive Practices by Bad Actors



Protects IP & Innovations from Theft or Misuse



Protects Sensitive Information



Minimizes Foreign Government Interference

Collaboration and Knowledge

Integrity: Relies on trust to ensure attribution, acknowledgement, and dissemination of findings.

Security: Facilitates collaboration and protects IP and sensitive data.

Both: Promote collaboration and responsible knowledge sharing

Trust and Credibility

Integrity: Ensures processes and results are consistent with core values and ethics

Security: Ensures results are protected from unauthorized access or manipulation by external parties

Both: Help establish and maintain trust

Compliance

Integrity: Complies with guidelines and regulations governing ethics, human subjects, and animal welfare.

Security: Complies with regulations and best practices related to data, export controls, and IP protection.

Both: Require adherence to regulations, policies, and guidelines.

Protection of Research Assets

Integrity: Gives high confidence in accuracy and reliability of findings.

Security: Focuses on safeguarding data, IP, and sensitive information from unauthorized access, tampering, and theft.

Both: Aim to protect valuable research assets.

Core Values of Academic Research

Openness and transparency

Accountability and honesty

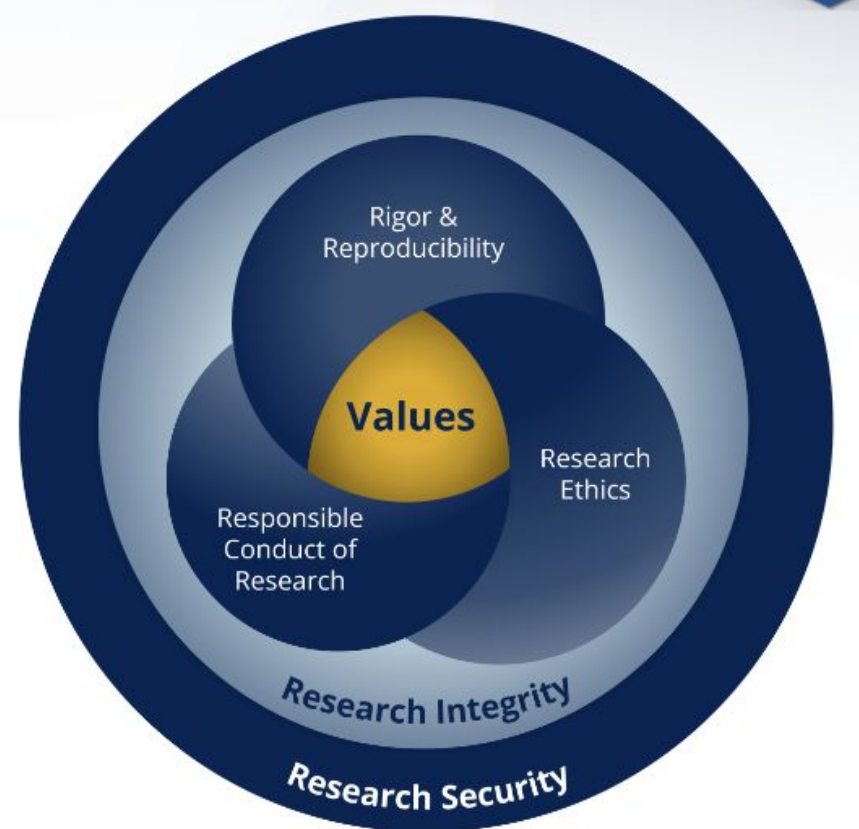
Impartiality and objectivity

Respect

Freedom of inquiry

Reciprocity

Merit-based competition



Countries of Particular Concern

The most recent Countries of Particular Concern designations were made by the Secretary of State on December 29, 2023:

Burma, People's Republic of China, Cuba, Eritrea, Iran, the Democratic People's Republic of Korea, Nicaragua, Pakistan, Russia, Saudi Arabia, Tajikistan, and Turkmenistan.

<https://www.state.gov/countries-of-particular-concern-special-watch-list-countries-entities-of-particular-concern/> accessed February 15, 2024

End for today

Questions?

