BIORISK MANAGEMENT CASE STUDY: AMERICAN SOCIETY FOR MICROBIOLOGY JOURNALS

Science

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SUMMARY

Science is the flagship journal of the American Association for the Advancement of Science (AAAS). The journal is highly competitive, publishing manuscripts that demonstrate significant innovations in their methods or results that significantly advance scientific understanding. *Science*:

- **developed its dual-use research risk management processes in response to a high-profile debate** over its publication of an H5N1 influenza gain-of-function experiment.
- **piloted a Materials, Design, Analysis, and Reporting framework and checklist,** which included a field for authors to report whether their experiments are subject to dual-use research of concern (DURC) oversight.
- **mitigates risks by communicating in its articles whether research received additional dual-use oversight** or involved additional biosafety and biosecurity safeguards.
- **relies on the individual expertise of its reviewing editors and a small network of peers** when making dual-use review decisions.

DISCLAIMER

Biosafety and biosecurity risk management practices can change over time. This case study represents one point in time and is a sample of an evolving set of risk management practices. For additional information on current practices please contact the organization directly.

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THE VISIBILITY INITIATIVE FOR RESPONSIBLE SCIENCE (VIRS)

The goal of the Visibility Initiative for Responsible Science (VIRS) is to share information about the value of biorisk management and how life science stakeholder organizations approach the issue. VIRS was conceived by a multi-stakeholder group during an April 2019 working group meeting of the Biosecurity Innovation and Risk Reduction Initiative (BIRRI) program of NTI Global Biological Policy & Programs. With support from NTI, Stanford University Bio Policy & Leadership in Society VIRS produced a set of Case Studies in biorisk management, and The Biorisk Management Casebook that provides cross-cutting insights into contemporary practices.

THE BIORISK MANAGEMENT CASE STUDIES

The Biorisk Management Case Studies describes biorisk management processes for a diverse set of life science research stakeholders. The collection serves to evaluate the feasibility and value of knowledge sharing among both organizations that have similar roles and those that have different roles in managing research. Case studies were developed in consultation with organizations through a combination of research based on public sources, interviews, and providing a template with guiding questions for organizations to complete directly. Additional analysis can be found in The Biorisk Management Casebook: Insights into Contemporary Practices[1] in this collection. Project Directors: Megan Palmer, Stanford University; Sam Weiss Evans, Harvard University.

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ORGANIZATION BACKGROUND

As the flagship of six peer-reviewed journals published by the American Association for the Advancement of Science (AAAS), *Science* has the stated mission of serving "as a forum for discussion of important issues related to the advancement of science" and publishing "those papers that are most influential in their fields or across fields and that will significantly advance scientific understanding."[2]

> Science *has been at the center of important scientific discovery since its founding in 1880. […] Today,* Science *continues to publish the very best in research across the sciences, with articles that consistently rank among the most cited in the world. […] The* Science *family of journals is published by the American Association for the Advancement of Science (AAAS), the world's oldest and largest general science organization. The nonprofit AAAS serves 10 million people through primary memberships and affiliations with some 262 scientific societies and academies. A voice for science and scientists everywhere, AAAS fulfills its mission to "advance science and serve society" by communicating the value of science to the public, helping governments formulate science policy, promoting advancements in science education and diversity, and helping scientists develop their careers.*[3]

In 2012, *Science* published a paper describing changes in H5N1 avian influenza that enable respiratory transmission among mammals.[17] The controversy regarding the initial decision to publish this research—which contained information that might enable misuse—prompted *Science* to retract the initial publication and pursue an additional dual-use risk review involving the authors, government officials, and other experts. Ultimately, *Science* republished the article with additional supplements detailing the risk management processes undertaken by the authors and their research institutions. This sequence of events ultimately laid the foundation for their dual-use risk assessment processes.

In addition to its efforts to manage dual-use risks, *Science* has advanced efforts to improve standards surrounding reporting and reproducibility in publishing. The most significant of these efforts was the Materials, Design, Analysis, and Reporting (MDAR) framework and checklist, which were piloted until 2019. The framework "establishes a minimum set of requirements in transparent reporting applicable to studies in the life sciences," while the checklist "is a tool for authors, editors, and others seeking to adopt the MDAR framework for transparent reporting in manuscripts and other outputs." The primary goal of the pilot was to develop a "minimum set of requirements generally applicable to reporting studies in the life sciences … to increase reporting transparency, taking into account the current reporting practices and the direction of improvements that are necessary to improve reproducibility."[4]

Included in the MDAR framework was a minimum requirement to "[d]isclose whether [the] study is subject to consideration as dual-use research of concern," and to "describe [the] authority granting approval and provide [the] reference number." Additionally, the framework provided the best practice that "when material that could be harmful outside the laboratory context is used, the manuscript should describe appropriate biosafety and biocontainment procedures."[5] Dual-use concerns were represented in the MDAR checklist through a single question: "If the study is subject to dual-use research of concern regulations, state the authority granting approval and reference number for the regulatory approval" (Figure 1).[6]

Science's experience with the MDAR pilot informed the design of its current biorisk management system, and the MDAR checklist, including its dual-use oversight reporting question, and? remains an element of their dual-use risk mitigation strategy.

Dual Use Research of Concern (DURC)	Indicate where provided: page no/section/ legend	n/a
If study is subject to dual use research of concern regulations, state the authority granting approval and reference number for the regulatory approval.		

Figure 1: Dual-use oversight reporting question included in the MDAR checklist.

PROCESS

Scope of risks considered

Science evaluates manuscripts for potential dual-use risks based on the definition for "dual-use research of concern" (DURC).[7] DURC is defined by the U.S. National Science Advisory Board for Biosecurity as "life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security."[13]

Science considers the potential for development of dual-use technologies, what barriers currently exist, the time horizon for development, and who would be involved at various stages of development when determining whether and how to accept a submission. *Science* does not expect editors or reviewers to anticipate every possible application of new discoveries, but rather flags manuscripts for special handling and scrutiny if they exhibit obvious potential for misuse.

In response to the increase of SARS-CoV-2 related manuscripts submitted over the course of the COVID-19 pandemic, *Science* further refined the scope of risks it considers related to research with pandemic pathogens. Example concerns considered in this refined scope include:

- gain-of-function mutations matching wild type variants found in surveillance and screening
- lab evolution under pressure via passaging of convalescent serum or antibodies
- screening of proteins displayed on phage or yeast for enhanced functionality (e.g., in ACE2 binding)
- use of population genetics to identify those most susceptible to infection and illness
- synthesized viruses

In addition to biological DURC threats, *Science* has also debated whether chemical research poses comparable risks. However, no specific processes for mitigating those risks have yet been explored.

Overall sequence of steps

DURC review begins when authors first submit their manuscript to *Science*. Authors are expected to notify editors if their manuscript could be considered to report Dual-Use Research of Concern (DURC) via the cover letter submitted alongside the manuscript.[8] Following submission, the manuscript is assigned to a professional staff editor with appropriate scientific expertise for an initial triage. Authors' DURC disclosures are documented by the staff editor in an internal manuscript tracking database. The staff editor will share the manuscript with appropriate member(s) of the Board of Reviewing Editors (BoRE) for their assessments of its scientific merit; members of the BoRE can also flag potential DURC during their review. The staff editor then decides whether to send the manuscript for peer review. Staff editors, not members of the BoRE, make all final judgements as to whether manuscripts proceed toward publication.

Manuscripts that are rejected from *Science* prior to the peer review stage—approximately 80% of manuscripts received—do not undergo in-depth DURC review. By assessing DURC potential after assessing scientific merit, *Science* can better allocate the attention of its reviewing editors and consulting stakeholders. However, no notes are taken on the DURC potential of manuscripts that are rejected without in-depth DURC review. Some authors have elected to provide pre-submission inquiries related to the DURC potential of their manuscripts. However, in general presubmission enquiries are discouraged. *Science* would rather authors submit their entire manuscript so editors can make a more informed judgment rather than base assessments on incomplete information. Assessments of pre-submission inquiries focus primarily on whether the manuscript presents a major technical breakthrough meriting publication in *Science*. One example is described in detail here:

> *The authors were seeking our initial reaction to the concept of the manuscript. Based on the information that we had available, we did not sense that there was a major technical breakthrough. And, too, we did see that the topic would raise dual use concerns. Based on this feedback, the authors chose not to submit their work to Science. If they had submitted it, we would have judged the entire submission and, as part of that, we would have considered sending this to one or more members of our Board of Reviewing Editors for their evaluation, following our normal practices.*[16]

Science prefers to perform its in-depth DURC review concurrently with the peer review process, but this is only possible when dual-use research concerns are identified by authors at the point of submission or by the BoRE prior to sending the manuscript to 2-3 referees. Referees are also expected to flag manuscripts for potential DURC during peer review in their comments to the editors.[8] If DURC issues are not noted until during or after peer review, then DURC review begins once peer review is complete. Normally, the peer review process takes 4-6 weeks from the point of submission. If DURC potential needs to be assessed following peer review, the consultation process can add another several weeks of review.

If at any point a manuscript is flagged for potential DURC or analogous risks in the physical sciences, it "will be brought to the attention of the Editor-in-Chief" for an in depth DURC review.[8] The Editor-in-Chief reviews the manuscript, consults members of the BoRE about the risks, and asks referees to comment on DURC and biosafety. Ultimately, the Editor-in-Chief is responsible for deciding whether a manuscript is published or modified to address DURC concerns. Authors may be notified on a case-by-case basis that their manuscript is being reviewed for DURC and may be engaged during initial review or peer review to gather additional information.

Risk assessment

At *Science* there is no standardized form or structure for conducting DURC review. Instead, the publisher relies upon the expertise of their editorial staff and recruited referees. The only standard questions asked of authors is whether their research is subject to DURC regulations, who is providing oversight, and reference numbers for regulatory oversight (see Figure 1 above). This information is only requested when a manuscript is being revised after the in-depth review is complete.

Risk mitigation

As a publisher, and unlike a funding agency or government oversight entity, *Science* believes it is not able to manage DURC directly. However, *Science* does have the ability to check whether authors have been explicit in their methods sections about the conditions under which the work was performed, such as what biosafety levels were applied. To this end, *Science* aims to improve the transparency of the DURC oversight applied to the research described in the manuscript, if any, via the MDAR checklist. *Science* also requests that authors include supplementary materials describing any biosafety, biosecurity, and DURC risk mitigation steps implemented by the authors and their institutions. For example, in one case a DURC manuscript's publication was delayed due to a research moratorium, and a timeline supplement was included describing when work was done relative to the implementation and expiration of the moratorium. Manuscripts must pass their in-depth technical and DURC review before authors are asked to complete the MDAR checklist and provide supplementary materials.

In the case of its 2012 H5N1 paper, *Science* was asked by the U.S. National Science Advisory Board for Biosecurity (NSABB) to redact some methodological details and the identity of mutations resulting in mammalian transmission. *Science* agreed, contingent upon the creation of a mechanism for sharing the unredacted manuscript with privileged groups such as public health agencies or other research teams operating in facilities with appropriate biosafety and biosecurity safeguards. Barbara Jasny, a *Science* editor at the time, then attended a related World Health Organization convening where a majority of participating experts concluded that the papers should be published in full.[9]

Science revisited its policies in light of the SARS-CoV-2 pandemic and decided it would continue to publish DURC and gain-of-function manuscripts only if the experiments were reviewed by relevant oversight bodies to determine their medical value and experimental necessity and that the authors documented their biosafety and biosecurity protocols.

Expertise required

Science primarily relies on the expertise of its editorial team and reviewers to assess DURC risk and maintains a pool of professional editors with DURC expertise whose role is to identify particular concerns. *Science* also has editors on the BoRE who play a role in identifying DURC issues. In contrast to the professional editors, BoRE members are generally academics, with expertise in domains including structural biology, molecular biology, cell biology, immunology, microbiology, biomedicine, neuroscience, genetics, ecology, and plant sciences, and many others.[7] *Science* maintains an internal and confidential Standards of Practice document that is used to train editors, including on potential DURC.

Science also asks referees to comment on DURC and on biosafety, sometimes enlisting additional referees specifically for that purpose. Each manuscript is assigned

2-3 referees for technical merit and DURC potential review. Referees' domains of expertise are matched to the content of each manuscript.

Science also sometimes consults outside reviewers when necessary.[8] *Science* leverages the expertise of editorial staff at other publishers (e.g., Arturo Casadevall with the American Society for Microbiology family of journals) when soliciting outside reviewers.

IMPACT

In-depth assessment of a biosafety and biosecurity risks can impose a significant burden on *Science*. It would be impossible to give every paper the level of scrutiny that a specialty microbiology or virology publisher could do. When *Science's* editorial board is fully staffed, managing the responsibilities of its DURC review is not too challenging, but during periods of staff turnover, it becomes very challenging.

FEEDBACK

Science reviews and updates the entirety of its Standards of Practice document for editors every few years and will make *ad hoc* updates of specific sections when the need arises (e.g., in response to a change to its website or to external policies). The primary sources of feedback informing decisions are the judgments and experiences of the lead editors informed by previous decisions; however, this information is not systematically recorded beyond the memories of individual editors. *Science* tracks many of the traits of manuscript submissions, their authors, their referees, and their editors, but none of this data is specific to a manuscript's DURC considerations. Reviewers' comments and identities are kept confidential as is standard practice among academic journals. As such, reviewers do not have access to specific assessments of DURC potential from previously submitted manuscripts.

A 2019 review of the MDAR pilot provided feedback on the MDAR framework and checklist from manuscript authors and reviewers.[14] Of the 336 responses to the DURC question on the MDAR checklist, 324 (96%) were "not applicable," indicating that a large majority of authors did not consider DURC to be relevant to their manuscripts. Some reviewers identified manuscripts that involved work with human pathogens or changes to host-pathogen relationships, but that authors did not flag as receiving DURC oversight. These reviewers reported being unsure of how to evaluate the potential DURC of these cases. Other reviewer comments noted ambiguity in whether the agent used in research was subject to different national or regional select agent lists. In addition, some reviewers may not have understood the expectations for the review process. There were at least two cases in which they claimed to use keyword searches of terms like "DURC" and "dual-use" in the manuscript to judge dual-use potential, rather than using knowledge of the experimental work and its goals.

In the feedback survey for the overall checklist, a large majority of reviewers (84%) and authors (80%) found MDAR to be at least "somewhat useful," though some found it burdensome.[13] Twenty-six percent of respondents reported that editorial expectations were unclear for some items, which may have included the DURC question. Some respondents indicated that some questions would be easier to understand if example responses were provided.

SHARING

There have been a few convenings of publishers and other stakeholders in which *Science* has discussed its DURC risk management processes. In April 2019 *Science* participated in a working group meeting of the Biosecurity Innovation and Risk Reduction Initiative, a portfolio of programs driven by Nuclear Threat Initiative Global Biological Policy & Programs (NTI | bio). This working group conceived of a "Visibility Initiative for Responsible Science" pilot concept aimed to improve the performance and recording of risk-benefit assessments before, during, and at publication of biological research.[14] In July 2020 *Science* participated in the "Dual-Use Life Science Research (DUR/C) Dialogue with Science Editors and Publishers," a convening of the Science Division of the WHO Emerging Technologies, Research Prioritisation and Support Research for Health Unit.[11]

In January 2021 *Science* convened a meeting of other journals and biosecurity experts to discuss concerns arising from the rapid influx of SARS-CoV-2 related submissions. The meeting included representatives from the American Society for Microbiology (ASM) family of journals, bioRxiv, medRxiv, the National Academy of Sciences Board on Life Sciences, and Harvard University. The participants shared their internal processes and methods for recognizing dual-use issues in submitted transcripts.

Science faced challenges in public messaging surrounding the 2012 H5N1 publications and anticipated that these challenges would continue in the face of the COVID-19

pandemic. *Science* believes it is important for journals to transparently document and publicly state how they are handling DURC and has encouraged other journals to co-sign statements to that effect with them.

REFLECTIONS

Science believes that there is a tension between the management of biosecurity risks and recent movements among publishers to improve standards for reporting and reproducibility. Journal editors tend to value the latter, as they are fundamental elements of quality research across fields. *Science* believes that it is funders and authors who have the greater responsibility to explicitly consider safety and security concerns associated with the research they fund and perform.

Science emphasizes that their DURC risk management process has always depended on human beings flagging manuscripts for review, but they are uncertain about whether this is an optimal approach. The editors responsible for making decisions about potential DURC are time- and resource-limited, so there is little incentive to invest additional time and resources in refining their decisions or anticipating hypothetical concerns.

Science recognizes that specific biosafety and biosecurity concerns can become more or less salient over time. After an initial period of debate among peers surrounding a particular concern, the cultural moment passes and ideas for how to frame or address those concerns are not translated to the greater life science research community. *Science* observes that the research community is ineffective at accumulating and systematically preserving the tacit knowledge of the individual experts who drive those debates. When those individuals leave the community or their organizations, their wisdom leaves with them.

The question of where or with whom dual-use risk responsibility lies at *Science* has not been designated to any one office or purpose-built committee. This has introduced challenges for the editorial staff; however, formalization and standardization of dual-use risk management has been a lower priority to the senior editors than other immediate needs and competing initiatives.

The January 27, 2021 meeting of journal editors and other stakeholders raised many lingering questions about how *Science* and other journals should manage dual-use risks in a changing publication landscape:

- Whether research can be considered DURC if it does not involve infectious viruses
- The extent to which benefits from DURC outweigh risks
- Where responsibilities for DURC oversight lie among various stakeholders
- In an international context, which policies should govern DURC oversight (e.g., those of the US or WHO)
- What criteria should be used to identify papers that require additional scrutiny, what form that scrutiny should take (e.g., consultation outside of *Science*), and when documentation of biosafety measures should be required as a condition for publication
- What responsibility publishers have for managing DURC issues that were identified post-publication
- How to determine when to consult with external experts as opposed to relying on in-house expertise
- How to identify risks that fall outside of the scope *Science* typically considers

A final consideration is the increasing role of pre-prints in the publication space in the years since the H5N1 papers were published, which could enable researchers to publish information prior to submission and subsequent DURC review at a journal. Efforts to restrict access to information hazards may require either coordination with preprint servers, or shared standards and methods for publishing research with dual-use concerns. The participation of bioRxiv and medRxiv in the January 2021 convening of editors indicates that coordination with preprints to address biosecurity challenges may be possible.

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