Let's Talk About Risks!

A Workshop for Identifying and Anticipating Uncertain Risks for Safe Biotechnology Applications

TU Delft

t-tripp | Tools for Translation of Risk Research into Policies and Practices

This document provides a manual for researchers to organize an (interactive) stakeholder workshop on how to take care of emerging risks during the development of a new biotechnology or biotechnological application. A script is included that elaborates the necessary steps to identify and assess uncertain risks, and formulate anticipatory strategies and implications for research designs.

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Management Summary

This manual provides a script for researchers working with emerging biotechnologies to organize an interactive stakeholder workshop for identifying and anticipating uncertain risks. These uncertain risks refer to unexpected matters arising of which the possible detrimental effects or magnitude might not be completely known yet or completely unknown. Using a case concerning an emerging biotechnology or biotechnological application, the workshop provides researchers insights into:

- Different estimates of uncertain risks: which risks are identified, on what basis, degree and nature of uncertainty;
- Effective anticipatory strategies to mitigate or lower the uncertain risk;
- What is needed to implement the defined strategy/strategies in research practices?

Thereby, a range of partaking stakeholders (e.g. toxicologists, ecologists, (bio)ethicists, social scientists) is encouraged. Not only to increase awareness of safety but also to gain a more holistic view on possible emerging risks and suitable anticipatory strategies to mitigate or lower these risks. In response, necessary adaptations in terms of research design can be formulated and implemented, thereby ensuring safe and responsible biotechnology research.

This manual was constructed based on an iterative process consisting of five workshops, with a total of 32 partaking stakeholders over the periods March 2021, June 2021, and January – February 2022. All workshops were conducted online due to covid-19 with a maximum duration of 2.5 hours.

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Let's talk about risks

The fields of biotechnology and synthetic biology are developing at a vast pace, and therefore, safe and responsible development must be ensured. This manual describes a workshop for 'designing for safety'. That is, a protocol is provided for how to take care of possible emerging risks during the development of a new biotechnology or biotechnological application, particularly during the early stages of design (i.e. composing a research proposal).

First, this document provides an answer to three questions, namely: *What does this workshop entail and for what purpose? When should this workshop be organized?*, and *Who should participate in this workshop and why?* Secondly, this manual provides a script for an interactive stakeholder workshop, explaining what steps must be taken and their respective stages of thought. Lastly, we provide some recommendations for execution of the workshop, e.g. platforms to use, alternatives etc. In addition, throughout the document, relevant literature is mentioned and examples are provided that help create a mindset needed to 'design for safety'.

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A workshop for identifying and anticipating uncertain risks

Biotechnology aims to develop new technologies or applications through exploiting biological processes, organisms, cells or cellular components. Thereby, emerging technologies or applications may give rise to uncertain risks, which can be either not completely known or completely unknown (Aven & Renn, 2009). For instance, it might not be known what the order of magnitude is of a possible detrimental effect, or it might not be known what the possible detrimental effects are, to begin with.

To ensure safe and responsible development of biotechnologies, uncertain risks must be identified and anticipated during the early stages of development, ideally in an iterative way and already starting during the composition or design of a research project. To facilitate a constructive discussion about emerging uncertain risks and how to anticipate these, we developed a workshop format that provides an important moment of reflection while designing a research project. In addition, a broad group of partaking stakeholders (e.g. participants outside the research group) would be encouraged as this provides a more holistic view on the issue of possible emerging risks and respective anticipatory measures.

Why?

First of all, why should one organize this workshop during the composition of a research design? An increasing emphasis is being placed on responsible and safe research and innovation where not solely technological and scientific advancements are deemed important but also value is attached to contributing to societal challenges and managing emerging risks. In that sense, tensions, conflicts or differing perspectives might emerge between stakeholders (e.g. microbiologists, biotechnologists, researchers from other expertise, policymakers, funding organizations, etc.) who adhere more to technically and scientifically innovative research, and those that value the societal relevance of research to a greater extent. This can create diverging

perceptions of emerging risks and what would be deemed acceptable. Therefore, perceptions on these matters must be identified by means of an open and constructive discussion about how to handle these potential risks. In addition, one might identify potential risks that otherwise might have been overlooked preventing any future delays in the research or permit application process.

What?

To facilitate researchers in developing their research safely and responsibly, we have developed a workshop. The goal of the workshop is three-fold: to gain insights into different estimates of uncertain risks; construct suitable, anticipatory strategies to mitigate or lower the earlier identified uncertain risk(s); and to determine what would be needed to implement or operationalize the defined anticipatory strategies in researchers' practices.

Box 1: Goals of Workshop

To facilitate researchers in designing their research safely and responsibly, we have developed a workshop with the following aims:

1) **Gain insight into different estimates of uncertain risks: which risks are identified, on what basis, degree and nature of uncertainty;**
2) **Define effective anticipatory strategies to mitigate or lower the uncertain risk;**
3) **Determine what is needed to implement the defined strategy/strategies in research practices.**

Firstly, during the development of new biotechnologies or applications of such, there may be a lack of data or knowledge concerning the order of magnitude and/or the detrimental effects, to begin with. Also, depending on one's expertise, experience or professional role, whether or not these uncertain risks are considered acceptable differs (Bouchaut & Asveld, 2020; De Witt et al., 2017). Therefore, it makes sense to take into account a variety of perspectives by means of a broad range of partaking stakeholders in the workshop. Not only to gain better insight into the order, possibility or magnitude of the associated uncertain risks but also to possibly identify risks that may be overlooked if only stakeholders from one specific area would participate. For example, an ecologist, toxicologist or (bio)ethicist may be able to point out uncertainties or possible issues that may not be directly technically related, but related to the direct or indirect receiving ecosystem (e.g. when engineering plants) or societal matters (e.g. societal scrutiny or resistance). By gathering different perspectives, a broader set of uncertainties or uncertain risks can be identified and a constructive discussion could help in providing a framework or boundaries to assess whether or not these would be acceptable.

Secondly, in response to the identified uncertainties or uncertain risks, one can formulate anticipatory strategies to ensure a safe and responsible research design. Of course, deciding on the acceptability of an uncertain risk and choosing appropriate anticipatory measures during such early stages of research design is difficult, but it is a meaningful exercise that helps to increase risk awareness and preparedness. In terms of formulating strategies to ensure safety, one could choose to reconsider and accordingly adapt certain design choices to completely circumvent an identified possible issue (Robaey, 2018). For instance, contemplating whether the devised 'route' to the intended research goal is the only one, or whether there would be

alternative routes that lead to the same result but perhaps would make use of a different organism or process route, thus without the earlier identified possible issue. However, if this alternative 'route' would require many extra steps or require other necessities, this would be a matter to take into account in the trade-off of what anticipatory strategy would be most suited (Bouchaut et al., 2021). In addition, it might become apparent that for choosing the 'right' or most suitable anticipatory strategy, more research is required. Therefore, designated risk research should become part of technically innovative research, ideally running parallel to each other (see also Rathenau Instituut (2021) 'Samen voor Bioveilig'). Thereby, an active exchange of principles, methods/ research design, results and analyses should take place, creating an iterative process in which risk research feeds into technical research, and vice versa.

Thirdly, as already touched upon, more research could be needed to be able to identify suitable strategies that can be implemented in research practices. Also, other preventive or anticipatory measures could be needed based on current regulation and legislation, or for instance, the laboratory facilities available. To be able to take these matters into account during the composition of research, stakeholders with practical experience/knowledge such as Biosafety Officers must be included in the workshop. That way, the discussion about what measures would be appropriate to take and to what adaptations in the design that would lead is much more effective and realistic in terms of outcomes and decisions.

When?

Box 2: When to Conduct this Workshop?

1) When researching emerging biotechnologies;
2) Prior to composing or submitting a research proposal;
3) When a risk assessment asks for extra information on emerging risks;
4) After consultation with organization's BSO.

This workshop adds most value to research concerning emerging biotechnologies as this could give more rise to uncertainties (e.g. lack of data or knowledge) and uncertain risks (i.e. the order of magnitude is uncertain). Emphasizing uncertainties and uncertain risks leads to new knowledge concerning these emerging risks, which is crucial for biotech research to continue responsibly.

Ideally, this workshop should be organised *before* composing a research proposal and/ or submitting an application for funding. Not only to ensure safe and responsible research design but a greater emphasis on identifying and anticipating uncertain risks could also speed up research later in the process. For instance, when an experiment is initiated, extra information regarding possible risks may be required by an organisation's BioSafety Officer (BSO) or the Dutch GMO Office (in Dutch: Bureau GGO). Having already invested in a more extensive analysis of emerging risks, such processes might be accelerated or prevented at all. However, it can also occur that a risk assessment (e.g. at the start of a new experiment) reveals that the experiment involves uncertain risks and more data or research would be needed. This would also be a moment to initiate organising the workshop to be able to complete the risk assessment in a more thorough way. Also, consultation with an organisation's BSO throughout the application process could create an incentive for organising this workshop.

For Who?

Box 3: Whom the workshop is intended for

1) Researchers that are working with biotechnologies or biotechnological applications;
2) Researchers from other relevant areas of expertise, such as ecology, toxicology, as well as social scientists;
3) Stakeholders from the regulatory regime, and other scientific disciplines such as (bio)ethicists, social scientists and BSOs.

This workshop is intended for researchers that are working with (emerging/new) biotechnologies or biotechnological applications, during the composition of a new research proposal or at the start of a new project or experiment. Depending on the type of biotechnology, other associated stakeholders should be partaking in this workshop. Besides ideally stakeholders from the regulatory regime, BSOs, (bio)ethicists and/or social scientists, one could think of consulting ecologists and/or toxicologists (e.g. for white and green biotechnology), or stakeholders associated with the (national) health domain (red biotechnology) to be involved in the decision-making process of the research.

Organization & Script

As researchers find themselves at the cradle of emerging biotechnologies, it is important that safe and responsible development is ensured. By accommodating this workshop, researchers can see to it that this is done. This would be beneficial not only because safe and responsible development is highly endorsed by funding organisations, but also, in later experimental stages, it could prevent research to be delayed due to unforeseen issues arising, complicating matters such as conducting an adequate risk assessment and permit application. For instance, an issue could occur for which no policy is equipped yet. By identifying and anticipating these issues during early stages of experimental development, such delay or complication could be circumvented. Therefore, we provide a script (with complementary protocol in Fig. 1) that elaborates each step, the respective stages of thought to go through and the desired outcome or deliverable of each step. As mentioned, the ideal results of the workshop are a list of potential issues or uncertainties that need to be anticipated, suitable strategies to do so, and a list of design adaptations and/or requirements.

Eight notes of importance prior to the workshop:

1. First of all, when *inviting participants* it should be clear why they are invited for the workshop, how their specific contribution would be meaningful for the researchers and vice-versa (what's in it for them?). Thereby, the subject of the meeting and what will be discussed during the meeting should be clearly explained in the invitation.
2. As to avoid very general discussions about risks and uncertainties that lead to unclear recommendations, the subject of the meeting (i.e. the reason for organising this workshop) should be presented as a *specific case* that is in line with the (intended) research and forms the framework for the discussions. So, for instance, the development of a new type of application or proceeding from a laboratory environment (contained) to a non- or semi-contained environment (e.g. field trials) where new types of uncertainties can emerge.

3. The case should be sent to all participants prior to the workshop. Thereby, a balanced amount of information must be provided. It should be balanced in a way that experts can form a realistic idea of the different factors that may lead to new risks, and non-experts with less technical knowledge can place the 'case' in a broader picture.
4. Thirdly, it must be decided if an external *moderator* or *discussion leader* will be needed or whether one directly involved in the research project will act as discussion leader. We would recommend an external moderator due to the ability to act and summarize the discussions neutrally and who can create a positive and relaxed atmosphere. However, depending on the specific content the workshop will be focusing on, the moderator might require to have relevant (technical) knowledge considering the topic(s) for discussion. If this is not found to be possible, someone directly involved in the research project can act as discussion leader but should bear in mind to mostly focus on guiding, summarizing and reflecting on the discussion itself, instead of (perhaps subconsciously) letting one's opinion influence the discussions. Another option is to have a moderator that focuses on the discussions and have a 'second moderator' who focuses more on technical related matters. However, when choosing this option, the two moderators must make good arrangements of who answers/moderates what aspects.
5. Appoint a *rapporteur* with good reporting skills before the workshop for making a written report of the discussions.
6. Determine the *composition of break-out groups* (preferably balanced with different types of expertise in each group).
7. Make sure you are *well prepared* and have everything properly installed and tested: whiteboards, post-it notes, (felt-tip) pens, a camera to photograph results, tools for online support etc.
8. Lastly, if making recordings or if personal information will be used in the meeting's written report, ask participants for their permission using a *form of consent*[1]. This form of consent can be sent to the participants with the official invitation and should be handed in before the start of the workshop.

Script

In addition to the script, **Fig. 1** illustrates all steps to be followed and can be used as a supplementary tool during the workshop.

	Explanation	Outcome/ Deliverable
Welcome	The discussion leader welcomes all participants. Also, participants can be reminded of filling in the form of consent for making recordings during the workshop.	-
Introductions	All participants, including the discussion leader, shortly introduce themselves and indicate how they are involved with	-

[1] For informed consent templates, see https://www.tudelft.nl/en/about-tu-delft/strategy/integrity-policy/human-research-ethics/informed-consent-templates-and-guide

	biotechnology and/or the relevant context under discussion.	
Step 1: Identification and Prioritization of Risks		
1.1 Introduction of aim/content workshop	The discussion leader or researcher from the project introduces the program for the day and the aims of the workshop. Participants can ask questions regarding the aims, set-up or other details concerning the workshop. Thereafter, the discussion leader or researcher from the project pitches the case on which the participants will focus during the workshop (point 2 above). Ideally, the case should be explained through several bullet points on a slide, thereby clearly stating the context (contained use or introduction to the environment, rationale of the research) and the central problem (complexities, uncertainties). Participants can ask questions to clarify matters regarding the case.	-
1.2 Identifying potential risks	Participants discuss in small groups (max 5 people in a physical setting and max 4 people when organised online) what possible risks are emerging according to their view or perspective. For this, participants are given 20 minutes to come to a consensus of 3 emerging issues, listed in order of importance. Before the discussion starts, one of the participants should be appointed to make notes of the top-3 of potential issues. After the discussion in small groups, the lists will be discussed plenary. For online settings, members of the research group can act as 'discussion leader' for the smaller groups to stimulate discussion and to provide more (technical)	A top-3 list (per group) of identified potential issues or uncertain risks

	information when asked for by the participants.	
1.3 Plenary discuss and estimate severity of potential risks	Every group briefly presents their top-3 plenary. If groups weren't able to reach a consensus regarding a top-3, they should elaborate on the issues they ran into. Other participants can ask questions for clarification. A plenary discussion (15 minutes) is devoted to the plausibility and severity of the identified issues, led by the moderator.	Overview of all listed potential issues. Written report (by the rapporteur) with details concerning the estimated plausibility and severity of the identified potential risks, and an overview of issues that did not make the 'top-3' or was a lot of disagreement on.
Step 2: Formulating Anticipatory Strategies		
2.1 Defining strategies	Each small group (same composition as in step 1) discusses what anticipatory strategies they can think of for circumventing their top-3 of identified issues. To stimulate or help discussion, the moderator can point out several technical strategies, e.g. kill-switches, auxotrophy, choice of an organism or implementing control mechanisms using, for instance, light. In addition, other measures on (work)organisation can also be mentioned to spark discussion, e.g. proper lab training of staff. Again, one of the participants in each small group should be appointed to provide a summary in the plenary session that follows. *Note*: one strategy can anticipate multiple possible issues. For more information and examples, see Robaey (2018).	List with anticipatory strategies for each respective group's top-3.
2.2 Plenary discussion of anticipatory strategies	Every group briefly presents their defined anticipatory strategies plenary. Other participants can ask questions for clarification. A plenary discussion (15 minutes) is devoted to the effectiveness and feasible	Overview of all anticipatory strategies, and a list of which strategies are the most suitable.

	implementation of each strategy, and which would be the most effective to circumvent the earlier identified risks. Thereby, the defined anticipatory measures are also placed in the context of current regulation and legislation. Participants identify where there might be a lack of knowledge to adhere to the established norms to ensure safety.	Identification of knowledge gaps necessary to adhere to existing legislation and thereby ensuring safety. Written report (by the rapporteur) with details concerning the estimated effectiveness and implementation of the defined strategies, and details concerning what strategy was deemed more suitable than another.
Step 3: Design & Research Adaptations		
3.1 Formulating design adjustments	First, participants are given 5 minutes to think of how the earlier identified strategies can be implemented in research. Or in other words, what would have to be adjusted in terms of the research design? For instance, there might be a need for more knowledge and/or additional risk research, more budget required for setting up the needed risk research, hiring extra staff, or more intense collaboration with the organization's BSO, etc. Participants put their suggestions in the chat (online environment) or write them down for themselves (physical meeting). Following up, a plenary discussion is devoted to all suggestions made. The discussion leader addresses the participant's suggestions one-by-one, either from the chat or from what each participant has written down, and asks the participants to elaborate. Participants are encouraged to respond to each other's proposed adjustments.	Proposal for adjustments in the research design and complementary experiments specifically devoted to risk research.
Lessons learned and action points	All participants share their thoughts about the workshop and its outcomes. Also, participants formulate a take-home	List with suggestions for follow-up steps and/or research.

	message and suggestions for follow-up steps. The rapporteur makes notes of all suggestions.	Feedback from participants on the workshop and the outcomes.
Summary workshop	The discussion leader provides a recap of the workshop, and briefly summarizes the main outcomes of the meeting. Participants are allowed to respond and/or ask questions.	-
Thank you & closure	The discussion leader thanks the participants and concludes the workshop by summarizing how this workshop may contribute to adjusting the research (proposal).	-

Based on the outcomes of the workshop and the written report containing more detail concerning the discussions, the organizers of the workshop (i.e. the research consortium/PI/main applicants) should decide on what measures to take and implement them in their research design accordingly.

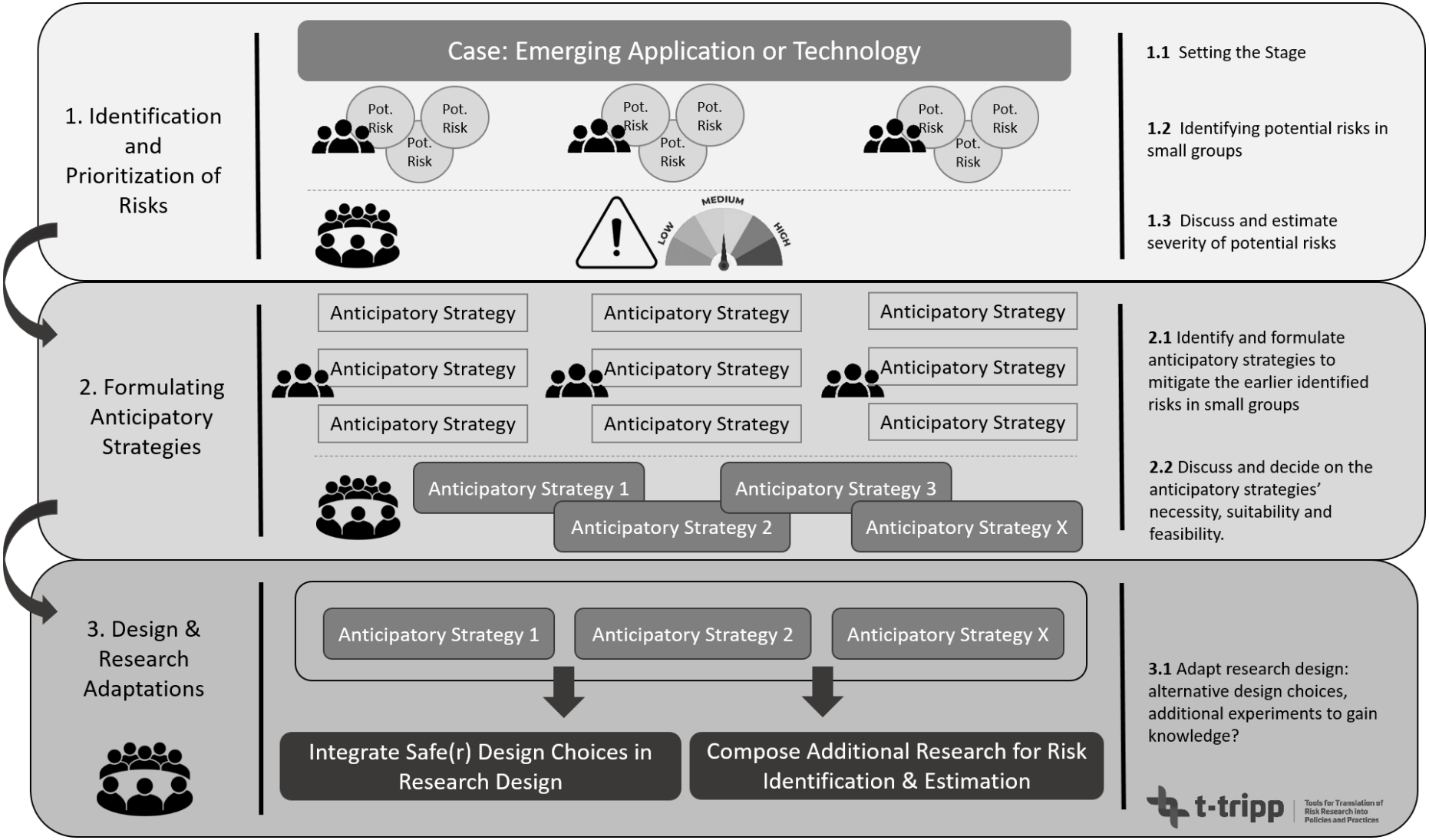

Figure 1. Protocol for workshop.

Box 4: Complementary Material

Complementary information and tools are available via the respective Rathenau Instituut website: www.rathenau.nl/en/biotechnology-and-safety. The three 'serious games' that have also been developed within T-TRIPP can be played independently, but can also act complementary to this workshop. The Rathenau Instituut report 'Samen voor Bioveilig' (in Dutch) provides more background about the current governance ecosystem regarding biotechnology.

1) Cards for Biosafety
   The card game Cards for Biosafety is intended for biotechnologists and students. The game aims to raise safety awareness and teaches professionals and future professionals how to deal with issues regarding safety in laboratory settings in a better way.

2) MachiaCelli Switch
   The board game MachiaCelli Switch allows players to experience the design and implementation phase of a biotechnology project from the perspective of scientists as well as policy makers or risks assessors. The focus of this game is on experiencing the different roles and responsibilities in biotechnology.

3) MachiaCelli Teams
   The board game MachiaCelli Teams builds on MachiaCelli Switch, and focuses on collaboration and communication between biotechnology researchers and policy makers. By having different roles working together, it becomes possible to reveal communication barriers and let players work on possible solutions. It has a more comprehensive risk and impact system than Machiacelli Switch.

4) Report 'Samen voor Bioveilig – De noodzaak van een sterke interactie tussen onderzoek en beleid voor veilige biotechnologie.'
   This study examines the interaction between biosafety research and policy. It examines how research and policy can learn from each other in a sensible way. The report is aimed at researchers, policy makers and other stakeholders in the governance of biosafety in the Netherlands.

Additional Notes and Recommendations

The organisation, processing and evaluation of a workshop can take up a considerable amount of time. We understand that when a deadline for a research application is approaching fast, organizing a workshop would simply not be feasible. However, to be able to take multiple perspectives on emerging risks into account for 'new' techniques or applications, consulting or interviewing a few stakeholders (from differing expertise) is highly recommended. In addition, such consulting is also recommended for relatively 'small' emerging uncertainties, for example, possible risks associated with one specific element or aspect compared to a radically new application or technique.

Also, one could choose to use one of the 'serious games' that have also been developed within the T-TRIPP project, namely Cards for Biosafety, MachiaCelli Switch or MachiaCelli Teams. These games can be played individually, but can also function as complementary to this workshop. For instance, one of the games (depending on which focus is most suitable with an eye on the workshop's case) could be played before the workshop to 'set the stage' and already create awareness for safety and risk-related matters amongst the participants.

Lastly, the report 'Samen voor Bioveilig - De noodzaak van een sterke interactie tussen onderzoek en beleid voor veilige biotechnologie.' by the Rathenau Instituut is recommended to researchers who want to gain more insight into the current governance ecosystem regarding biotechnology in the Netherlands.

Practical Tips

Due to covid-19, all workshops organised for the development of this manual were held online. We made use of Zoom and MS Teams, but every comparable platform could be used to host the workshop given that there is an option to use break-out rooms for the discussions in smaller groups. Furthermore, as online meetings are more tiring compared to physical meetings, we set the maximum duration of the workshop to 2.5 hours, including a 10-minute break. Also, when hosting online meetings, be aware that participants' connection problems cost extra time, and the possible malfunctioning of one's camera makes having a discussion online even more difficult.

When meeting physically, a whiteboard and/or post-its could be used for the plenary sessions. Also, the duration of the workshop could be extended although this would also depend on the complexity of the case, the agendas of the invitees and the desired outcomes of the workshop.

Survey

If you have organised a stakeholder workshop by means of this script, we kindly ask you to partake in the following survey: T-TRIPP Google Forms (the survey can be filled out anonymously and you do not need to log in or have a google account to fill out the survey). Through this survey, we would like to inquire how *you* experienced the workshop, whether it has been helpful and in what way(s). Also, through this survey, we aim to gain insights into what risks were identified, and the anticipatory strategies that were formulated. This information helps to keep track of the state-of-the-art in biotechnology, and to possibly identify trends in its development. The survey will take up approximately 5 minutes of your time. We thank you very much in advance.

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