Research Ideas and Outcomes 9: e105198
doi: 10.3897/rio.9.e105198

Research Article

How open science can support the 3Rs and improve animal research

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Reviewed v 1

Academic editor: Editorial Secretary

Received: 19 Apr 2023 | Accepted: 01 Aug 2023 | Published: 31 Aug 2023

Citation: Janssens M, Gaillard S, de Haan JJ, de Leeuw W, Brooke M, Burke M, Flores J, Kruijen I, Menon JM.L, Smith A, Tiebosch IA.C.W, Weijdema F (2023) How open science can support the 3Rs and improve animal research. Research Ideas and Outcomes 9: e105198. https://doi.org/10.3897/rio.9.e105198

Abstract

Open science in its broadest sense can make better science and provide benefits to researchers. When applied to animal experimentation, it can prevent unnecessary use of animals, because knowledge and experiences about past animal experimentation are shared openly to be consulted and used by other researchers. By extension, open science can accelerate the much anticipated transition towards animal-free innovations or New Approach Methodologies (NAMs). The purpose of this paper is to bring together and further share the preparations and findings of a symposium held at Utrecht University on aspects of open science that researchers doing animal experiments can and should take into account to improve their research and benefit themselves. The paper offers a one-figure guideline for that purpose.

Keywords

open science, animal experiments, research quality, 3Rs

Introduction

In 2021, the open science programme of Utrecht University and the Animal Welfare Body Utrecht (a body of Utrecht University and the University Medical Centre Utrecht supervising the welfare of animals used in science) joined forces to organise a symposium on open science and animal experiments (named: Better Animal Research through Open Science). We listed all the steps of animal research and showed how open science is relevant at each point. We turned the list into a symposium programme and an infographic in order to visualise these steps. We shared our figure on our websites and on social media and found out that it was appreciated and reshared on social media. We also shared the figure as a poster at the 2022 congress of FELASA (Federation of European Laboratory Animal Science Associations). The purpose of this paper is to share the figure further and offer some context and explanation, so that it can be applied more broadly.

The value of open science is unmistakably high and even more so in the case of animal experiments (see also Table 1) (Diederich et al. 2022). It can prevent unnecessary animal use and discomfort, for example, when researchers can find out through information about earlier experiences that their research plan is unrealistic, not rigorous enough, more harmful to the laboratory animals than expected or not as novel as they had hoped it would be. This can then also prevent unnecessary work for the researcher. Although these benefits are known already, what is missing from the literature is a concrete exposition of how open science directly benefits individual animal researchers and prevents unnecessary use of animals, accelerating the transition towards animal-free innovations and improving research.

Table 1.

The value of open science for research using animals in experiments.

Value of open science	Reason
Prevents unnecessary animal use	Possibility to find out that research plans are, for example, unrealistic, biased, more harmful than expected or less novel, or have been tried unsuccessfully before.
Better science	Possibility to include existing knowledge of and experiences with the research design.
Reduction of animal use	Possibility to assess reliability of studies and exact protocols, to prevent the need for replication or pilot studies.
Refinement of in vivo procedures	Possibility to find very specific details of refinements of in vivo techniques and apply them and, therefore, improve the welfare of laboratory animals.
Better professional networks	Possibility to find researchers working on similar topics in an early stage, for collaboration or exchange of ideas and experiences.

Value of open science	Reason
Better interaction with animal and patient NGOs	Possibility to learn from critical views on animal research, research questions and outcome measures; possibility to explain your research in a more understandable way.
Better interaction with the public	
Better interaction with the media	
Replacement and a faster transition to NAMs	All the above reasons, including improving research and animal welfare.

Open science can make science better when existing knowledge and experiences are included in the research design. Learning from each other's applications of the 3Rs (Replacement, Reduction and Refinement) can reduce animal use and enhance the welfare of laboratory animals. In the same way – by learning from each other's research and data – reduction of animal use and even replacement of animal usage can become possible.

Interaction with the public, the media and animal welfare and patient NGOs can lead to interesting exchanges, which can make it possible to learn from critical views on animal research. For example, such exchanges can lead to researchers contemplating the right questions and right outcome measures and, at the same time, it can help researchers explain their research and convey the usefulness and necessity of science to a wide audience. It can also make clear to critical parties how researchers apply the 3Rs.

Transparent and thorough reporting is crucial to excellent animal research. It allows the reliability of studies to be assessed, meaning that results can be relied upon. Additionally, it prevents the unnecessary use of animal lives in replication studies. As a result, this stimulates reduction in animal use. Transparent and open reporting of experimental design (in manuscripts) and protocols (by deposition in protocol repositories and regular updating) allows for exact reproduction of methods. This means that a technique can be adapted to a different study without the need for animal lives to be wasted in unnecessary pilot studies. This also stimulates reduction.

Reduction of animal use can also be obtained by sharing experimental data. Data sharing allows those data to be reused in other analyses, avoiding further unnecessary replication studies. Data from animal and human studies can even contribute to *in silico* and data mining NAMs (New Approach Methodologies).

Refinement of animal studies through learning from other experiments becomes possible when details of refinements of *in vivo* techniques are shared openly, so that they can be applied in other laboratories, reducing animal suffering during procedures.

Finally, transparent and open reporting of *in vitro* methods (e.g. NAMs) that are used in combination with *in vivo* methods, helps to build confidence in those (already validated) techniques as credible replacements for animal studies, accelerating the transition to non-animal methods (replacement).

All this together can lead to a faster transition towards NAMs. By connecting to other networks, researchers can find inspiration to create solutions for issues that hinder this transition. Out of the box ideas about directions to take for designing NAMs can come together and make things possible.

In preparation for the symposium, we laid out the steps a researcher should take to apply open science to animal research. This figure was taken as a guideline to compose and guide the symposium. This guideline is shown in Fig. 1 . Although in practice the steps will intermingle, we put them in a logical order to make the figure more easily applicable and practicable.

Figure 1. doi

Steps for applying open science to animal research.

Open Science

Open science is a movement which stands for a way of working that is as open and transparent as possible in all stages of the research process. Elements of open science are open education (De Knecht et al. 2021), public engagement (Boon et al. 2022), openly sharing results and being open about the research flow. The overall aim of open science is to increase the quality, progress and scientific and societal impact of research and scholarship (see also Fig. 2) (Fecher and Friesike 2014, Miedema 2022).

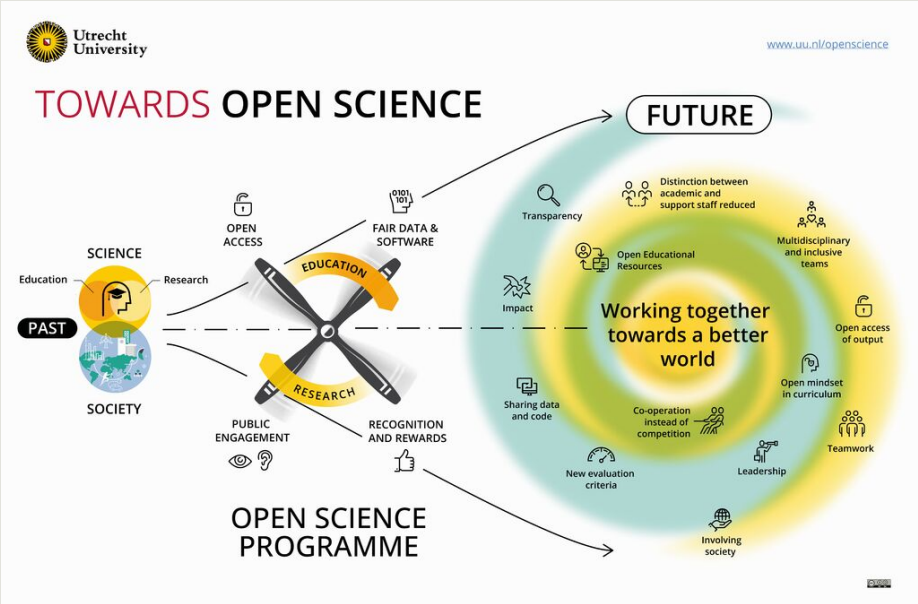

Figure 2. doi

The route towards open science in education and research at Utrecht University.

Various movements and causes have led to what open science looks like today. The emergence of the internet has made a huge contribution, as it removed printing as a limiting factor of publishing. At a certain point, libraries had to select for which journals a prescription would be necessary and, further down the line, they started advocating open access publishing, because their main goal is to make knowledge widely available and accessible. Open access publishing further opened the door to openly sharing not only articles, but also data, code, methods, protocols and software with the rest of the world (Fyfe et al. 2017).

Around 2010, there was an increase in evidence that the biomedical field had a huge problem with translation of preclinical research to clinical practice, so-called translational failure and with replicating studies, the so-called replication crisis (Ioannidis 2005). Studies showed poor quality and low reproducibility of research. High competition, positivity bias and a very narrow and one-sided evaluation system are a few of the reasons leading to this translational failure and replication crisis. Open science is part of the answer to these issues. By being transparent, the quality of the research can be assessed and thereby stimulate the enhancement of quality. Preregistration, for example, can help to reduce publication bias of only positive results in clinical trials in cardiovascular disease (Kaplan and Irvin 2015) and psychology (Scheel et al. 2021) and also increase the rigour of methodology and analysis (Soderberg et al. 2021). Transparent methods and data will give the opportunity to reproduce (and replicate) the study, thereby making the conclusions more robust.

By publishing open access, knowledge will be widely available to move the whole community forward. To achieve this, it is essential to also adapt the assessment system to the standards of open science. If researchers are judged by the quantity of publications instead of quality, where they publish instead of what they publish and the values of open science are not integrated into funding requirements, there is relatively less incentive to be transparent and open. Therefore, at all levels, the recognition and reward system is also an integral part of the open science movement (Miedema 2022).

We will now explain in brief the steps a researcher should take to apply open science to their research as presented in Fig. 1: PREPARE, INFORM, DESIGN, PLAN, PREREGISTER, CONNECT, EXCHANGE, SHARE, ARRIVE and PUBLISH.

PREPARE

It is no coincidence that the preparations for a study constitute the first step on the pathway to ethical and scientifically valid research. Nowadays, no one performs animal research in isolation: a large number of professionals need to be consulted by scientists. These include, not least, the staff who will be caring for the animals, managing the animal facility and performing procedures. Laboratory animal professionals will also be able to advise scientists on how to search for 3R alternatives: Replacement, Reduction and Refinement. Each stage of the research project must be described, discussed, evaluated and communicated to all those involved. In this way, there will be no doubts about practical issues, such as responsibilities for the various stages, the division of labour and costs and communication of the results from the research. These must be finalised before the research starts.

PREPARE consists of guidelines for planning animal experiments and complements reporting guidelines such as ARRIVE (Norecopa 2023). There is some overlap of topics and both should be read before a project is started, but they address different needs.

PREPARE is the result of over 20 years' experience in managing accredited laboratory animal facilities, design and supervision of animal research and discussions on courses in Laboratory Animal Science for scientists, animal care staff and veterinarians. PREPARE consists of a 2-page checklist, available in over 30 languages and three formats and a website. The website expands upon the topics on the checklist and provides links to quality guidelines and scientific papers for each topic. PREPARE is offered to funders, institutions, scientists and animal care staff on a voluntary basis to help them in their work of preparing for studies which appear to involve animal use (Smith et al. 2018).

By ensuring adequate planning, scientists should find that their research is easier to publish. They will already have thought about and reacted to issues which they may be confronted with at the reporting stage, when they are asked to demonstrate compliance with the ARRIVE guidelines: "We ARRIVE'd because we were PREPARE'd".

INFORM

Organisations within the European Union (EU) that conduct animal experiments are required to provide a Non-Technical Summary (NTS) in one of the official languages of their country (Directive 2010/63/EU on the protection of animals used for scientific purposes, Article 43). All NTSs are published in a central database, the AnimaL Use Reporting EU System (ALURES) (European Commission 2020). To comply with that requirement and, at the same time, reach out to a lay audience to explain your research in a transparent and accountable way, as was recommended in section Introduction, it is helpful to apply the following rules of thumb (European Commission 2023b).

Use every-day words

'Intravascular' is the same as 'in the veins'. 'Subcutaneous' means 'under the skin'. A 'neuron' is a 'nerve cell' to ordinary people. 'Epistaxis' is 'nose bleeding'. If it is hard to come out of a jargon bubble, use a dictionary, try Wikipedia or ChatGPT or call your aunt or uncle and explain your research to them in simple words. Unless they are scientists, of course.

Make the title short and clear

Imagine this project title: 'In situ engineering of vascular access grafts'. It is short, but difficult. Using simple language that explains what it is really about would lead to this title: 'Creating new vessels for patients with kidney failure, through local tissue constructions'. That is too long. The short version is: 'New blood vessels for patients with kidney failure'. Don't worry if you lose some scientific precision. The simple title in the NTS is what it means to the public.

Cut long sentences into pieces

Let us try this sentence: 'Freshwater bathing, although effective at removing the amoeba from the gills, can result in increased levels of fish mortality due to the stress associated with exposure to freshwater when the salmon have reached a saltwater life stage' (European Commission 2022). It is rather long, right? Our version would be: 'Freshwater bathing removes the amoeba from the gills. However, it can lead to more salmon dying of stress when they reach a saltwater life stage.'

Distinguish between objectives and benefits

Your objective is about what you are trying to find or do: Finding a medicine for… / Finding out how… works. Benefits are what it will bring patients (now or in the future) or science, such as: less pain / less people inactive / knowledge about…

Add what the laboratory animals experience

The NTS form asks about 'predicted harms', but it does not really ask what the animals will experience. However, this is exactly the information that people who are concerned about

laboratory animals are interested in. Thus, we recommend to tell a bit more about that instead of limiting yourself to the clinical signs. Instead of stating ‘Predicted harms can be weight loss’ you could write ‘Mice are operated in the stomach under anaesthesia. After recovering, they might experience pain and/or an overall bad feeling, which could result in weight loss.’

Use spelling control to check your final draft for typos

This rule of thumb is the easiest to apply, but possibly one that is the least applied.

Ask for help

If you are not a native speaker, ask a colleague who can take a critical look. Ask your communications department or press officer for some last comments. It is their expertise. Be open to it and you will create a good basis to communicate your research results to a broad lay audience later (see section SHARE).

DESIGN

Basic science training does not always prepare researchers sufficiently to design animal experiments properly. Animal research faces the challenge of dealing with relatively low numbers to detect specific characteristics or small induced differences in animals with potentially high biological variation. This is a challenge that needs rigorous design with a good predetermined statistical analysis plan.

Analysis plan

Planning the analysis in advance means that your hypothesis is very clear, as well as your knowledge on variation, relevant differences you mean to detect (giving a signal to noise ratio) and risk of false positive or negative interpretations. This allows you to establish the right parameters and number of animals needed to validate answers to the biological questions you have and to transfer that into the best design for which analysis can be planned (Gosselin 2018). However, even then, risk of bias needs to be assessed explicitly in the next step before you start.

Bias prevention

Two of the most important tools for preventing bias in data values can be achieved by randomisation and blinding (Macleod et al. 2008, van der Worp et al. 2010). However, this requires careful planning and cooperation as well as knowledge of relevant variables to be randomised and methods to do so effectively. Additionally, one should establish predetermined exclusion and inclusion carefully which reflects again on the analysis plan.

Training

Guidelines like PREPARE (Smith et al. 2018) and ARRIVE (Percie du Sert et al. 2020) already state the importance of the above, but still, proper training can be extremely helpful

to learn how to address this correctly and effectively. In experimental design training, dedicated to animal research, you can obtain an overview of what is needed to design your experiment, to optimise the chance of generating sensible results. You learn that such a design is an integrated consideration of animal welfare, the ethical use of animals, financial and/or technical limitations, the risk assessment of several types of bias and the right choice of statistical analysis. Sometimes, creative problem-solving is needed to find the best way of taking all of these factors into account. Only by mastering them all, one can make educated choices towards the optimal design of an animal experiment in practice.

Tool for experimental Design

Specific support for researchers designing *in vivo* experiments is available via the NC3Rs Experimental Design Assistant (EDA) (NC3Rs 2019). The EDA is a free online tool, with a supporting website, that helps researchers design more robust *in vivo* experiments. It uses computer-based logical reasoning to provide bespoke feedback on and highlight the implications of researchers' experimental designs and recommend the most appropriate statistical test(s) for an experiment. The EDA also provides dedicated support for carrying out sample size calculations, performing randomisation and implementing blinding. In the EDA, experiments are represented by diagrams, which can be shared between users to help plan and critique experiments. Researchers can also export a PDF document that summarises key experimental design information, which can be used to communicate experimental plans within and between laboratories, be included in grant submissions or shared with ethical review committees.

Tools for training

Free online tools to support training are available and can be used in scientific training dedicated to the design of animal experiments. One was made with support of the European Committee for harmonisation purposes within the EU and to train according to learning outcomes of module 10 and 11 as stated in the guidance document on education and training, based on Directive 2010/63/EU (Guidance on Education and Training) (European Commission 2014) and these online modules were published on the 'Education and Training Platform for Laboratory Animal Science' (ETPLAS) (ETPLAS 2014). Other resources are made available by the 'Enhancing Quality In Preclinical Data' (EQIPD) consortium focussing on the generation of robust pre-clinical data (EQIPD 2017). They gather all info and add new info where needed. By using online training tools, you can concentrate on training researchers, saving yourself the time to develop these background resources.

PLAN

Data Management Plan

Creating a Data Management Plan (DMP) is another step in the list of preparations before starting an animal study. When the study design is there, a more technical exercise is to think ahead about the data tools and infrastructure available and whether or not they can

cover all the needs of data collection, storage and sharing during the project. It is tempting to fill-in a DMP quickly, by simply checking boxes and copying default answers. However, there are many reasons to not just tick the box, but to think ahead and plan carefully how the data will be managed during the research. Many points in the DMP, mainly on the technical data infrastructure, can be filled in very similarly for all projects at the same institute. Having these generic points pre-filled in saves time. The focus should be on the project and data type specific elements of the DMP and on properly following-up whether the data was managed correctly.

There are ample examples of hard drives that crash or are suddenly full or essential software companies that go out of business. This can be prevented by planning ahead and thinking of all the data that will be produced and used during the project. In the long run, that is faster and more efficient, which (potentially) saves researchers precious time and money. A DMP also often asks researchers to think about making their data open and to describe how they plan to do it. By thinking about it at an early stage, the data can be prepared and organised in such a way to facilitate opening the dataset. This attains even more importance when privacy is involved.

At this point, there is not one single template to write a DMP. Yet, many funders and institutes do ask for very similar information and all revolve around the FAIR Principles (Wilkinson et al. 2016). Using DMP Online (DMPonline 2023), researchers can use the different templates and obtain guidance throughout the form. The main points in all templates are: Data exploration, data storage and archiving and data sharing and reuse. Since the similarities in all forms are clear, most funders now also accept DMP templates from other institutes (NWO 2023), which makes filling these in easier.

Data exploration

Data exploration deals with determining the research phases in which data are generated, as well as assessing the availability of adequate storage space and processing power. Schematic visualisation of this process quickly shows if data need to move from the animal facility to an office or across borders. Some data formats can only be used with proprietary software or tools (i.e. Excel (.xls), MATLAB (.mlx), SPSS(.sas)) and this limits the availability of the data. To circumvent this, consider converting or exporting the data into an open format such as .csv or .txt whenever possible.

The largest distinction between data types is between physical and digital data. The DMP focuses on digital information. These data can be divided into sensitive and non-sensitive data. Sensitive data contain personal or identifiable information, that is subject to strict European regulations (European Commission 2023a). However, the absence of sensitive information does not mean that all other data are freely available or should not be secured, only that it is not subjected to legal regulations. Sensitive data collection should be limited to necessary information only and access to the data should be limited to only those who need the information.

Data storage and archiving

The exploration phase results in a (rough) estimate of the data types and storage needed. The available storage should allow access or sharing for those who need it and not for those who do not need it. It is often overlooked that the need for data storage extends the project time. A common research standard is to have data underlying a publication available in storage for at least 10 years. This is often stated in institutional policies. Research hospitals may expand this to 15 years for medical research involving humans. Once a project is finished, the data should be archived, which is not the same as simply 'not deleting it'. Archiving the data ensures that data for a certain paper, calculation or outcome, can be easily retrieved, that raw data cannot be overwritten and that the process of data analysis can be repeated using the archived dataset. In short, once finished, the data should be described, secured and moved to the archive storage. Archiving may come with storage costs. Although these costs are generally not too high, storing data for any amount of years still needs to be funded.

Data sharing and reuse

Sharing data is the main motivation for writing DMPs. To share research findings via journal articles is and has been the main road to sharing knowledge. Yet, to fully build further upon prior knowledge, re-analysing or verifying the data related to the publication is essential. Therefore, this section addresses how sharing can be reported in the DMP. The section SHARE contains detailed information on what is necessary to effectively share data. This again revolves around the FAIR Principles (Wilkinson et al. 2016), ensuring that data can be reused.

Facilitating the reusability of data (such as excel-files, code, images etc.) can often be time-consuming. Similar studies may result in datasets that vary in various aspects, from formats used to field names in tables. Yet, reuse works best when similar datasets can be grouped and combined with relative ease: this can be achieved by using standardised metadata (see also section SHARE).

The benefits of proper data management, not just filling in the DMP, are clear and will benefit both the lab that has their data management at par and (animal) science in general in the long run.

PREREGISTER

Once a clear data management plan and protocol has been designed, the next logical transparency step is to preregister.

Preregistration – the act of registering a research protocol before the start of the experiments – anchors transparency early in the research process. When registering their research protocols, researchers display a priori their hypotheses, study design and analysis plan (in an openly available source). Consequently, it is easier to proceed with preregistration once the first transparency steps (sections PREPARE, INFORM, DESIGN)

have been accomplished. Once preregistered, the protocol receives a unique persistent identifier that researchers can use to refer to it and a time stamp to prove the date of registration.

Preregistration enables later comparison of the planned approach with the final manuscript and, hence, increases reliability and trustworthiness of the results reported. In this context, reporting biases (e.g. selective outcomes reporting) or questionable research practices (e.g. creating a hypothesis after results are known, p-hacking) can no longer prevail (van der Naald et al. 2022). Furthermore, some platforms enable linking manuscripts or data to preregistered protocols. This increases the probability that studies which usually have a lower chance of being published, will remain accessible (e.g. interrupted studies, negative data). This promotes the reduction of publication bias. Altogether, preregistration increases reliability of the planned approach and the final results.

On top of this, preregistration does not only benefit the registrants. Indeed, this process makes available methodological information that is otherwise overlooked or dismissed in publications, which helps reviewers' understanding, but also increases reproducibility. Above all, by browsing the registries, researchers can easily have an overview of existing (ongoing) animal studies and, thus, avoid unnecessary duplication (van der Naald et al. 2022).

Despite these advantages, animal study preregistration is not yet a common standard, partly due to concerns and lack of awareness. Below is some information on the practical process and answers to recurring concerns about preregistration.

Where to preregister?

As of 2022, two platforms exist for animal study protocols preregistration: preclinicaltrials.eu (PreclinicalTrials.eu 2018) and the animal study registry (Animal Study Registry 2019). They both use a format of "form to fill" to register, which complies with the ARRIVE guideline. Of course, the use of broader repositories, like the Open Science Framework, is also possible and valuable.

Safety of the preregistered protocol

Platforms like preclinicaltrials.eu have an embargo to protect ideas and intellectual property. This feature ensures that the study designs remain a priori defined while being hidden until a later date. If needed, information about intervention or procedure can also be blinded.

Flexibility

Once preregistered, the protocol is not fixed and can easily be amended to allow unpredicted research changes and enable research creativity. A change in methodology is never an issue, as long as the reasons behind it are clearly explained.

Time management

One might believe that registration will be time-consuming, but that is actually far from the truth. With a well-prepared protocol, preregistration can be fast and easy – so to register efficiently, use the final version of your protocol rather than a draft. Besides, the time taken is well invested, as a well-planned study can save a lot of time later in the publication process.

Eligibility

Despite common beliefs, all animal studies, regardless of their type (i.e. exploratory or confirmatory), are valuable for preregistration.

Once your preregistration is finalised, the experiment can start and, with it, connection and communication around and about your research.

CONNECT

When communicating and connecting with the public, including NGOs and research organisations, academics contribute to society in a crucial way (Geller et al. 2002). This is even more true for an ethically sensitive subject, such as animal experimenting. Connecting with journalists and joining the public debate via online and offline media help share valuable research insights and difficult ethical considerations with interested individuals. This can then lead to receiving helpful insights from partners in society.

When employing easily comprehensible language, particularly in accordance with the guidelines outlined in section INFORM for the Non-Technical Summary (NTS), the potential audience for such forms of public engagement surpasses the audience reached by publishing scientific papers and the NTS. Although the NTSs are written for a lay audience, it cannot be expected that the ALURES website (European Commission 2020) of the European Union where they are published is found on a large scale by said audience.

This increased visibility allows individual researchers to connect with the general public and with specific groups within the public, such as healthcare professionals, patient organisations, animal advocates and policy-makers. It makes science more open, as it opens the door to new contacts and collaborations, new input and ideas, valuable feedback and the possibility to learn from critical views. The benefit? Better research and better public accountability overall.

How to achieve this? Start with these four key tips:

If you want to be found, put yourself out there. Publish an informative and easy-to-find online profile page that clearly states your area(s) of expertise. Use the same name everywhere and have a good, recognisable portrait photo taken. Mention if you speak multiple languages and share media items and video content that you are proud of.

Tap into the news and show your expertise. Tap into current affairs and react to the news by sharing your area of expertise. For example by writing a (guest) blog for a website, a Twitter thread or an opinion piece for a local or national newspaper.

Formulate your key message. What is the key message the audience should remember, and why should they care? Summarise those elements in one sentence or one paragraph at most. Always keep your key message clear, short and free from jargon. You can enrich it with examples, numbers and anecdotes in the following paragraphs of your text or the rest of the interview.

Get support. Reach out to your organisation's press officer or communications department and tell them about the relevance of your research and how you would like to connect with journalists or join the public debate. They will be able to help, also in case you receive baseless criticism, insults, intimidation or threats.

EXCHANGE

Besides connecting with the public, it is also vital to exchange and share with your colleagues not only information and data, but also tissue and other physical materials.

In biomedical research, animals are also used as sources of tissue. This often involves no more than a single organ or a small piece of tissue. In most cases, the remains are either destroyed immediately after collection or are kept in freezers. However, the existence and availability of this material is often unknown to other researchers.

In addition, a substantial amount of redundant laboratory animals – those with no research purpose – remain unused (NVWA 2020). These are healthy animals that are redundant after use in breeding, animals that have been bred, but for which there is no useful destination or animals that are alive and healthy after use in an experiment. These healthy surplus laboratory animals can possibly be used in (other) experiments and take the place of laboratory animals that otherwise would have to be bred for this purpose.

When fellow researchers know in time which tissues and organs will become available and researchers inform colleagues in time about which organs or tissues they need, this creates the opportunity to make better use of laboratory animals. As a result, fewer laboratory animals are needed overall.

To bring together supply and demand of surplus animals and animal organs and tissues, the 3Rs Centre of Utrecht University and the Animal Welfare Body Utrecht initiated the web-based Animal and Tissue Exchange platform ATEX. The platform makes supply and demand visible in a user-friendly way and, thus, contributes to better use of animals, organs and tissues. It works for live surplus laboratory animals and fresh or preserved organs and tissue. It is a form of open science that connects peers who are willing to make the small effort to use the database and be open about what they either have to offer or will be needing soon in terms of animals or animal tissue.

ATEX was established by Utrecht University and the Utrecht University Medical Center, The Netherlands. External researchers can request for an account. The plan is to have other institutions join as well. One of the long-term objectives is also to gain insight into the available collections. There are research groups that maintain collections of preserved tissue. These collections are not always known to others in a transparent way. Making all available tissues findable via the platform would be a good step forward.

SHARE

Sharing data is an important aspect of research transparency and integrity. It enables other researchers to see your work in a raw format, so that they see how you arrived at your findings. Understandably, it may also be a scary process as it opens you up to scrutiny. However, this ought not to be feared, but embraced as a motivator towards creating robust and resilient datasets that can stand up to critique, benefitting you in the long run. Adding a dataset to your journal publication improves the findability of both the dataset as well as the article and may lead to more readers, downloads and citations (Colavizza et al. 2020).

Sharing data — as well as the actual organs or tissue as described in EXCHANGE — is also necessary for re-usability. Animals are a precious resource and the data we extract from them are rich and unique. It is easy and perhaps defeatist to assume that only your hypothesis can be tested from the data you have extracted. Especially when we use many automated means for observing and recording animal behaviour. Particularly, animal output from video and from operant conditioning chambers often record more variables than we can possibly analyse. It is for these reasons that sharing data can be unknowingly valuable to others who may be searching for aspects of behaviour that you may have overlooked when focusing on your own hypothesis. That is not to say that every dataset on animal behaviour will be re-used. However, if you have already established a transparent and managed workflow of your data, the steps required to share the data become negligible. Additionally, data can be shared with readers, reviewers and funders if needed. The time spent on making data reusable is related to rate of reuse and rate of total sharing. The quicker we share, the faster it benefits the scientific community (Pronk 2019).

If a dataset is relatively small (below 50GB), it is not difficult to publish the entirety of the raw data along with all the processing steps thereafter. Although storage space can be a limiting factor, it is one that can be overcome. More attention ought to be placed upon the accompanying data, the documentation and metadata, that you will make available alongside your data to make sure others can find it, read it with ease and use it without hesitation or doubt. This includes documents detailing data level metadata about your animal subjects and their environment (i.e. species name, day/night cycle, housing, grouped/paired/solitary, enrichment etc.). Even though this may be information that can be found with ease in the methods section of the underlying publication, it is strongly recommended to provide this information in a .csv file or .txt document. Information about equipment, equipment settings, painkillers and anaesthesia can also be added in such a document (Fugazzola et al. 2022).

Similarly, the data you plan to share should be in formats that can easily be read by others and are interoperable. Although excel files are common ways of working with tabular animal data, a .csv file is far more interoperable.

When to share?

Ideally you would share your data immediately upon publication of the journal article. However, it is also well accepted to provide an embargo (delay) on the data publication to some months after the initial paper publication. A reason for delaying the publication of your data may be because you have plans to publish another paper with the same dataset. The funder may require to share upon publication or project completion as well.

Considering that you pre-registered your dataset (see above in the section PREREGISTER), then there would inevitably be a journal publication. Nevertheless, if you for whatever reason decide not to publish an article and the data are sound, then you should proceed to sharing the data anyhow (see also below in the section PUBLISH).

How to share?

The easiest way to share your data is to use a data repository, either field specific or generic. A field-specific repository, such as methodology-specific or species-specific, will increase the findability within the field, but can be difficult to find and limit the overall visibility of the dataset. Sites such as Re3data or FAIRsharing can help you find such repositories (FAIRsharing.org 2009, Re3data.org 2012). As sharing data becomes more widespread, field specific repositories may become more common but, in the meantime, it is well accepted to use generic repositories, such as Dataverse, Dryad, Open Science Framework and Zenodo (Dryad 2008, Open Science Framework 2011, Zenodo 2013, DataverseNL 2014).

Reduce the time needed to share a dataset by preparing a DMP, using metadata standards and a data repository. Your dataset is then easily found and reused, not only by others, but also by your own future self or a future colleague in your department.

ARRIVE

Transparent and accurate reporting is a cornerstone of open science. If an animal study is to influence future research, policy and clinical practice, it is essential that it is reported in enough detail that its reliability and methodological quality can be assessed and its methods can be reproduced. Evidence suggests that scientific publications describing animal research very often lack important information, limiting their usefulness to readers (Kilkenny et al. 2009, Macleod et al. 2015).

The ARRIVE guidelines are a checklist of reporting recommendations, designed to help researchers ensure that *in vivo* experiments are reported transparently and thoroughly (Percie du Sert et al. 2020). The guidelines list 21 items (pieces of information) that should be included in any manuscript describing animal research. They cover a variety of topics,

including some items that are important for understanding the internal validity of experiments, some that address reproducibility and others that provide details of the context and scientific relevance of a study. Each item is accompanied by a comprehensive explanation (Percie du Sert et al. 2020a), giving details of the background and rationale for its inclusion in the guidelines and providing illustrative examples of good reporting from the published literature.

To facilitate their implementation, the guidelines are prioritised into two sets: The Essential 10 and The Recommended Set. The Essential 10 contains the items that represent the basic minimum information that should be included in any animal research manuscript. Without this information, the reliability of a manuscript's methods and results cannot be effectively assessed by readers. The Recommended Set complements the Essential 10 and adds important context to a study. Prioritising the guidelines in this way allows researchers, journals and other organisations to focus initially on the reporting of the most crucial pieces of information (the Essential 10).

The ARRIVE guidelines are endorsed by over 1000 journals and many major research funders around the world. Consulting them during the conduct of a study and when writing a paper can help to ensure that all the relevant experimental information is collected and included in a manuscript. The guidelines also contain detailed information on good experimental design, which is helpful to consult during study planning, to help researchers to design rigorous and reliable experiments.

Reporting in line with ARRIVE helps to ensure that *in vivo* studies are not replicated unnecessarily, which can occur when the reliability of published findings cannot be evaluated. Transparent reporting also ensures that animal lives are not wasted in follow-up studies, based on unreliable results. Complying with ARRIVE when reporting can, therefore, contribute to reduction in animal use.

PUBLISH

Publication is an integral aspect of our research environment: it facilitates the sharing of knowledge, it tracks the accumulation of knowledge and its products serve as a repository for knowledge. If we want to answer a question, what is our first step? Some sort of literature review, of *published* papers. Published literature helps us to, for example, generate new hypotheses and formulate precise questions for future studies. Publishing standards determine what is published, which, in turn, determines which research is easily available and which research can serve as guideposts for future science.

It is reasonable to assume that researchers aim to have a system for publishing that would make all ethical, methodologically sound scientific research readily available to our peers. However, not all research is published. Positive publication bias refers to tendency in academia to predominantly submit and publish positive results. As a result, a significant portion of research lacking positive outcomes remains unpublished. Consequently, such research remains unknown to researchers other than the author(s) (Mlinarić et al. 2017).

Nevertheless, these are important contributions to our knowledge economy, which unfortunately remain in proverbial file drawers, never to be seen by the scientific community, never to stimulate a question or direct the choice of method. If we want to improve science, we ought to improve how we deal with these sorts of research products.

First, we need to consider the impact that positive publication bias has on the availability of evidence. In order to practise evidence-based medicine, we need to have a clear and robust understanding of what the total evidence actually *is.* When negative and null results are excluded from the picture, we are automatically going to be dealing with a less-than-complete picture. Let us consider the well-known example of antidepressants in the treatment of unipolar depression (Ghaemi et al. 2008). Around the turn of the century, the detrimental impact of the positive publication bias began to receive more attention within the biomedical research community. With this greater attention came greater scrutiny, eventually culminating in a review conducted by the United States' Food and Drug Administration. This review found that the available, i.e. published, literature vastly misrepresented the efficacy of antidepressants in the treatment of unipolar depression. When reviewing the published literature, 93% of randomised control trials (RCTs) showed a positive, or statistically significant, result. However, when the unpublished *negative* results were considered, this statistic dropped significantly. The total available evidence, published and unpublished, showed that 51% of RCTs had a positive outcome and 49% had a negative outcome (Ghaemi et al. 2008). In conclusion, positive publication bias can deeply warp our understanding of treatment efficacy and the practice of evidence-based medicine.

A second, perhaps more invisible, but equally harmful impact of the positive publication bias, is the treatment of living subjects. We want to limit the degree and frequency of harm and suffering living subjects are exposed to. However, if negative results are not shared, then unsuccessful research must be simply repeated in independent laboratories across the world by researchers who have no knowledge that others have already tried and failed with the same approach. This has material consequences – resources are wasted, grant money is wasted, time is wasted – and this practice also ensures that the frequency of animal testing and experimentation is going to be unnecessarily increased. The positive publication bias, thus, has a direct link to the infliction of unnecessary harm upon living study subjects (Hey 2018).

The third and final negative impact of the positive publication bias that we would like to address is more personal. There is a pervasive 'publish or perish' culture in academia. This moniker is given to the cultural expectation within academia that researchers ought to be judged on the basis of their research output, i.e. the frequency of their publications (Rawat and Meena 2014). It has long been known that this culture has deleterious impacts on the well-being of researchers and can have severe impacts on career trajectories for early career researchers (ECRs). Open science initiatives, such as improvements to rewards and recognition systems and the diversification of career pathways, have been initiated in an attempt to ameliorate the impact of this "publish or perish" attitude.

Negative and null results are the product of good research practices and, thus, ought to occupy the same status as positive results, including being recognised as research

products, i.e. published papers, that can count towards an individual researcher's publication count. While we are optimistic that the academic culture will eventually come to embrace these novel recognition and rewards systems, in the meantime, the publication of negative and null results can relieve some of the stress produced by the intersection of the positive publication bias and the "publish or perish" culture.

Conclusions

We provide in this paper a concise overview of the most important steps that contribute to open science within animal research, including tips and benefits for individual researchers. Open science allows for greater transparency, replication of studies and collaboration amongst researchers. Starting with the stage where animal researchers prepare their study, in close collaboration with the animal facility (PREPARE) and ending with publication (PUBLISH), we highlight the most important steps a researcher using animals should take to apply open science to animal research. Although in practice the steps will intermingle, we put them in a logical order to make the accompanying figure (Fig. 1) more easily applicable and practicable. This figure was used as a guideline to compose and guide a symposium on the use of open science for animal research and forms the core of this article.

Through this figure, we have shown how using open science tools and methods during all steps of animal research benefits not only individual researchers themselves, but also laboratory animals and relevant societal stakeholders, such as funders. Sharing all aspects of scientific research, including data, methods, materials and results, allows for greater transparency, replicability of studies and collaboration amongst researchers. By making information about past animal experimentation openly available, researchers can consult and use this information to design their own studies in a way that reduces the number of animals used. This not only benefits the animals but also improves the quality of the research by reducing the chances of repeating experiments that have already been done.

Author contributions

Matthew Brooke: Writing - Original Draft and Writing - Review and Editing.

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Conflicts of interest

The authors have declared that no competing interests exist.

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