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Global Spotlights

Preclinicaltrials.eu: prospective registration of animal studies

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Preregistration: the next step in animal research

Animal studies play an essential role in biomedical research, including a significant portion of cardiology studies. However, concerns have been raised regarding their validity, robustness, and quality of reporting.[1] This can manifest as insufficient reporting of study designs and methodological details, which hinders understanding and accurate evaluation of internal and external validity, as well as statistical robustness. Moreover, reporting biases, including selective outcomes reporting and publication bias, worsen these limitations and increase the risk of unnecessary duplication of animal studies due to limited data access. Questionable practices like hypothesizing after results are known (HARKing) or p-hacking further undermine trustworthiness. Biases and poor reporting lead to wasted resources and jeopardize the reliability, accessibility, and ethical justification of animal research.[1]

To overcome these issues, various methods and tools have been implemented to enhance the planning, execution, reporting, and sharing of animal research. Examples include the adoption of guidelines such as PREPARE and ARRIVE, as well as the practice of preregistration. Preregistration, or prospective registration, consists of recording a protocol prior to the start of the experiments. Typically, a protocol includes the hypotheses that will be tested, information about the outcome measures, details on measures taken to reduce bias (e.g. randomization and blinding), a justification of the chosen sample size, and an analysis plan. This information will usually be made available publicly upon registration or after a given time.[1,2]

Past research has shown that preregistration and the use of registered reports have positive effects on clinical and psychology research, notably by improving reporting and publication of neutral and negative data.[3–6] While considered of added value and therefore mandatory for many types of clinical research, preregistration has only just started to emerge in animal research. Preregistration of animal study protocols yields similar benefits by:

- *Increasing transparency and improving reproducibility*, by disclosing *a priori* the study intentions in detail and making them publicly available. This also helps prevent involuntary duplication since it is mandatory to conduct a (systematic) investigation before commencing new animal studies to avoid repetition, formulate pertinent research questions, and optimize the animal model.
- *Reducing biases, questionable practices, and increasing accountability*, by enabling the community to compare publications with the preregistered study protocols, a strong incentive is created for investigators to report deviations from the planned approach in their publication. If such deviations are not reported, the cases of HARKing, selective outcomes reporting, or p-hacking can be more easily detected, and thus, interpretation of study results improves.
- *Providing a complete overview of all animal studies and reducing publication bias*, by displaying all studies, including those that remain unpublished and by giving the possibility to share or link protocols to related data.
- *Promoting proper study design*, by encouraging in-depth consideration prior to starting the experiments, especially about methods to reduce risk of bias.

Due to the novelty of preregistration in preclinical research, still only a limited number of registries exist to facilitate animal study preregistration, among which preclinicaltrials.eu.[1,2]

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Preclinicaltrials.eu: a platform dedicated to animal study preregistration

In 2017, we launched preclinicaltrials.eu: the first platform dedicated to animal study protocol preregistration (www.preclinicaltrials.eu).[7] This platform is an online registry accepting all animal studies from basic to translational research, which aims to provide an overview of (ultimately) all animal study protocols. The platform is currently hosted on the servers of Utrecht University and affiliated with the Netherlands Heart Institute. Since 2020, the Dutch Ministry of Agriculture, Nature and Food Quality has been funding the platform.

Several stakeholders, including university medical centres, animal welfare bodies, and individual researchers from the Transnational Alliance for Regenerative Therapies in Cardiovascular Syndromes (TACTICS[7]) group, supported us during the development of this initiative to create a robust and solid base. Their help was valuable in the design and validation of our registration form, creating a sufficiently detailed form to impact research rigour while minimizing additional administrative tasks for the researchers. Since its creation and several years since its launch, researchers' concerns have been and remain a priority. Therefore, we created several solutions to ensure that preregistration could be as safe and easy as possible, e.g. by preventing the risk of data theft and threat to intellectual property via an embargo option and reducing administrative burden to a minimum (*Table 1*).[1]

To date, the registration process is easy, free, and anonymous (*Figure 1*). The registration form can be swiftly completed by using an ethical approval form as a basis, which typically contains all the necessary study protocol details. Based on our experience with Dutch protocols, preregistration can be accomplished within 20–30 min on average. Additionally, data export functionality between protocol management software and the preclinicaltrials.eu platform has been established to streamline the preregistration process, making it a matter of a few clicks to register.

When submitting a protocol, researchers can use an embargo to protect their data or even blind part of the methodology (*Figure 1*). The protocol will remain concealed until the end of the default 1-year embargo period, with the possibility of multiple extensions if justified (e.g. delays, need more time to publish, and patent application). Embargo extensions are validated case by case by an administrator. Furthermore, researchers' personal information is anonymized, except for the institute where the experiment takes place, and users are required to create an account and log in to access complete protocols, adding an extra layer of protection. An encrypted chat system is available to facilitate collaboration and enable contact with authors. Lastly, users have the flexibility to modify their registered protocols an unlimited number of times, while all previous versions remain available.

Since its introduction, preclinicaltrials.eu has gained global recognition for its role in promoting rigour in animal studies. The initiative received multiple awards, e.g. Science-based Refinement Award from the Johns Hopkins University Center for Alternatives to Animal Testing and 2nd place Cochrane-REWARD prize, and has been presented at international congresses, e.g. FELASA 2022, WC 11th and 12th, EUSAAT 2022, and ESCI 2023. Several funding agencies within the Netherlands support preregistration and make it a requirement or recommendation for animal studies (e.g. Netherlands Organisation for Health Research and Development, and Dutch health foundations). Currently, >2000 users from both industry and academia have embraced the platform in over 30+ countries worldwide.

Table 1 Concerns voiced by investigators and solutions offered by preclinicaltrials.eu

Concerns	Solution
Cost	Free submission of protocol
	Free use of database
Administrative burden	Data export from existing study protocols and software
	Guiding documents
	Personalized help (registering live with the researchers)
Limited flexibility/creativity	Tracked-changed amendments allowed
Misuse by animal activists or data hackers	All data are encrypted to prevent misuse
	Log in required to see protocols
	Anonymous registration
Data theft	Embargo
	Blinding of (part of) the methods
Threat to intellectual property	Embargo
	Time-stamped protocols

Unfortunately, despite international recognition and the support of various stakeholders, the number of registered protocols remains relatively low. As of 13 July 2023, 158 protocols have been registered, of which 31 are currently under embargo. Of the 158 protocols, 48 studies (30.4%) were registered before the start of the experiments. Cardiology is the most represented field, with 46 studies (29.1%), followed by neurosciences ($n = 27$, 17.1%) and nutrition ($n = 16$, 10.1%). The 127 non-embargoed protocols are mainly confirmatory studies ($n = 73$, 57.5%) and use both small animal ($n = 76$, 59.8%) and large animal ($n = 51$, 40.2%) studies.

The future of preclinical preregistration

Preregistration enhances transparency and improves the effectiveness of preclinical research. While there are existing platforms to facilitate preregistration, the number of registered protocols remains low. Here, we presented the benefits of preregistration and discussed the development and functionality of preclinicaltrials.eu, highlighting the growing interest in preregistering of animal studies. Several Dutch stakeholders have already taken the lead in implementing preregistration, thereby increasing the number of registered protocols. We continue to prioritize and advocate for preregistration in our discussions with relevant stakeholders and follow a strategy to promote, facilitate, and increase understanding of the process. We see a role for the cardiology field as a frontrunner in this implementation, as the initiative is already supported by large cardiology groups such as TACTICS and the European Society of Cardiology.[8] However, it is time for the entire scientific community, including researchers, policymakers, funding agencies, and journals, to jointly take responsibility and embrace, promote,

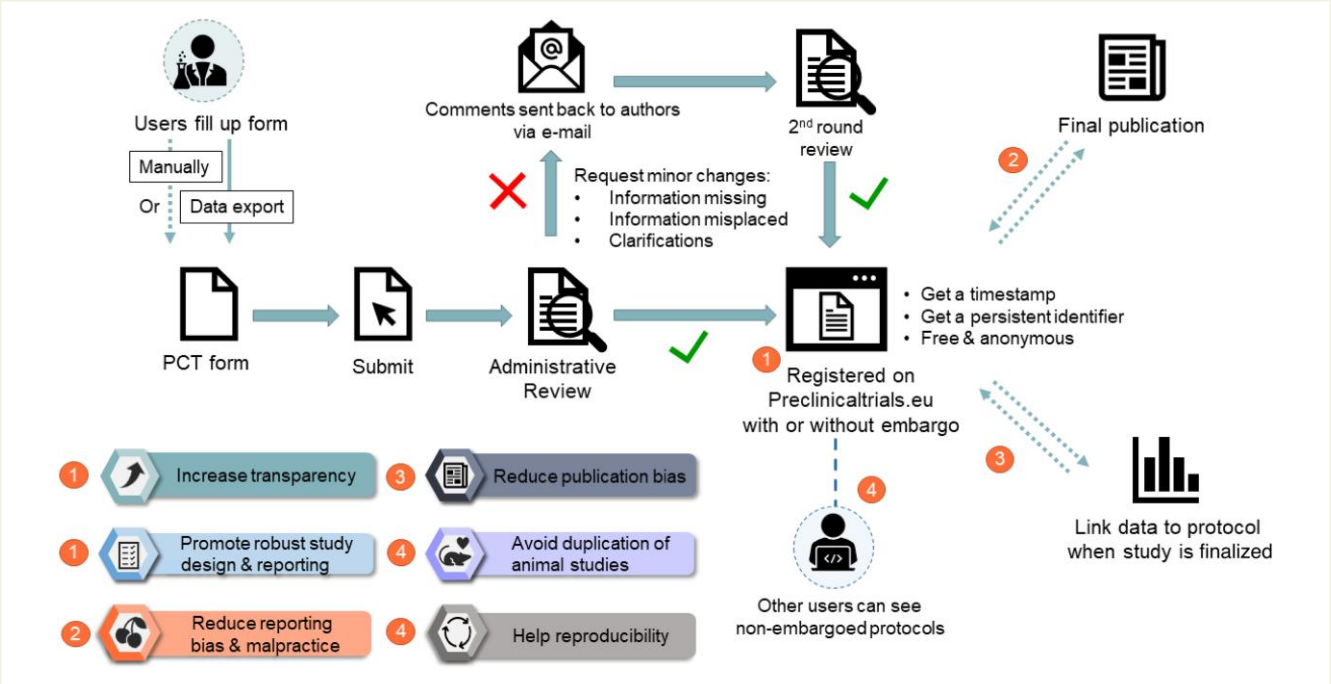

Figure 1 Preregistration process on preclinicaltrials.eu (PCT) and its benefits.

and require preregistration of animal studies, thereby further advancing the rigour and quality of preclinical research.

Declaration

Disclosure of Interest

All authors declare no conflict of interest for this contribution.

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