




Introducing the COST Action ‘Improving the Quality of Biomedical Science with 3Rs Concepts’ (IMPROVE)

Alternatives to Laboratory Animals
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The purpose of the ‘IMPROVE’ COST Action

A multitude of entities, spanning from research groups to associations and public institutions, are currently committed to moving forward the principles of the Three Rs (*replacement*, *refinement* and *reduction* of animal use in experiments) through research, funding, education and training, information

dissemination, and advocacy. These entities, which are supported by various sources — such as individual initiatives, government funding and non-profit organisations — exhibit a wide spectrum of objectives, tasks and organisational structures, resulting in a fragmented landscape in their approaches to furthering progress in the Three Rs.^{1–3}

The European Union-funded COST Action, ‘Improving the Quality of Biomedical Science with 3Rs Concepts’

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(IMPROVE), which kicked-off in October 2022, presents an unprecedented opportunity to harmonise and synergise efforts in moving the Three Rs forward.⁴ European Cooperation in Science and Technology (COST) is a funding organisation for research and innovation networks, supporting interdisciplinary research networks to investigate a specific topic from all different research fields.⁵ The ‘IMPROVE’ COST Action aims to establish an interdisciplinary network dedicated to refining, harmonising and promoting the adoption of the Three Rs principles, in order to enhance the quality of biomedical research.

By consolidating efforts from the grassroots level upwards, IMPROVE endeavours to catalyse a paradigm shift toward a scientific way of thinking based on the Three Rs. Central to IMPROVE’s mission is the conviction that further adoption of the Three Rs principles will inherently lead to better research practices and outcomes. This conviction is particularly pertinent in the context of the reproducibility crisis, where heightened awareness has sparked critical discourse within the research community regarding the reliability of data from animal studies.⁶ The Three Rs principles play a pivotal role in this discourse, fostering stakeholder engagement and promoting shared responsibility for ethical scientific conduct as an imperative. Therefore, there is an opportunity to improve science as we develop new models, reframe scientific questions, and advance the Three Rs even further through initiatives focused on:

- *replacement*, via the use of, for example, human-derived tissues, 3-D microphysiological systems, *in silico* studies, meta-analyses;
- *reduction*, as the result of better study design, improving research outcomes and avoiding waste in terms of any animals used;
- *refinement*, by ensuring that any animals used live more fulfilling lives and avoid distress as a confounding factor.^{7–12}

IMPROVE’s strategic focus revolves around capacity building and coordination across four key domains, namely: researcher and general education, Three Rs implementation, information dissemination, and scientific quality and translatability. Through the collaborative efforts of dedicated working groups comprising network members, IMPROVE aims to implement the targeted activities outlined in this introductory paper. Moreover, IMPROVE serves as a nexus for fostering collaboration among diverse stakeholders, including Three Rs centres, learned societies, academia, industry, regulatory bodies, animal welfare organisations and the general public. By adopting a bottom-up approach and avoiding redundancy with existing initiatives, IMPROVE seeks to establish an interconnected network that facilitates the exchange of best practices, expertise and resources. This collaborative framework

fosters information sharing, concept development and research project collaboration, ultimately enhancing the standard of biomedical research.

This *Comment* article introduces IMPROVE’s initiatives and underscores their potential to unite and strengthen the fragmented landscape of Three Rs practices. By engaging young scientists, established researchers and other stakeholders through a range of strategies such as conferences, workshops, training schools, online discussions and social media forums, IMPROVE aims to substantiate the notion that the principles of the Three Rs are intrinsically intertwined with the pursuit of good science.

The current status

The IMPROVE network has expanded steadily since its inception in October 2022 — from a 135 participant-count after two months, through 172 participants at the 8-month stage, a count of 201 participants was achieved after the initiative had been running for just over one year. As detailed in [Table 1](#), these 201 participants are from 41 countries, indicating a high level of interest of the scientific community in the Three Rs across Europe and beyond.

The vast majority of the members come from universities, followed by research institutes ([Figure 1a](#)). Small and medium-sized enterprises (SMEs), industry and Three Rs centres constitute the other main groups of the network, followed by a smaller percentage of members from animal welfare organisations. The background of the participants is quite diverse, including disciplines such as veterinary science, biology, ethics, engineering, etc. ([Figure 1b](#)). It is worth mentioning that young scientists under the age of 40 (e.g. PhD candidates, post-doctoral researchers, early career researchers, junior investigators), who are defined here as ‘Young Researchers and Innovators’, comprise 40% of participants, while 55% of the network participants are women, outlining the diversity of the ‘IMPROVE’ COST Action.

Overview of the Working Groups

The overall aim of IMPROVE is to establish an interdisciplinary network to refine, harmonise and promote data, documents and information on the Three Rs, in order to improve the quality of biomedical science. The action goals are carried out by specific Working Groups (WGs), as depicted in [Figure 2](#). All WGs are interlinked, so achievements on single topics are applicable to the other topics as well.

WG1: Quality and translatability of science

The relevance and translatability of preclinical (including toxicological) findings to humans is one of the most crucial concepts in biomedicine. When it comes to animal experiments, it is always important to be clear about the

Table 1. Number of IMPROVE participants per country.

Country	Number of participants
Albania	3
Austria	9
Azerbaijan	1
Belgium	5
Bosnia and Herzegovina	10
Croatia	3
Cyprus	2
Czech Republic	3
Denmark	3
Estonia	4
Finland	4
France	5
Germany	11
Greece	2
Hungary	2
Ireland	5
Israel	1
Italy	17
Japan	1
Kosovo	2
Latvia	5
Lithuania	7
Luxembourg	2
Malta	2
Moldova	1
Netherlands	8
North Macedonia	3
Norway	3
Poland	2
Portugal	11
Romania	12
Serbia	9
Slovakia	3
Slovenia	3
Spain	7
Sweden	2
Switzerland	5
Tunisia	1
Turkey	27
Ukraine	2
United Kingdom	10
United States	2
Total	201

translatability of the outcomes to the human species. Moreover, since the human body is composed of multiple organ systems that interact with each other, *in vitro* models must be evaluated accordingly. Therefore, WG1 focuses on defining quality criteria for *replacement* methods, to address methodological issues affecting the reliability and reproducibility of research outcomes, and the validity of New Approach Methodologies (NAMs) for use in research. A

second topic that WG1 aims to address is to propose guidelines to improve the quality of both animal and non-animal derived research data. These activities include, for example, the evaluation of how animal welfare improvements made through *refinement* measures can affect the scientific output of animal studies.

WG2: Implementation

In order to implement concepts related to the Three Rs, guidelines such as the Guidance on Good Cell Culture Practice (GCCP)¹³ for cell culture, or the Planning Research and Experimental Procedures on Animals (PREPARE) guidelines⁷ for animal experimentation, should be distributed and adopted routinely. Development chains for novel practical methods and technologies should be established. To reach these goals, it is imperative that stakeholders, including users and developers (i.e. industry, regulators, biotech companies, research laboratories and policy-makers), communicate with one another. The work of WG2 focuses on the analysis of stakeholder attitudes and the development of strategies for mainstreaming the use of NAMs. This will be carried out in close collaboration with WG1, working on a clear definition of what constitutes a NAM, as well as ensuring that the Three Rs are used as guiding principles — and not just as checkboxes — by all stakeholders, right through the NAMs development and implementation process. WG2 includes the additional aim of developing techniques for evaluating the implementation effort.

WG3: Dissemination

Globally accessible and user-friendly dissemination channels for scientific concepts and their associated methods are crucial in promoting innovation and advancement in science. The success of the IMPROVE network depends on both internal communication and external dissemination of the resulting Three Rs-related information to the international scientific community and the general public. To this end, a website (<https://cost-improve.eu/>)⁴ for the 'IMPROVE' COST Action has been launched, including sections on the outcomes, news and events, calls and grants. The resources section of the website contains information about Three Rs centres, platforms and data repositories. An internal repository is available to facilitate efficient information exchange between IMPROVE members, and an internal database with the members' scientific profiles has been created. Moreover, various social media accounts (LinkedIn, X, Facebook, Instagram) act as further communication channels to publicise activities and raise awareness of the Three Rs principles and NAMs within the scientific community and the general public.

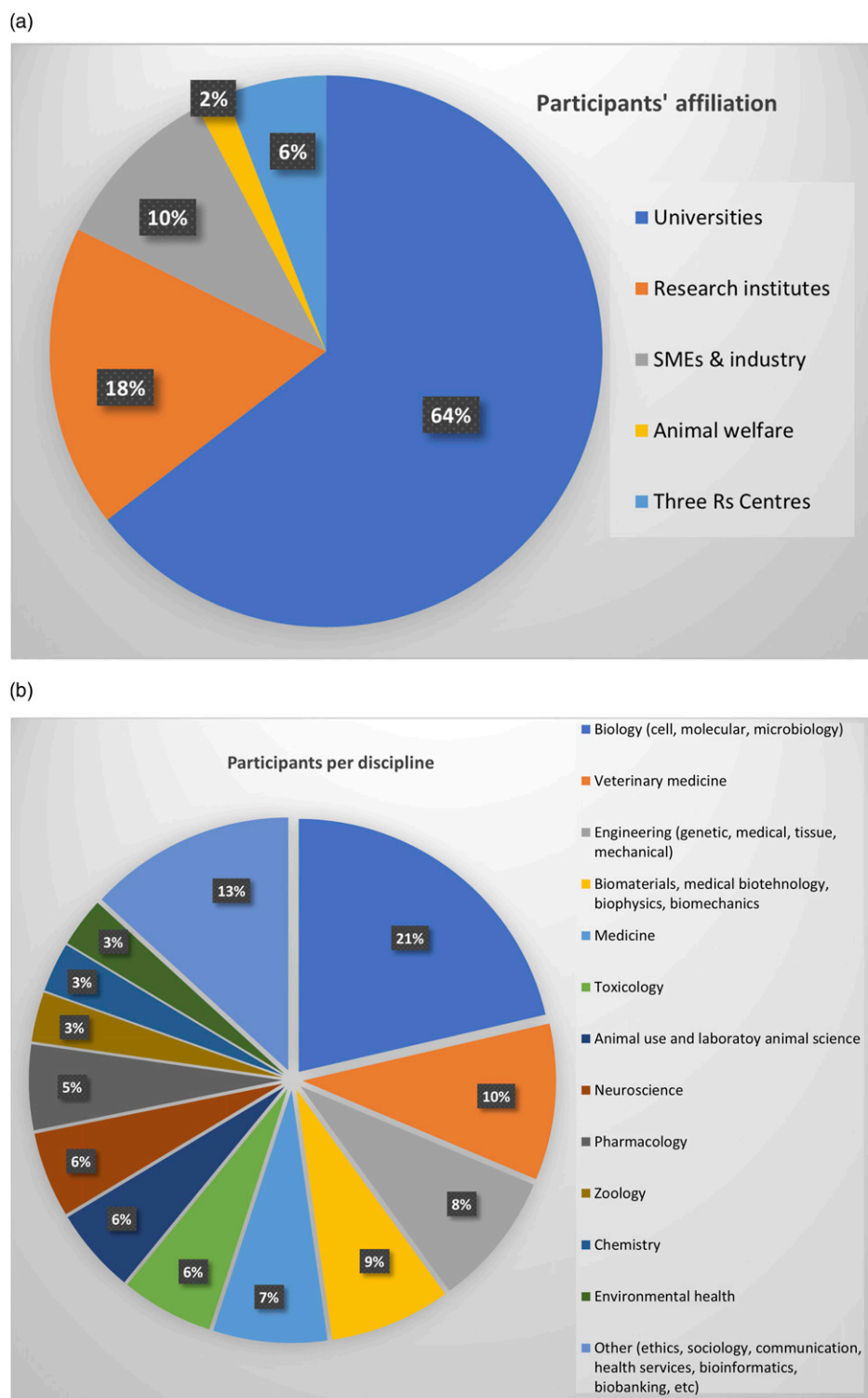


Figure 1. The demographic information of the IMPROVE participants. The participants' affiliations and background are shown in (a) and (b), respectively; $n = 201$.

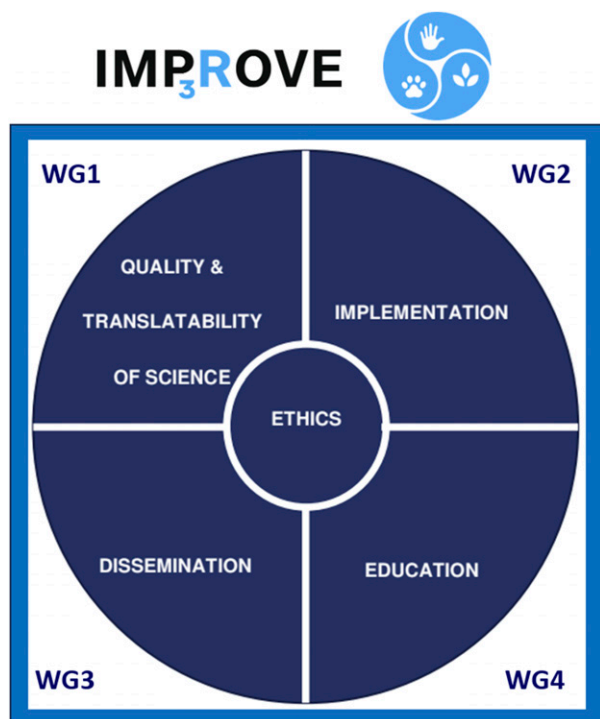


Figure 2. The IMPROVE Working Groups and the connections between them.

WG4: Education

It is important that the ‘IMPROVE’ initiative takes a broad approach to Three Rs education. As part of its focus, WG4 will consider all three principles, with the aim of establishing and maximising connections between educational activities carried out at various levels, both inside and outside Europe. The main pillars for achieving this goal include communication with stakeholders involved in education and the sharing of education strategies and teaching resources, both within the network and externally. WG4 is mapping the current availability of Three Rs-related educational activities, resources and training programmes, through the development of a database for the project. This will provide a much-needed actual picture of the current status of Three Rs education and training within the IMPROVE member countries. An in-depth analysis of the database will identify the strengths, and also the limitations, of the current Three Rs education network, laying the grounds for further educational strategies. In parallel, the group is exploring the usefulness of interdisciplinary approaches in potentiating Three Rs-related education and training. The aim is to identify situations in which such interdisciplinary approaches could be helpful in overcoming obstacles to the implementation of the Three Rs, and then to develop suitable strategies to facilitate the use of such approaches.

The ethics crossover group

An Ethics Crossover Group has been formed with members from all four WGs. This group deals with the ethical issues associated with improving the quality of biomedical science. In fact, the quality of a research task (in terms of its usefulness to society and the planet, knowledge impact, innovation, etc.) also depends on a scientist’s capacity to make value judgements about the task(s). This requires an awareness of the explicit and implicit normative premises upon which the research is based. Furthermore, this is a prerequisite for transparency, which is another research quality criterion. Morally correct behaviour toward humans and non-humans is also important. The Ethics Crossover Group focuses on supporting the discussions within all WGs on the different ethical points of view that research, with or without animals, generates. It benefits greatly from the different professional and cultural backgrounds, and diversity, of the participants. The Ethics Crossover Group is an integral element of the four above-mentioned WGs, ensuring the consideration of ethical aspects within each of the WG focus areas.

Additional sub-groups

Sub-groups have also been established on specific topics of special interest. For example, one sub-group highlights the importance of communication between researchers, animal care staff and laboratory technicians during the planning and performing of experiments. The aim is to generate recommendations for better science and improvement of human and animal wellbeing. A different sub-group comprises a community of ‘Young Researchers and Innovators’, with the aim of strengthening the professional and human development of future leaders in the Three Rs field. Yet another sub-group is involved in the preparation of a white paper that provides scientific arguments on why ‘physiological relevance’ can also be demonstrated by using *in vitro* techniques. Efforts are also ongoing to create a sub-group specifically to work on setting up a NAM expert pool.

Focus on stakeholders

Experts from a variety of fields are actively contributing to the advancement of the Three Rs. These include ethicists, *in vitro* and *in silico* method developers, and also people who are currently involved in animal experimentation. By encouraging dialogue and discussion, their combined efforts could increase the effective comparison, validity and significance of both animal and non-animal methods. This can be achieved by promoting best principles and practices in evidence-based model selection, quality control, and critical reflection of current possibilities and limitations of existing models and methods. Through the engagement of a

wider group of stakeholders, these efforts could also facilitate the integration and use of non-animal methods in such areas as basic science, regulatory affairs, and training and education.

IMPROVE employs an interdisciplinary approach, to build a unique network that brings together and compounds the endeavours of Three Rs experts from various fields. These experts represent the views from basic science, academia, regulatory authorities and industry, thus facilitating an active dialogue between the different stakeholders. Moreover, IMPROVE envisages attracting the next generation of scientists — e.g. PhD candidates, post-doctoral researchers, early career researchers, junior investigators — to foster their education and support them in learning about the manifold subjects, topics and possibilities in the Three Rs field. It is hoped that, in the longer term, this will contribute to the improvement of biomedical science in general.

Even though awareness of the Three Rs needs to be reinforced in general, the focus of IMPROVE is on expanding the network of stakeholders in the basic science areas of neuroscience, cardiovascular diseases and oncology, as these disciplines are among the research areas that use the highest number of animals (besides studies on the immune system).^{14,15} The planned strategy includes, for example, communicating with the various discipline-related scientific societies, in order to investigate the potential options for promoting the Three Rs to their members, to discuss technologies and present relevant case studies on the use of novel Three Rs-based advanced methodologies (e.g. organs-on-chips, 3-D cellularised scaffolds, human induced pluripotent stem cells, multicellular spheroid arrays, and computation and machine learning).^{16–19}

Contribution to the network of Three Rs centres in Europe

In recent years, a growing number of Three Rs centres and platforms have been formed, not only to develop new methodologies but also to share knowledge and to help with the implementation of the Three Rs principles in policies and education. The adoption of *Directive 2010/63/EU* on the protection of animals used for scientific purposes gave a strong impetus to the creation of Three Rs initiatives in the form of centres and platforms, finally resulting in the EU3Rnet association.²⁰

Currently, 25 countries have at least one Three Rs centre, platform or group represented in EU3Rnet (namely: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden, Switzerland, The Netherlands, UK, Ukraine).^{21–23} These various centres and platforms can

serve as role models for other countries by giving examples of how to organise and establish a Three Rs centre or platform, as well as offering guidance on dealing with a range of impediments that might be encountered.²⁴

IMPROVE is, in fact, based on a scientific network that has evolved from the original members and activities of the EU3Rnet association, which was formed over time by individuals dedicated to and/or interested in the Three Rs and in the quality of science. The IMPROVE network works hard to interact directly with European Three Rs centres, in order to identify strategies for the long-term sustainability of Three Rs activities and to attract the interest of those who are new to the field (either individual researchers, or whole institutions or companies). Moreover, many of the IMPROVE members have active collaborations with international organisations who are working on common initiatives, projects, publications and resources — for example, the various societies for alternatives to animal experiments that are based in the USA or in Asia (e.g. the Society for Alternatives to Animal Experiments in India (SAAE-I), the Japanese Society for Alternatives to Animal Experiments (JSAAE) and the Korean Society for Alternatives to Animal Experiments (KSAAE)).

Importantly, at a time when there is growing awareness of the societal and ethical implications of biomedical research, as well as greater appreciation of the role of Three Rs centres and societies, networking initiatives such as IMPROVE can play a key role in shaping future directions — in terms of the drafting of legislation, the adoption of new methodologies, and the promotion of shared, collaborative practices. For example, in 2021 the European Parliament voted on a plan to accelerate the transition to innovation without the use of animals. The vote was very much in accordance with initiatives of the European Food Safety Agency (EFSA) and the Environmental Protection Agency (EPA) in the USA to implement NAMs in regulatory processes.^{25–27} In the same direction, on 29 December 2022, the *FDA Modernization Act 2.0* was signed, allowing for alternatives to animal testing.²⁸ More recently (25 January 2024), the National Institute of Health (NIH) Common Fund's *Complement Animal Research In Experimentation (Complement-ARIE)* programme was announced,²⁹ which aims to expedite the development, standardisation, validation and use of human-based NAMs. In this scenario, a unified network such as IMPROVE is ideally placed to take a leading role, to facilitate access to all relevant data and documents, and to enhance the dissemination of information and guidelines for the use and application of the Three Rs concepts.

Concluding remarks

IMPROVE encourages bottom-up Three Rs capacity building in Europe, launches and promotes new interdisciplinary and intersectoral research initiatives in this area, and thus expands access to crucial financing and cutting-

edge infrastructure in the Three Rs field. Currently, IMPROVE has over 200 participants. It offers several opportunities for networking and provides funding for initiatives such as: Short-term Scientific Missions (STSMs); Inclusiveness Target Countries (ITC) conference grants; and participation in training schools, workshops, conferences and public activities such as exhibitions, school workshops and open campus days. We actively encourage stakeholders from fields such as science, industry, regulatory affairs, national contact points, animal welfare, education and training, to participate in our research network. Additional information is available on the IMPROVE website,⁴ as well as on various social media accounts (LinkedIn,³⁰ X,³¹ Facebook³² and Instagram³³), where you can ‘Follow us’ and read about the past, current and future activities aimed at promoting the Three Rs principles in biomedical science.

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