

Exploratory study on the rationale and drivers influencing methodological choices

in cardiovascular research



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Supervisory committee

In terms of the procedure, this study was guided by a supervisory committee consisting of: Leane van Weereld (the Netherlands National Committee for the protection of animals used for scientific purposes, NCad); Henk Smidt (NCad); Floor Kroese (National Institute of Public Health and Environmental Protection, RIVM)) and Anne Kienhuis (RIVM). This supervisory committee did not influence the findings and conclusions of this study in any way.

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About Inspire to Act

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1 INTRODUCTION

Objective

The Netherlands National Committee for the protection of animals used for scientific purposes (NCad) is keen to find out which rationale and motives play a role when researchers choose whether the research model they use will involve laboratory animals. In this exploratory study, we focus on the methodological choices (*in vitro*, *in vivo*, *in silico*, human and *ex vivo*) in fundamental and translational cardiovascular research. Choosing cardiovascular research as the field of study for our research was prompted by the publication of the 2022 European Society of Cardiology (ESC) consensus report¹ and the *Streefbeeld Cardiovasculair Onderzoek* (i.e. ‘Target image on cardiovascular research’). Behavioural analysis identifies the key behavioural-psychological factors involved when deciding on whether or not to choose a research model that involves the use of animals.

Research questions

This report gives answers to the following three research questions:

1. What behavioural-psychological factors are the main drivers for the target group when deciding to choose a research model that is either animal-based or animal-free, particularly when new animal-free models are available?²
2. What are the main barriers hindering the use of new animal-free methods?
3. Which players strongly influence the choice and use of animal-based or animal-free research models?

Research design

A literature scan was conducted to gain a better understanding of the key behavioural-psychological factors that affect the choice of the research model. Subsequently, in-depth interviews with six stakeholders and twelve scientific researchers were held to investigate the extent to which these behavioural-psychological factors actually play a role in practice when choosing an animal based or animal-free research model.

¹ Van der Velden, Asselbergs, Bakkers, Batkai, Bertrand, Bezzina, ... & Thum (2022).

² By law, the use of non-animal research models is mandatory if they are available and appropriate for answering the research question. Deciding whether models are suitable is a somewhat subjective exercise, and switching to new models costs a lot of money and time and it requires specific expertise. This study examines what behavioural-psychological factors play a role in accelerating this process.

2 BEHAVIOURAL ANALYSIS

2.1 Literature scan

State of the art of cardiovascular research

Replacing animal models

The idea that biomedical sciences can progress without having to use laboratory animal research is a notion that is gaining in popularity across the world. It can be done by replacing *in vivo* experiments with (human) *in vitro* models. According to the European Society of Cardiology (ESC) consensus report,³ this belief is justified to some extent because various research questions can be answered without using animals. Nonetheless, research with animals is still necessary, for instance for implanting medical devices (such as stents, new catheter-directed endoscopy systems, implants); *in vivo* drug testing; and identifying mechanisms underlying the various types of cardiovascular diseases. Although stem cell research and human stem cell research is taking on a more prominent role in testing the toxicity and efficacy of new drugs at the cellular or organ level, it lacks the complexity found in various kinds of cardiovascular disease. According to the consensus report we currently still dependent on research using laboratory animals because cardiovascular diseases are complex, multifactorial disorders, and our knowledge of these diseases is still limited.

Refining and reducing animal models

In vitro models will be further refined in the years to come and made more 'human-like' based on big datasets from human studies.² New 2D and 3D *in vitro* technology and advanced computer analyses are producing more sophisticated experimental designs, which will reduce the number of laboratory animals currently needed in research and for testing medicines. Validation presents a major challenge when refining models derived from iPSC.⁴ Currently, there is a gap between iPSC-derived heart models and the patients' clinical phenotypes.⁵ As a result, these models can only be applied to a limited degree for studies into pathophysiological mechanisms and use in clinical settings. For a proper translation of cardiovascular research, the results obtained from three types of studies (i.e. using laboratory animals, non-animal models and patients) have to be integrated.

Selecting a research model

In vivo, *in vitro* and *in silico* models are all used in cardiovascular research. Similarly, different types of models (*in vivo*, *in vitro* and/or *in silico*) are also often used within research groups. All three types of models have advantages as well as disadvantages and limitations. Ideally, the research question should always guide the decision on which is the best model, i.e. the one that answers the research question most effectively. That said, several other factors play a role in this decision. The behavioural analysis focuses on the researchers' motives when deciding on a research model. In other words, what behavioural-psychological factors affect the decision to work with the research models used by the research group or to opt for a different (innovative) research model?

³ Van der Velden, Asselbergs, Bakkers, Batkai, Bertrand, Bezzina, ... & Thum (2022).

⁴ In other words, whether the models capture human pathophysiology.

⁵ In other words, not compared with individual patient attributes and human heart tissue samples.

Factors for innovative behaviour

Working with other (innovative) research models is an example of innovative behaviour at work. We define 'innovative behaviour at work' as follows: employee behaviour aimed at creating, introducing and/or applying ideas, processes, methods, technologies, products or procedures that are new and presumably beneficial to work being performed.⁶ Based on the literature scan, we observe the following factors are important predictors of innovative behaviour among staff at knowledge-intensive organisations:⁷

Category	Examples of factors
Intrapersonal characteristics	<ul style="list-style-type: none">• Knowledge/expertise• Attitude• Personal norms and values• Tolerance for uncertainty• Self-confidence
Task characteristics	<ul style="list-style-type: none">• Variation in the work• Autonomy• Working in multidisciplinary teams• External work contacts
Interpersonal characteristics	<ul style="list-style-type: none">• Type of leadership• Support for the innovation by colleagues• Tolerance for deviating opinions
Organisational characteristics	<ul style="list-style-type: none">• Organisation's innovation strategy• Availability of resources for innovation• Rules and procedures within the organisation• Remuneration system
Institutional characteristics	<ul style="list-style-type: none">• Research funding• Options for publication• Role of the pharmaceutical industry• Politics, the media and the social debate• Laws and regulations

In the in-depth interviews with stakeholders and researchers, the above factors were considered and the extent to which they play a role in the choice to work with the research models used by the research group or a different (innovative) non-animal research model was explored. As an exploratory step prior to the in-depth interviews, discussions were held with Professor Robert Passier.

⁶ De Spiegelaere, Van Guyes, & Van Hootegem (2014), cited in: Van Essen & De Leede (2020); King & Anderson (2002), cited in: De Jong & Den Hartog (2005).

⁷ De Jong & Den Hartog (2005).

2.2 In-depth interviews

Respondents

Stakeholders

We spoke to employees of the following six organisations:

1. the Dutch CardioVascular Alliance (DCVA)
2. the Ministry of Education, Culture and Science
3. the Ministry of Agriculture, Nature and Food Quality
4. the Netherlands Heart Foundation
5. the Dutch Research Council/Netherlands Organisation for Health Research and Development (NWO/ZonMw)
6. the Dutch Society for the Replacement of Animal Testing (Stichting Proefdiervrij)

The NCad gave us the names of the contact persons at the first four organisations. We contacted the Dutch Heart Foundation and DCVA using the contact form on the websites of these organisations. We also contacted Harteraad, the Dutch association for people with cardiovascular diseases. Harteraad was not willing to cooperate with our research because it is not part of their policy plans, mission and vision.

Scientific researchers

We spoke to twelve cardiovascular science researchers.⁸ This group of researchers was heterogeneous in terms of the following dimensions:⁹

Dimension	In the sample
Institution	Amsterdam UMC; Erasmus MC; Netherlands Heart Institute; University of Applied Sciences Utrecht, Life Sciences course; Radboud UMC; UMC Groningen; UMC Utrecht; Maastricht University and Leiden University
Type of research models	<i>In vivo</i> ; <i>in vitro</i> ; and <i>in silico</i>
Type of research	Fundamental and translational
Seniority	Junior, mid-level and senior researchers

We have chosen a heterogeneous target group in order to paint as broad a picture as possible of the motives and drivers in the choices of research models. From the NCad, we received a list of researchers who could be relevant to our research. In addition, the NWO/ZonMw drew our attention to several researchers who might be relevant to our research. We spoke to four researchers from

⁸ One respondent was a recent graduate and not doing work involving cardiovascular research. This respondent told us about the decisions and experiences during and just after studying Biomedical Sciences.

⁹ When the interviews were conducted, it was agreed that the findings would be reported anonymously. For this reason, an overview of the respondents was not included in the report.

NCad's list and five from the suggestions put forward by NWO/ZonMw. One researcher was recruited using the snowball method. We selected two researchers using desk research.¹⁰

Findings

Below is a description of the most important findings from the in-depth interviews. First, we describe the different moments in a scientific career when research models are selected (consciously, subconsciously or unavoidably). We go on to describe the various factors involved, including behavioural-psychological ones, when deciding on whether or not to select a research model that involves the use of animals. The findings below are based on the interviews with stakeholders and researchers. We only noted the findings mentioned by several respondents.

Moments of choice

During the study programme

Both methodological work and new models receive little attention in the Biomedical Sciences curriculum. Models using laboratory animals are still presented as the gold standard. Yet it seems as though change is on the way and there is more balance in the curriculum between non-animal innovations and animal experiments. For instance, guest researchers working with animal models as well as guest researchers who work with animal-free models are invited. More attention is also being paid to bioinformatics and *in silico* models.

In addition, academic education (which includes education at universities of applied science) is increasingly focusing on the use of new animal-free models and methodological working practices. Paying more attention to different models and method-based practices helps students to make informed decisions about the research models they use later in their academic careers.

In addition, students can obtain certificates for working with animals during their studies: Article 9 of the Experiment on Animals Act for setting up animal experiments and Article 13f2 for conducting animal experiments.

- More attention should be paid to methodical working practices: How do you conduct research? When do you choose which model? Which research questions can you answer based on animal-free models and which do not lend themselves to this? Which model do you select and what are the pros and cons of the different models?

During PhD research

PhD students are usually hired for research projects that use the research models already present within the research group. When they apply for the position, PhD students know where they will be working, what the professor or principal investigator (PI) has published and what research models are used by the research group. They can take this into account when selecting a PhD position. Yet in practice, it turns out that PhD students do not actually know very well what they are getting into. They don't really know what working with those research models means and entails. Nor do they know whether a model is good or not and whether that model is the best model to answer the research question with. Many PhD students do not make a conscious decision when it concerns research models. Instead, they go along with the professor's or PI's research tradition. As an example, if the research team has been using mouse research models for 20 years, then it is likely that the PhD student will do so too.

It is often very problematic if a PhD student prefers to work with a research model that is not the

¹⁰ This selection method may have resulted in the respondents not being representative of the population of researchers in the field. We have compensated for this as much as possible by looking for relevant researchers ourselves based on desk research and the snowball method. The sample included proponents as well as opponents of using animals models in research.

same as those available at the research group. You can debate whether there are other models that answer the research question more effectively than the ones used at the research group, but those models are then not readily at your disposal.

Setting up new research models during a PhD programme is virtually impossible¹¹, as it is a lengthy process. A PhD programme takes four years and within that time, students need to publish their work.

Also, the professor or PI has a lot of influence on the choice of research model. If the professor or PI is not open to using new models, it is not possible for a PhD student to set one up during the PhD programme.

That said, working with a new model during PhD research is not completely out of the question. It occasionally happens, provided the professor or PI is receptive to the idea; provided the PhD student can make a good case for why a new model would be better and has good scientific potential; and provided there are sufficient resources, facilities, knowledge and expertise. But this is often the exception.

- Exchange opportunities could be promoted so that PhD students are given more chances and the opportunity to work with different research models. PhD students gain inspiration from other fields, come into contact with new research models they could work with (temporarily or otherwise) and gain experience with new research methods if they work in other research groups for a while.

During postdoctoral research

When choosing a postdoc position, researchers are already much more familiar with what working with different research models means and entails. They are then in a position to make more well-informed decisions about the research models that they want to work with. During this phase, researchers shape their scientific careers and have the opportunity to specialise in certain research models or lines of research. Whether a postdoc researcher is able to set up new research models depends, among other things, on the length of the appointment.

- Committing postdocs to the knowledge institution for a longer period of time creates more opportunities for the creation/development of new research models.

As mid-level/senior researcher

Mid-level and senior researchers have a good scientific base and experience with a range of research methodologies and models. Often, they will have also made a name for themselves. Mid-level/senior researchers with around ten years of research experience usually still have enough time left in their scientific career to pursue different paths.¹²

- It would be good to challenge and encourage mid-level/senior researchers with around ten years of research experience to conceptualise and set up new research models and research lines, alongside the research they are working on.

¹¹ Unless the purpose of the PhD programme is to develop new research models.

¹² Ten years of research experience is indicative. Developing new lines of research takes around five to ten years. Senior researchers approaching retirement age within five to ten years generally do not have enough time to set up these lines. That said, because of their expertise and experience, they can play an important role in guiding other mid-level and senior researchers in setting up new lines of research.

Factors at an intrapersonal level

Insufficient knowledge about innovative models

Not everyone knows what innovative models are out there, what they can be used for and what opportunities they offer when answering research questions. In that case, researchers are inclined to go for research models they are familiar with or for which their department has expertise.

- Systematic review

A systematic review (such as the one published by the European Society of Cardiology, ESC)¹³ enhances this knowledge, and with that improves the ability of researchers to choose the best research model for their research question.

- Literature review

At Radboud UMC and elsewhere, PhD students begin their programmes by carrying out a literature review in which they investigate which research models are relevant to their research question. In the process, they learn about alternative models and are in a better position to weigh up which research model best suits their research question.

Attitude, standards and values

Some researchers prefer not (or no longer) to work with animals, based on their personal convictions. These researchers will be more likely to look for research jobs where they can work using non-animal research models.

Tolerance for uncertainty

New models are sometimes viewed with scepticism because they arrive on a wave of hype but have not yet proved their worth. Thanks to this scepticism, it can sometimes take an unnecessary long time for them to be recognised in terms of their value.

Factors at a task level

Autonomy and time

The more seniority a researcher has, the more autonomy they are given. PhD students have little autonomy. It is virtually impossible for PhD students to set up research lines or models. They are expected to use the models described in the PI's research proposal. In addition, PhD programmes are too short to establish new research lines or models.

While postdoc researchers do have more autonomy, their opportunities to set up new research lines or models are still limited because they are usually on temporary contracts.

Researchers who are given a permanent or long-term appointment after postdoc research often have enough autonomy and time to set up new research lines or models.

Professors have the most autonomy. Depending on their age and whether and when they retire, they may have either sufficient or insufficient time to set up new research lines and models.

Working in multidisciplinary teams

Working in multidisciplinary teams ensures that researchers look beyond the boundaries of their own research areas and interconnect with others. They are more likely to encounter different types of research models, giving them the opportunity to make more informed decisions when selecting a research model that most effectively answers the research question.

¹³ Van der Velden, Asselbergs, Bakkers, Batkai, Bertrand, Bezzina, ... & Thum (2022).

External work contacts

Having good connections with researchers at other research groups that work with different models also increases the likelihood of researchers working with models other than those available at their own research group. If the various researchers or research groups work together with trust and confidence in each other, consortia can work with a wider range of models.

In addition, if researchers interact with research groups in other research fields, they are more likely to come up with ideas to apply models from other research fields to their own research. Consider, for instance, the exchange of researchers between research groups or internships at other research groups or in other research fields.

Factors at an interpersonal level

Type of leadership

The professor or PI is the person ultimately responsible for the research and therefore has a lot of influence on the choice of the research model. The extent to which professors or PIs are open to new models varies from person to person. A new model will be adopted sooner if it is properly substantiated from a scientific perspective and has good potential for producing new insights or a breakthrough in the research.

Tolerance for deviating opinions

Junior researchers sometimes find it difficult to go against the opinions of the professor or PI. Because they are in a dependency relationship, they are afraid that this could affect their scientific careers.

Support for the innovation of colleagues

People are very sensitive to what significant others think and do (social norms).¹⁴ Researchers are therefore more likely to opt for a different research model if it has the support of colleagues. Switching to another model is much more difficult if colleagues are not receptive to new models.

Factors at an organisational level

Availability of resources for innovation

Launching new models or research lines requires knowledge and expertise, technologies and skills, and facilities. And it requires a lot of money, time and effort. In other words, it is a major investment. Working in multidisciplinary teams (internally) or working in consortia (externally) can offer solutions. A systematic review of different research models helps in making an informed decision when selecting a model. But this costs time and money too. Often there is no funding for this and it cannot always be achieved within the time available for the research.

Some universities are investing in the development of new research facilities for specialisation in new research models; the IPS facility in Leiden is an example of this. This facility makes stem cell research accessible to many researchers because they can order and buy cell lines.

Rules and procedures within the organisation

Some universities, for instance in Nijmegen and Utrecht, work according to a pre-registration system. Researchers at these universities are strongly advised to register their research before, during and after performance of the study. This also makes the experiments that did not lead to a (full) publication accessible. This has several advantages: it reduces publication and reporting bias; it

¹⁴ Cialdini & Trost (1998).

enables data sharing; it helps to reduce unnecessary repetition of studies using laboratory animals; and it improves the quality of these studies. One disadvantage is that it has only been set up within the Netherlands. It would be even better if it had been set up internationally.

Applying patient record models also helps to reduce laboratory animal experiments. The General Data Protection Regulation is an important factor when using patient records. Hospitals and universities are inclined to view this as a 'hassle', which makes it less attractive to choose these models.

Factors at an institutional level

Research funding

If the research is shorter timewise, and consequently has a smaller research budget, there is less scope for the researchers to explore the options of alternative research models or to contribute to the development of alternative models. If the research takes longer, and therefore has a bigger research budget, there is more scope for the development and application of new research models and the validation of these models.

Some research funders (indirectly) influence the type of model to be used in the invitation to apply for research funding. On the one hand, this is done based on the formulation of the research question, which sometimes automatically fits a certain research model. On the other hand, the call for tender sometimes asks for the choice of research model to be substantiated.

New research models may not be sufficiently validated in some respects. When selecting a research model, it is easier and more attractive for a researcher to choose a validated research model. More investment in validation research will stimulate the use of new research models.

Some research funders are becoming more inclined to go for animal-free models. This seems to be a response to developments in politics, the media and the social debate, and sometimes it is a response to the views of the support base.

Publication options

Reviewers of high-impact journals seem to have a somewhat conservative attitudes. If an article is submitted based on a research model that does not involve animals, researchers are regularly asked to perform an animal experiment to validate the new research model. According to researchers, this is often not necessary at all. In contrast to the above, we also hear that studies using innovative research models are actually more easily published, because of the new scientific knowledge it provides and the attractiveness of such research.

Role of the pharmaceutical industry

Startups are necessary as an intermediate step between scientific research and the pharmaceutical industry. Pharmacists are inclined to take research conducted by a startup more seriously than research carried out at a university. If it concerns initial funding, it is often possible to raise more funding for startups through investors. Universities also benefit from startups because the patents are often vested in the university. Thus, some of the money and scientifically interesting insights from the startup flow back to the university and are then used for more research based on these patents and contacts.

Politics, the media and the social debate

In politics, media and the social debate there is a clear trend towards animal-free research. This makes some researchers feel uncomfortable, because research models involving animals are still necessary for various types of research. The opinions in politics, the media and the social debate are often scientifically unsound and unfeasible.

Laws and regulations

Conducting animal experiments is subject to many registrations and applications, for example, registration with the research institution, the ethics committee, the Central Authority for Scientific Procedures on Animals, justification for grant applications, and sometimes with other authorities. Being permitted to carry out animal experiments requires a lot of effort and time and is by no means a simple matter. Yet this does not always lead to methodologically well thought-out studies. Sometimes studies have to be redone, for example due to insufficient power. This results in unnecessary use of research resources and animals.

In most cases, animal models are mandatory by law for valorisation. For instance, if an artificial heart is produced, for safety reasons it is necessary to test it in animals before using it in humans. According to researchers, this intermediate step based on animal testing is not always necessary, for instance if human models have been used.

Permits for working with laboratory animals are also inflexible. Under the current system, it is virtually impossible to modify animal experiments if new insights/developments (for instance, publications from other research groups) render the approved experimental design no longer useful or outdated.

A statutory ban on research using laboratory animals can have negative side effects. The fact is that working with animal models also contributes to enhancing knowledge. If research with animals is no longer permitted in the Netherlands, we will weaken our position in the market as far as knowledge of pathologies and methods/skills is concerned. In addition, banning animal experiments in the Netherlands will most likely lead to animal testing going to other countries. The welfare of the animals will then be lost from sight.

3 REFERENCE POINTS FOR BEHAVIOURAL CHANGE

3.1 Key behavioural factors

Based on the above analysis, the main behavioural determining factors are classified in the COM-B model (see the behaviour change wheel). COM-B stands for capability, opportunity and motivation – behaviour.¹⁵ The basic premise of this model is that behaviour depends on:

- The **capacity** to display it. That is to say that people must have the physical strength, knowledge, skills, stamina and so on to display the behaviour.
- The **opportunity** to display the behaviour. In other words, the physical and social environment must be conducive to that behaviour: it must be physically accessible, affordable, socially acceptable and there has to be sufficient time for it.
- The **motivation** has to be strong enough. That is, people should be motivated to display the behaviour when it is relevant, and not display behaviour that conflicts with it.

The figure below presents the main behavioural determinants for deciding whether or not to use innovative research models.

Capacity	Opportunity	Motivation
<ul style="list-style-type: none">• Knowledge/expertise• Skills for working in multi-disciplinary teams	<ul style="list-style-type: none">• Autonomy• Working in multidisciplinary teams• External work contacts• Type of leadership• Support for the innovation by colleagues• Tolerance from the professor/PI for deviating opinions• Availability of resources for innovation• Rules and procedures at the organisation• Research funding• Publication options• Politics, the media and the social debate• Laws and regulations	<ul style="list-style-type: none">• Attitude towards animal testing• Personal standards and values

¹⁵ Michie, Van Stralen, & West (2011).

3.2 Key reference points for behavioural change

The most important reference points that we recognise for behavioural changes are listed below.

Capacity

Enhancing knowledge by paying more attention to research models and method-based working during the study programme

More attention for new models and method-based working practices during the Biomedical Sciences curriculum. Here we have in mind, for instance:

- Offer methodological work as a module: pose research question and then see which model is the most suitable for answering the question.
- Draft a research plan based on the research question: Investigate how you can solve it using animal-free models. Only if you are confronted with limitations, start looking at what is needed for animal-based testing.

Enhancing knowledge by publishing non-positive study results in journals

Publishing sound research based on non-positive study results¹⁶ in a scientific journal may avoid unnecessary duplication of research using laboratory animals.¹⁷ Publishing this kind of research in a scientific journal is preferable to using a registration system, as publications form an important incentive for researchers. Incidentally, it can be a barrier for researchers to publish negative study results.

Increase competency for multidisciplinary working practices

Working in multidisciplinary teams requires the team members to have certain competencies. These competencies can be improved by giving students the opportunity to gain relevant experience during their studies, for instance based on the interdisciplinary teaching of animal-free medical sciences.

Enhancing knowledge using systematic reviews

Make a systematic review mandatory for PhD studies or longer research projects and make funding available for this purpose. This can be very interesting for young researchers, because it may be their first scientific publication.

Opportunity

Make funding available for the innovation

Provide opportunities, including funding, for mid-level/senior researchers with around ten years of research experience to develop new models in addition to their current research. For example, consider prestigious research funding as an award for excellent research.

Encourage working in consortia and in multidisciplinary teams

Encourage consortia and multidisciplinary collaborations in which different research models can be combined. This could begin with education, for instance with interdisciplinary education on medical sciences that does not involve using laboratory animals. More attention could also be paid to

¹⁶ Research that has been conducted properly from a scientific perspective but that does not demonstrate any effects.

¹⁷ See also: Abarkan, Wijen, Van Eijden, Struijs, Dennis, Ritskes-Hoitinga, & Visseren-Hamakers (2022).

exchange courses in PhD programmes. A good relationship of trust is key to collaborating in consortia. Researchers do not want other researchers to run away with their ideas or research findings. It is also important to monitor the quality, intensity and added value of the promised cooperation by conducting interim and final evaluations. This is to ensure that it is not just a worthless construct on paper designed to secure the funding.

Promote validation research

Make more funding available to validate promising results and new technologies and models. For instance, having a bigger research budget will allow for validation being an integral part of the research. Alternatively, initial financing for startups can be made available. In addition, the validation of new research models can be encouraged in a line of research using different research models.

4 CONCLUSION

This section gives the answers to the research questions.

4.1 Behavioural-psychological factors

Research question 1. What behavioural-psychological factors are the main drivers for the target group when deciding to choose a research model that is either animal-based or animal-free, particularly when new animal-free models are available?

Our exploratory research shows that it is having the **opportunity**, in particular, that influences the choice of a research model. Whether a researcher chooses a different (innovative) research model than is customary in the research group depends mainly on the following:

The physical environment

- The extent to which the researcher has access to other (innovative) research models, for instance by working in multidisciplinary teams or through external work-related contacts.
- The extent to which resources for developing or applying other (innovative) research models are available or made available, which could for example include research funding, facilities and time.
- Publication opportunities.
- Laws and regulations and rules and procedures at the research institute.

The social environment

- The extent of the researcher's autonomy.
- Support from the research group, both from the professor or PI and colleagues.
- Politics, the media and the social debate.

Capacity is also a key factor.

Knowledge and expertise

More knowledge and expertise on other (innovative) research models, can stimulate the development and application of other (innovative) research models.

And finally, **motivation** plays an important role.

Attitude

- Attitude to animal experiments.

Personal standards and values

- Personal standards and values concerning animal experiments.

4.2 Barriers

Research question 2. What are the main barriers hindering the use of new animal-free methods?

The most significant obstacles that emerged from our exploratory research are as follows:

- Availability of resources for developing and applying new animal-free methods, for instance research funding, facilities and time.

Insufficient or no access to (new) animal-free methods.

- Support from the professor or PI for applying (new) animal-free methods.
- Insufficient awareness of the existence and potential of (new) animal-free methods and expertise in this field.

4.3 Those involved

Research question 3. Which players strongly influence the choice and use of animal-based or animal-free research models?

Our exploratory research suggests that the following people and organisations are very influential when deciding on and using animal experiments.

- Professors/Pis
- Collaboration partners (multidisciplinary teams/external work contacts)
- Organisations that fund research
- The pharmaceutical industry
- Politics, the media and the social debate
- Editors/reviewers at high-impact journals
- Laws and regulations

The media and social debate influence politics; politics influences funders; funders influence the type of research.

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