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Research Article

Learning from Negative Results-Critical Incident Reporting System in Laboratory Animal Science (CIRS-LAS.de)

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Abstract

In 2016, almost 3 million animals were used for scientific experimental purposes in Germany. In view of this large number, the aim of the project presented here is to contribute to the refinement of animal research practice and to the reduction of laboratory animals in accordance to the guiding 3R-Principles for ethical use as far as possible in the field of laboratory animal science. For this purpose, the Central Experimental Animal Facility of the University Hospital Jena established a "Critical Incident Reporting System in Laboratory Animal Science" (CIRS-LAS) in 2014, based on established CIRS in human medicine. The reporting system should help to clarify negative events and to enable the development of error avoidance strategies by means of a cause analysis. The aim is thus to contribute sustainably to an increase in quality and efficiency in the working environment of laboratory animal science in the sense of the 3R principles. The CIRS-LAS project is supported by the German Federal Ministry of Education and Research (BMBF) since 2017. The domain "www.cirs-las.de" currently exists as a functional beta version, over which 40 reports of critical incidents have been received and evaluated in the sense of descriptive statistics within a reporting period of approximately 18 months. The results show that a large number of different categories ("animal species" involved in incidents, "occupational group" involved, the "estimated degree of stress" for the respective laboratory animal species, the "context of the incident", the "usability of results from experiment" and also "visitor numbers" on the portal) are suitable for evaluation and statistical analysis. Based on the case reports evaluated in the present study, initial statements can be made regarding the underlying causes of the occurrence of critical events. However, reliable statements on observed effects necessitate further analysis and collection of case reports in this regard. Overall, it was possible to demonstrate the high potential of a CIRS for laboratory animal science with regard to the consideration of the 3R principles in daily scientific operations. This is also proven by an ever faster growing number of registrations of new portal users. Critical incident reporting in laboratory animal science can thus serve as a valuable tool to monitor the quality of animal care and give insight into the nature of critical incidents.

Keywords: Adverse events; Critical incident reporting system; Laboratory animal science; 3R-Principles; Reduction; Refinement

Introduction

For many years the public discussion about animal welfare and scientific research for the benefit of human being is emotionally charged. Key elements of this debate concern the fundamental questions of ethics and over all, the reverence for life [1]. Mankind faces an ethical conflict between animal protection and human health [1]. On one hand, the "Declaration of Helsinki" states that, in the context of biomedical research, experiments on humans can only be justified by the maximum possible minimization of health risks for the subject. This requires the exploitation of all scientifically offered possibilities of knowledge, in particular experiments on animal models [2]. On the other hand, man is subjected to moral and ethical responsibility and needs to preserve and respect life [1]. Hence, the greatest care should be taken in order to alleviate the pain that has necessarily been inflicted in animal experiments [3]. The relevant legal bases therefore are formulated in the EU Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes [4]. In Germany, the EU Directive is applied within the legal regulations for animal experiments and laboratory animal science by the German Animal Welfare Act (TierSchG), [5] and the German Animal Welfare Ordinance (TierSchVersV), [6].

Both legislative texts were extended by the so-called 3R principles since 2010 [7,8]. In accordance with these principles, every scientist, veterinarian and animal keeper that works in the field of animal test should strives to reduce the amount of animal testing to a minimum and to improve the conditions for laboratory animals. As it is well known from experience in the field of human medicine, "Critical Incident Reporting Systems" (CIRS) can make an efficient contribution to clarify causal error chains in hospital operations and have the potential to minimize the risks to the patient's well-being [9-14].

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The high relevance of this topic in general is underlined by currently 3881 hits for the keyword "critical incident reporting system" in the database pubmed. In contrast, up to this point, no CIRS had been implemented in veterinary medicine and only reports on panel meeting discussions existed [15]. In our opinion, a CIRS for laboratory animal science, with the aim to improve conditions for laboratory animals by reducing avoidable incidents as cause of suffering, is long overdue.

Considering the "Declaration of Helsinki" and the current state of medicine, the use of animals in experimental medicine cannot be avoided completely. The need for a CIRS in laboratory animal science is due to almost 3 million animals that were used for scientific experimental purposes in Germany in 2016 [7]. Every year, a large number of scientific articles based on animal experimental studies are published. In view of the high number of laboratory animals, the Swiss Cheese Model [16] predicts the occurrence of critical situations with a risk potential for animals and/or humans. There is therefore a great need to clarify the number of unreported cases and to evaluate dangerous situations in order to further improve the conditions and procedures in the field of laboratory animal science. However, negative experiences gained from experiments get lost or are not referred in publications. The objective of the CIRS-LAS.de reporting system is the collection of negative experiences in the entire range of laboratory animal science and to avoid them in the future. In accordance to the 3R principles the evolved portal will therefore improve animal safety and reduce the number of laboratory animals.

Materials and Methods

General aspects

At the end of 2015, we [17] established a Critical Incident Reporting System in Laboratory Animal Science (CIRS-LAS) which is currently entering the beta phaseand counts already for 42 active members. The created database functions analogue to CIRS that are well established in human medicine [12,18]. CIRS-LAS is supported by German Federal Ministry of Education and Research (BMBF) since 2017 within its funding to support alternatives to animal experiments [1]. CIRS-LAS is managed as a network-wide online reporting system and database for the anonymized acquisition, analysis and sharing of safety-relevant incidents in laboratory animal science. The functionality, that is to say the generation and location of database entries, as well as the allocation of the graphical user interface of the portal are currently accomplished by a Commercial Content Management System (CMS) and managed under the domain "www.cirs-las.de". The web analysis tools Awstats [19] and Webalizer [20] are used to record global visitor statistics, such as the number of portal calls, generated traffic and the number of visitors at a certain time point in time. The collection and processing of personal data is carried out in accordance with the guidelines of the General Data Protection Regulation (GDPR) (EU) 2016/679, which came into forceon May 25, 2018 [21].

Case reports and user registration

The anonymous reporting of critical incidents in laboratory animal science is possible for everyone via an input form in the frontend without the need of prior registration or login. The report is sent to the administrators without a link to personal data. In the next processing step, the reports are checked for anonymity and technical accuracy, complemented and revised if necessary, made anonymous and then published by the administrators in a corresponding sub-category in the portal's case report archive via the blog post function. On CIRS-LAS portal, reports can be assorted to the following sub-categories: "anesthesia", "experimental cardiology", "experimental infectious disease", "experimental neurology", "experimental oncology", "experimental ophthalmology", "experimental surgery/othopedy", "genetic & laboratory animal breed", "laboratory animal care", "hygiene", "laboratory animal nutrition", "pesticide residues test", "process development", "product development" and "toxicological analysis". Here, incidents can be recorded and subjected to evaluationwith regard to further subcategories like "animal species", "hygiene status", "age group", "sex", "degree of stress" on the animal, "usability of the results from the experiment", "error factors" and reporting "occupational group", "location" as well as "context" (breeding, keeping, experiment or training) and "classification of severity on the animal". The scale for this is classified in accordance with the EU Animal Experiments Directive and the Animal Welfare Ordinance (TierSchVersV) in force in Germany since 2013 [5]. Further explanations of the incidents, for example descriptions of experimental specifications, possible causes, upload of supporting documents and already proposed conceivable solutions, can be provided. The registration of new users, that gain access to the contents of the case report archive, is controlled via a registration and log-in, which are implemented in the front end of the CMS via an input mask for personal data, such as name, e-mail address, and institute/workstation. After verification of the registration data and authentication by the administrator, the user has the possibility to log in with a self-chosen password. An overview of the functional data processing structure is given in figure 1.

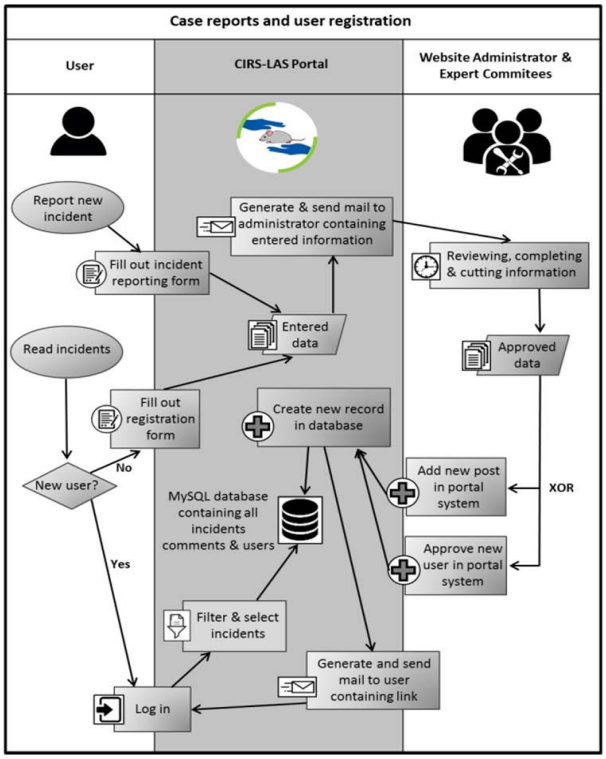

Figure 1: CIRS-LAS-portal data flow chart of reported incidents and user registrations (modified after Kobold M [22]).

Contact options

Both, registered and non-registered users can contact the administrator for feedback or information purposes. This is realized on the one hand via a contact form integrated in the frontend, which sends content to an incoming mail server and forwards it via an outgoing mail server. On the other hand, it is possible to contact the CIRS web administrators directly via the e-mail address info@cirs-las.de.

Public relations work

An important prerequisite for the acceptance and use of the reporting system, in addition to an intuitive handling, is comprehensive public relations work [23,24]. To this end, various in-house training events are initiated for scientists, veterinarians and animal caretaker. The main intention here is to change the perspective regarding the handling of error-based incidents and the error management in general [25]. Furthermore, the project was presented at various conferences of the GV-SOLAS [26], Felasa [27] and AAALAC [28]. In the future further international conference visits are planned. As part of the technical development of the CIRS-LAS project, web seminars are offered throughout Germany as continuing education events for groups working in the field of laboratory animal science.

Statistics

Various category-dependent frequency statistics are kept via the incoming CIRS reports. Up to now, the CIRS-LAS platform has been continuously revised and was temporarily out of operation due to maintenance work. During the effective period reportson critical incidents in laboratory animal science have been received with regard to various disciplines. These were evaluated in terms of the following subcategories: The field in which the incident occurred, the type of occupational group through which incidents were reported, the species associated with the incidents, the degree of injury caused by the reported incident, the degree of influence on the outcome of incidents during the performance of experiments and finally the context in which the event occurred. Reported cases are checked for plausibility by experts from the CIRS-LAS team [17] to ensure that only real events are included in the statistics. The key figures shown in the diagrams below are values standardized to percentages in order to highlight the relations between the categorical items. The statistical evaluation of the server log files via Webalizer [20] additionally enabled the display of a monthly overview of the number of portal visits to get an impression on the frequency of use. Here, the time that has elapsed since the last request is calculated. If the time span is longer than the server-dependent visit timeout of 30 minutes, or if this visitor has never received a request before, the request is noted as a new visit and the number of visits is counted up. Both for the site and for the IP address assigned to the visitor. According to the EU GDPR guidelines, personal data from the server log files, such as the IP address, are automatically made anonymous after 7 days, so that no conclusions can be drawn about the user.

Results

Over a period of about 18 months, 40 reports (n=40) on critical incidents in laboratory animal science were collected ($\bar{x}$=2.22 reports/month).

Figure 2 shows the absolute number of visits to the portal over a period of one year. From June 2017 till December 2017, the number of visits remained relatively constant. An increase in the frequency of visits can be seen within the months January 2018 to May 2018. The maximum number of visits here in March 2018 was 1248 on the page "www.cirs-las.de".

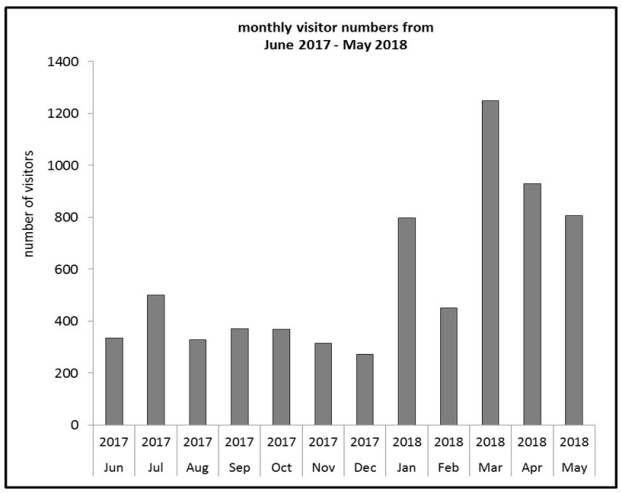

Figure 2: Monthly visitors on CIRS-LAS portal from June 2017 until May 2018.

The majority of the reported cases (45%) occurred in the discipline "experimental surgery/orthopedy". On the other hand, the discipline of "experimental ophthalmology" accounts for only 2.5% of all reported cases. The discipline of, "laboratory animal care" is also striking with the second highest share of all reports of critical incidents, at 17.5% (Figure 3).

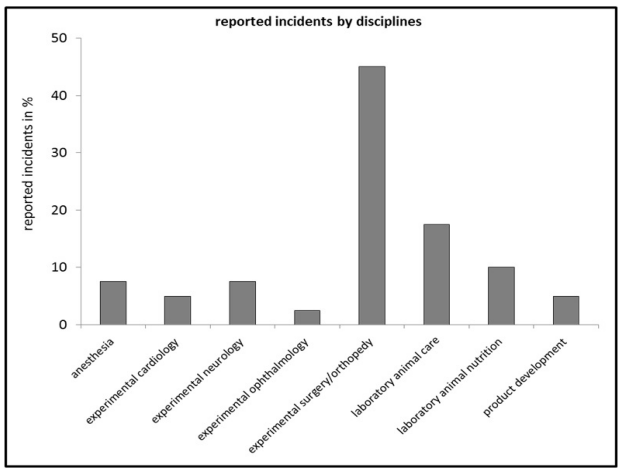

Figure 3: Reported incidents by "disciplines", relative frequency in percent of n=40.

As far as the profession is concerned, the main share of 55% of all cases received was reported by scientists working within the project in which the critical incident occurred. Different occupational groups, which were not directly involved in the experimental project reported an event in relatively equal shares, like "scientific coworker outside the project" (20%) and "non-scientific staff" (22.5%), (Figure 4).

Looking at the distribution of frequencies with respect to the parameter "estimated severity level", the highest values are found in a

middle range of the estimation continuum. Relatively high values are also found at the respective ends of the continuum ("no": 20%; "no recovery": 20%) (Figure 5). A "moderate" level of stress for the animals due to a critical incident was reported in the majority of the cases, with a total of 47.5%. The case numbers for an estimated "mild" level of severity (5%) and "severe" (7.5%) occur considerably less frequently at cumulatively 12.5% (Figure 5).

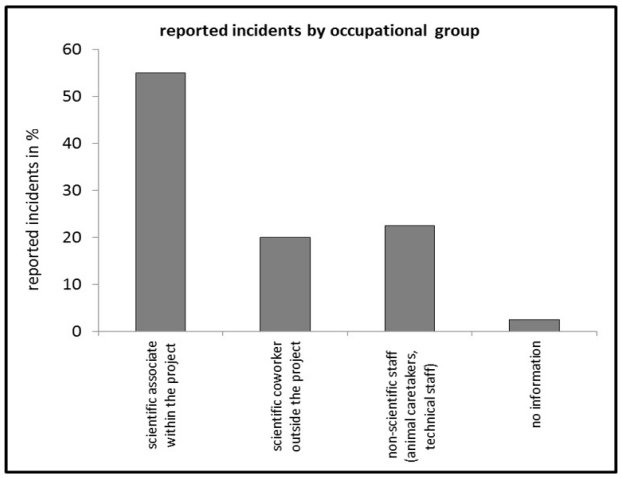

Figure 4: Reported incidents by "occupational groups", relative frequency in percent of n=40.

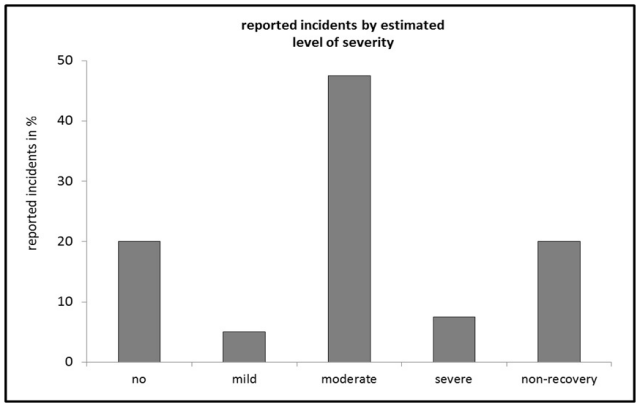

Figure 5: Reported incidents by "estimated severity level", relative frequency in percent of n=40.

Referring to the context of the occurrence of critical events, an accumulation of 72.5% of all reported cases is found in the "experiment/ experimental set up/ analysis" section. However, it is also striking that almost one in four cases reported (22.5%) relates to "animal husbandry". Consequently, the subcategories "education" and "animal breeding" each account for only 2.5% of the total number of reported cases (Figure 6).

The animal species-specific assignment of critical incidents shows in the present data set a maximum relative frequency for the experimental animal "sheep" (30%), (Figure 7). According to this study, the pig is the second most common laboratory animal involved at 22.5%. In 15% of all cases, the rabbits were involved in the occurrence of a critical incident. In 12.5% of the cases, rats and mice were the laboratory animal of the species concerned when an incident occurred. On the other hand there was no animal involved in 5% of the reported cases.

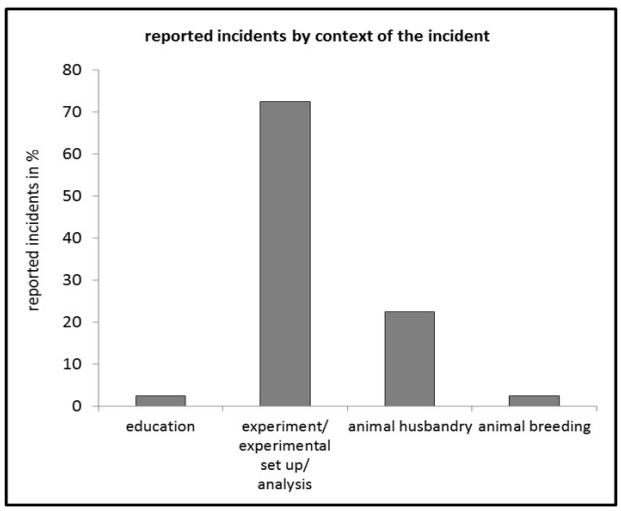

Figure 6: Reported incidents by "context of the incident", relative frequency in percent of n=40.

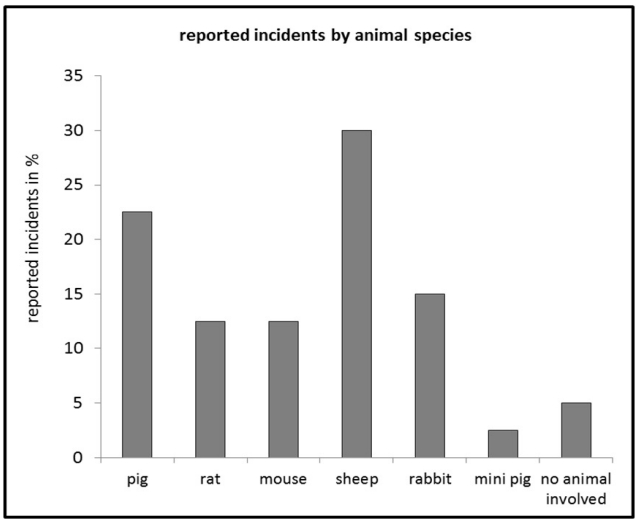

Figure 7: Reported incidents by "animal species", relative frequency in percent of n=40.

The animal species-specific assignment of critical incidents shows in the present data set a maximum relative frequency for the experimental animal "sheep" (30%), (Figure 7). According to this study, the pig is the second most common laboratory animal involved at 22.5%. In 15% of all cases, the rabbits were involved in the occurrence of a critical incident. In 12.5% of the cases, rats and mice were the laboratory animal of the species concerned when an incident occurred. On the other hand there was no animal involved in 5% of the reported cases.

Dark gray tone: Relative frequency including case reports where "no experiment" was conducted (n=40).
Light gray tone: Relative frequency event reports where an experiment was conducted (n=28).

In 27.5% of all case reports of the present data set there was no direct connection with an experiment (Figure 8). Of all case reports for which the question of the degree of influence of the incident on the experiment is relevant (excluding data of critical incidents without any connection to an experiment), the results were fully usable in less than one in four cases (21.4%). For another 21.4% of the reports, the results were only slightly influenced, so that an error-estimation in these cases was very probably still possible to correct the examination results. On the other hand, in the present data set, when critical incidents occurred, well over half (60.7%) of all experiments were either significantly disturbed (25%) or even completely unusable (35.7%), (Figure 8). Overall, the results provide an initial structured overview of the data situation. The conspicuous features mentioned here provide initial indications for further analyses or questions, examined in more detail as follows.

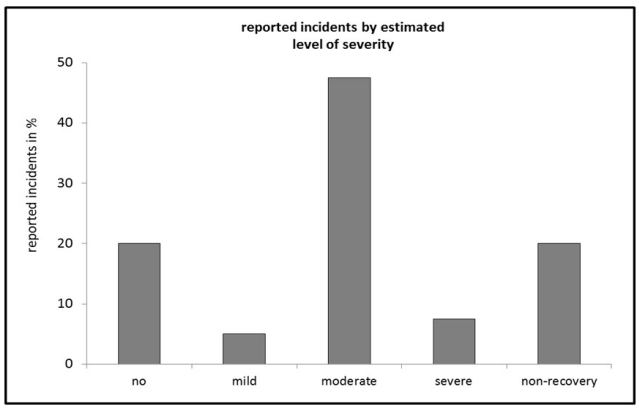

Figure 8: Reported incidents by "usability of results" relative frequency in percent.

Conclusion

The prepared data serve to give an impression of the extent to which a critical incident reporting system is able to clarify the frequency of errors with regard to work areas with potentially high risk. Against the background of the number of case reports received so far, the frequency distributions shown are to be regarded as exemplary and can therefore provide clues for possible conclusions. Even if the increased number of visitors in the period from January 2018 to May 2018 does not allow any conclusions to be drawn about the number of users, the observed effect can be interpreted in some ways as a consequence of the increased expenditure on public relations within the framework of the CIRS-LAS project and points to an increasing acceptance and use of the portal. However, to what extent the tendency observed in this regard can be attributed to increased further development and maintenance work on the portal by the administrators themselves remains open up to this point and requires further analysis of global user statistics. In the future, after reaching a sufficiently large number of case reports and a corresponding expansion of the database structure, further questions will be answered, for example, whether there are connections between the context of the reported event and the usability of the results from the experiments or whether the estimates of the severity level for an animal differ between the occupational groups. Furthermore, comparative statistical evaluations are planned with regard to the question of a connection between the degree of stress for an animal and the discipline in which a critical incident occurred.

The rate of 17.5% of reported cases from the discipline "laboratory animal care" (Figure 3) underlines the importance of analytical clarification of the occurrence of errors that lead to critical events even outside the actual core project of experimental investigations. The importance of interdisciplinary use of CIRS-LAS is illustrated by case reporting rates of 22.5% generated by the occupational group: "Non-scientific staff" and a cumulative share of 42.5% of reports submitted by staff who were not directly involved in the experimental project ("scientific coworker outside the project" with 20% and "non-scientific staff" with 22.5%) (Figure 4). About half of all reported cases originate from "scientific associate within the project" (55%) (Figure 5), whereby 72.5% (Figure 6) of the cases are attributed to the supposedly corresponding context "experiment/ experimental set up/ analysis". A further comparative statistical study could answer the interesting question of which "occupational group" assigns a critical event to which "context". The contextual attribution of the occurrence of critical events in connection with an "occupational group", however, could have conflicting effects in terms of a less condemning error culture [24]. This, insofar as the results provide scope for interpretation in the sense of a mutual error attribution effect between the respective "occupational groups".

In relation to the "estimated severity level" on the experimental animal (Figure 5), normally-distributed data would be expected according to the gradations of severity. Although the majority of cases report a moderate degree of severity, this cannot be observed here. It therefore remains open until further notice whether this anomaly can be attributed to the relatively small data set or whether it is based on real effects. The result of the frequency analysis of the corresponding "animal species" in the reported cases therefore also leaves room for open questions (Figure 7). For example, "sheep" are reported to be involved in 30% of cases (Figure 7). Whether there is a connection with an increasing number of reports by a certain working group, which is increasingly experimenting on "sheep", remains unclear within the scope of the anonymity agreement, since the corresponding data are not collected on the portal side. Independent interpretation possibilities, for example whether the sheep as an experimental animal is potentially more difficult to handle than comparatively other types of experimental animal, or whether the observed tendencies may also occur purely random, remain open here.

With regard to the usability of results from the cases with experimental context, the analysis of the data set evaluated here suggests a high potential for a significant increase in efficiency and quality through improved error detection in animal experimentation practice (Figure 8). Systematic error detection by a CIR system of laboratory animal science, combined with the development of a corresponding catalogue of measures for error prevention, thus form the cornerstones of a promising strategy for contributing to the refinement and reduction of laboratory animals.

However, to obtain more reliable information from the statistical analysis of the case report database, a higher number of reports are required. The aim is therefore to increase participation in the reporting

system in the future. Within the framework of further education lectures, participation in congresses and conferences as well as online lectures, a different awareness of the prevailing error culture [24] is to be initiated. On the other hand, however, the aim is also to pursue concrete educational work with regard to the degree of awareness, the mode of operation and the benefits of CIRS-LAS. In order to create the possibility of receiving ad hoc feedback on an individual case report, the formation of an expert panel is planned in the medium term, which will provide information on troubleshooting and avoidance. Independent of statistical meta-analyses, the planned expert panel will act as an additional feedback tool and generate a direct benefit for reporting a critical incident in the form of a learning effect. Additionally, the comment section of the collected incidents serves as a basis for fundamental discussions and an exchange of ideas between scientific peers on the portal. A detailed error analysis from the concrete incidents with proposals for measures which should contribute to their avoidance will be carried out separately and after further reports have been collected. The resulting error avoidance strategies form the basis for two of the 3R principles (reduction and refinement) so that failed projects are not repeated and the conditions for experimental animals in experiments, animal husbandry and breeding can be improved. In addition to the plausibility check of reported cases by the experts of the CIRS-LAS team [17], a further revision by an expert committee, which is currently under construction, is planned in the future. In this way, it is to be ensured that only cases that have actually occurred are entered into the database.

Over all the results show that CIRS-LAS portal has a great potential to serve as an essential contribution towards the implementation of two of the 3R principles. Anonymously shared negative experiences can have an influence on the experimental setup and execution of new scientific projects. In conclusion the realization of 3R-a reduction of the number of used animals in experiments (reduction), diminution of stressful experiments (refinement)-can be achieved by using the CIRS-LAS portal. It is furthermore conceivable that the implementation of the CIRS-LAS could serve to enhance the trust in laboratory animal science, both of the public and the scientific community. The time to rethink has been achieved-to learn from negative results in animal based research!

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