Review Article

Have the Non-Technical Project Summaries of Animal Experiments in Europe Improved? An Update

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Abstract

Following a review of Directive 2010/63/EU on the protection of animals used for scientific purposes in the European Union (EU), non-technical project summaries (NTS) of all approved projects must be published in a central database using a standard template. Our initial review of the NTS reported in *ALTEX* in 2018 had found the NTS to be deficient in their accessibility and quality, notably the "adverse effects" section where the harms to the animals are meant to be described. Here we repeat our review to see if these legislative changes have improved the accessibility and quality of the NTS. As before, we focused on the NTS from the United Kingdom (UK) and Germany; even though the UK has left the EU, it is using the same template. We found significant improvement in the reporting of five of the six elements we identified as essential to the "predicted harms" section. However, there was no significant improvement in the reporting of adverse effects. Only 41% of German NTS and 48% of UK NTS are fully reporting this important element of the "predicted harms" section. In our view, researchers need support in describing the impact of their research on the animals and to assist here we include a checklist for competent authorities and a list of suggested terminology for standard administration and sampling procedures. Unless the NTS improve further, their utility as a tool for sharing of good practices in the 3Rs or to support evidence-based policy-making will remain limited.

Plain language summary

All countries of the European Union (EU) are required to publish "non-technical summaries" (NTS) of research projects that use animals. To improve transparency, the public must have access to NTS and understand their content. Our previous review found that the information provided in the NTS was lacking in many cases. This is preventing a full understanding of what animals experience during experiments. In particular, NTS often failed to fully describe what procedures the animals would be subjected to, how often they would take place, how long they would last, and the harm they would cause. Here we repeat our review to see if recent legislative changes, including the requirement for NTS to be published in a central database using a standard template, have made a difference. While there has been some improvement in reporting, many NTS still fail to adequately describe the harm that animals will experience.

1 Introduction

Directive 2010/63/EU on the protection of animals used for scientific purposes (EC, 2010, the Directive) requires member states of the European Union (EU) to publish non-technical project summaries (NTS) of all authorized projects involving animals (Article 43). These NTS are to include information on the objectives of the project, including the number and types of animals to be used, the predicted harms, benefits, and a demonstration of compliance with the 3Rs (replacement, reduction, and refinement of animal experiments). From 1 January 2013, member states were to begin publishing NTS of all newly approved projects. To assist, the European Commission (EC) unit responsible for the Directive drafted together with them a "working document on Non-Technical Project summaries" (hereinafter referred to as the EU Guidance). It explained how a NTS should be written and included a template for the member states to use if they wished (EC, 2013).

The aim, according to Recital 41 of the Directive, was to ensure that the public is informed about the animal experiments being authorized and conducted in the EU. According to the revised EU Guidance on the NTS (EC, 2021), "*it is hoped that a well-written NTS can:*

1. *Enhance openness and transparency around the use of animals in research.*
2. *Facilitate improved accessibility and understanding of different animal use areas amongst the public and non-governmental organisations (NGOs).*
3. *Encourage scientists to develop and improve their communi-*

Tab. 1: Changes to the non-technical summary template – Predicted harms section only
Aspects in bold are those assessed in Taylor et al. (2018) and this review.

2013-2019 template UK and EU	2020 template EU	2020 template UK vol 2
Adverse effects	Predicted harms	Predicted harms
In the context of **what you propose to** do to the animals, what are the expected **adverse effects** and the likely/expected **level of severity**? What will happen to the animals at the **end**?	In what **procedures** will the animals typically be used (for example, injections, surgical procedures)? Indicate the **number** and **duration** of these procedures.	Typical **procedures** done to animals, for example injections or surgical procedures, including **duration** of the experiment and **number** of procedures. Typically, what will be done to an animal used in your project?
	What are the expected impacts/**adverse effects** on the animals, for example pain, weight loss, inactivity/reduced mobility, stress, abnormal behaviour, and the duration of those effects?	What are the expected impacts and/or **adverse effects** for the animals during your project?
	What species and numbers of animals are expected to be used? What are the expected **severities** and the numbers of animals in each severity category (per species)? (table to be filled in)	What are the expected **severities** and the proportion of animals in each category (per animal type)? (no table provided)
	What will happen to the animals kept alive at the **end** of the procedure? Please provide reasons for the planned fate of the animals after the procedure.	What will happen to the animals at the **end** of the study? (choice of Killed, Kept alive, Set free, Rehomed, Used in other projects)

cation skills and better explain their research interests to the public.

4. *Improve the quality of the scientific information available to the public and avoid the spread of misinformation.*
5. *Support the sharing of good practices in relation to the 3Rs.*
6. *Support evidence-based policy making by competent authorities.*"

As animal protection groups interested in better transparency on the animal testing issue, we performed a review of the publication of the NTS across Europe that was published in *ALTEX* in 2018 (Taylor et al., 2018). We found that by 2017, some four years after the implementation of the requirement to publish NTS, not all countries were yet publishing them (four were missing) and of those that were, seven were taking at least 18 months to publish the NTS following authorization of the project. Only 15 member states were using the voluntary template; most of the remainder was providing less information than specified there. There was variable use of identification of each NTS by title, number, or date, and most NTS were being uploaded as pdf documents to the website hosting them with no search functionality.

In Taylor et al. (2018) we had also performed a more detailed analysis of quality of the reporting in the "adverse effects" section of a representative selection of the first complete set of NTS from Germany (from 2014) and the United Kingdom (UK) (from 2013).

According to the working group template, the "adverse effects" section was meant to provide: "*In the context of what is being done to the animals, what are the expected* adverse effects *on the animals, the likely/expected level of* severity *and the* fate *of the animals*?" *[elements under review emphasized]*

We found that the NTS for the UK and Germany were deficient in providing sufficient, understandable information on the procedures (including their frequency and duration for the animals), the expected adverse effects, predicted severity of the project or the fate of the animals in this section. NTS scored particularly badly on describing the types of procedures to which the animals would be subjected, with only 31% of the UK and German NTS giving a clear description. 33% of the German NTS and 14% of the UK NTS did not appear to provide any meaningful information in this regard. Similarly, only 41% of the UK NTS and 39% of the German NTS adequately described the adverse effects the animals may experience. We recommended that member states addressed these deficiencies and that consideration was made to having a centralized database and a more detailed template for the NTS.

A review by Weber (2018) also criticized the inclusion of generic statements in the NTS to describe the benefits of the proposed project. Following these reviews and a review of the Directive (EC, 2017), which identified the same issues, the European Commission took the opportunity to address the problem when an initiative arose to reduce bureaucratic burden across EU environmental legislation. In 2019, Regulation (EU) 2019/1010 (EC, 2019) altered Article 43 of the Directive to require all NTS of projects authorized from 1 January 2021 to be submitted within six months of authorization to an open access EU database. In July 2021 the

Tab. 2: Publication of non-technical summaries (NTS) for 2022 by all 27 member states as of 1 May 2023

Member state, sorted by animal use in 2020	Animal use in 2020	Number of NTS for 2022	Publishing regularly?	Ratio animals used/ number NTS
Germany	1,897,640	2,791	Yes, continually	680
France	1,643,787	2,634	Yes, continually	624
Spain	732,831	1,300	Yes, continually	564
Italy	455,140	712	Batches, last one Feb 2023	639
Belgium	437,275	1,528	Yes, continually	286
Netherlands	406,724	273	Yes, continually	1,490
Sweden	274,076	285	Yes, continually	962
Denmark	261,750	217	Yes, continually	1,206
Czechia	238,575	351	Yes, continually	680
Austria	206,469	636	Yes, continually	325
Hungary	139,186	55	Biannually, last one Nov 2022	2,531
Ireland	138,690	86	Yes, continually	1,613
Finland	119,986	114	Yes, continually	1,053
Poland	113,341	487	Yes, continually	233
Portugal	66,099	27	Biannually, last one Feb 2023	2,448
Greece	52,991	145	Yes, continually	365
Malta	47,490	2	Annually, last one May 2022	23,745
Croatia	38,036	21	Continually, last one July 2022	1,811
Slovakia	15,211	22	Batches, last one April 2023	691
Bulgaria	11,214	36	Annually, last one Apr 2023	312
Romania	7,874	42	Annually, last one Mar 2023	187
Slovenia	5,796	12	Yes, continually	483
Luxembourg	5,457	11	Batches, last one Aug 2022	496
Estonia	4,089	20	Biannually, last one Feb 2023	204
Latvia	4,002	7	Continually, last one Jun 2022	572
Lithuania	3,788	50	Biannually, last one Apr 2023	76
Cyprus	3,746	7	Biannually, last one Nov 2022	535

European Commission published ALURES (AnimaL Use Reporting – EU System), the EU NTS database on the use of animals for scientific purposes under Directive 2010/63/EU that also includes retrospective assessment results (RA or RAR)[1].

Regulation (EU) 2019/1010 was followed by an Implementing Decision in 2020 (EC, 2020) that included a revised, mandatory template for the submission of the NTS and which was complemented by extended guidance (EC, 2021). Most notably, the "adverse effects" section of the template, renamed "predicted harms", was split into four subsections to ensure more detail was provided (Tab. 1).

In the meantime, however, the UK left the EU, and whilst it was not obliged to submit NTS to the ALURES database, it did adopt an extremely similar template to the revised EU one (Tab. 1).

We therefore wanted to take this opportunity to repeat the study in Taylor et al. (2018) to confirm that these legislative changes had improved the accessibility of the NTS, to see if the quality of the German and UK NTS had improved, and to make further recommendations where necessary.

2 Methods

Accessibility of the NTS

The ALURES database was reviewed on 1 May 2023 to assess the number of member states publishing and the usability of the website.

The number of animal uses in the EU in 2020 (EC, 2023) was used as a general indicator of animal use. These were compared

[1] https://webgate.ec.europa.eu/envdataportal/web/resources/alures/submission/nts/list

with the number of published NTS per year per member state (Tab. 2). Projects are approved for up to a period of five years, therefore the publication date of NTS never aligns with the publication date of the number of animal uses. Hence, it was not intended as a direct comparison between animal use and number of NTS, but to see if member states had similar ratios of NTS to animal use. The total animal use for each member state was calculated by adding the reported uses of animals "*for research, testing, routine production and training purposes*" (Section 2) to the reported uses of animals "*for the creation and maintenance of genetically altered animals*" (Section 3) (EC, 2023).

Improvement in the quality of the "predicted harms" section: German and UK NTS

To assess the quality of the reporting in the "predicted harms" section of the NTS for Germany and the UK, a statistically significant number of NTS were reviewed for the most recent complete year of NTS available on ALURES and the UK Home Office websites respectively.

On 1 January 2023 there were 2,791 NTS from 2022 for Germany in ALURES. A 95% confidence level that any results were representative of the whole sample would require 334 NTS to be reviewed, a 90% confidence level would require 246[2]. It was decided to review 300 NTS from 2022 for Germany, as this was the same number of NTS as the Taylor et al. (2018) review and would still give over 90% confidence of a representative sample. Approximately 10 NTS were randomly selected from each page of 100 NTS presented in ALURES to bring the total reviewed to 300. The NTS were reviewed by a German native speaker and animal welfare expert, Tilo Weber.

As of 1 January 2023, the most recent complete year of NTS for the UK was for projects granted in 2020. These were published as two pdf volumes on 6 June 2022 (Home Office, 2022). They do not include the NTS for Northern Ireland. Removing duplicates and NTS using the old template left 399 NTS. A 95% confidence that the real value is within ± 5% of the measured/surveyed value required the review of 196 NTS. We chose to do 200. Approximately every other NTS in each pdf document was therefore selected for review. The NTS were reviewed by an English native speaker and animal welfare expert, Katy Taylor.

While proportionately more of the UK NTS were selected for review (50% of the total number of published NTS) compared to the German NTS (where 11% of the total number of published NTS were selected), the sample size for Germany is still representative with a confidence level of over 90% (Fig. 1).

The "predicted harms" section (only) was reviewed for both German and UK NTS, looking at the same six elements from the Taylor et al. (2018) review. These were a description of:

– Typical *procedures*, including:
  • Number of procedures (*frequency*)
  • *Duration* of the experiment
– Expected *adverse effects*

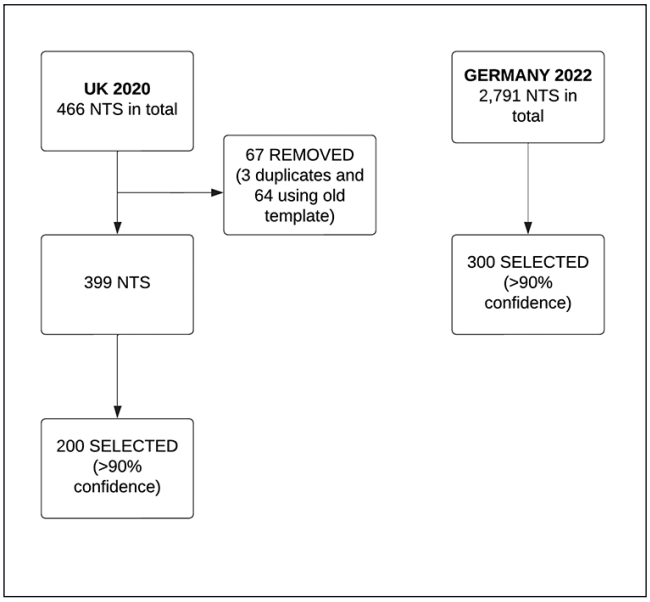

Fig. 1: Flow chart illustrating the NTS sample size selection process for Germany and the UK

– Proportion of animals in each *severity* category
– *Fate* of the animals at the end of the project.

We used the same scoring system that is described in Taylor et al. (2018). Following training, we assessed the agreement between the reviewers on the scoring of elements using a small sample of NTS that were not included in the final review. The "predicted harms" section was read through twice, and for each element the NTS scored a "yes", "partial" or "no" depending on the extent to which it had been addressed. Elements scored a "yes" if a reasonable attempt to answer the question had been given, i.e., the majority of expected procedures/adverse effects had been summarized clearly. Elements scored a "partial" if some of the procedures/adverse effects had been described but there was missing or unclear information. Elements scored a "no" if the element had not been addressed in any meaningful way. Taylor et al. (2018) includes several detailed examples of what we considered to be good and bad text in the "predicted harms" section.

We kept our review to the "predicted harms" section; if the required elements had been provided in other sections of the NTS, this was ignored, but we did award the answer if it was given elsewhere in the "predicted harms" section, e.g., if remaining elements of the procedure were given under "adverse effects".

Results were transferred into an Excel spreadsheet for analysis (available upon request). Results were compared between Germany and the UK as well as between this review and the previous one. To determine the significance of any difference in reporting between year or country, a chi-square analysis was conducted in the form of a two (year or country) by three (yes, partial, no) table[3].

2 Calculated using: https://www.calculator.net/sample-size-calculator.html

3 Calculated using: https://www.socscistatistics.com/tests/chisquare2/default2.aspx

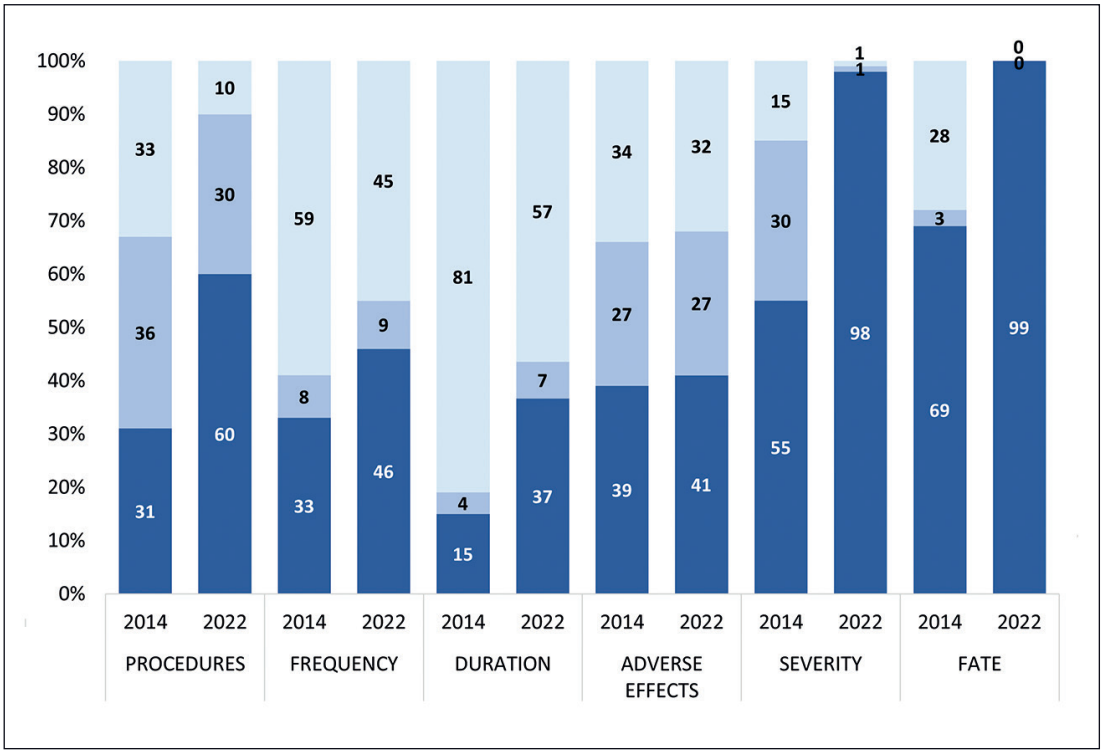

Fig. 2: Comparison of the percentage scoring of German NTS from 2014 and 2022 (N = 300 each) for each element of the "predicted harms" section Complete (dark blue), partially complete (medium blue) or incomplete (light blue).

3 Results

3.1 Accessibility of the NTS

The NTS in ALURES are presented in publication date order and listed by country, language, title, EC NTS/RA identifier (ID that provides country, date and number)[4], publication date, version[5] and EU submission[6] (yes/no) with a link to open the NTS itself in another browser tab. NTS are typically written in the national language of the member state, but both the list and individual NTS webpages can be easily translated using the Google translate website extension.

ALURES is simple to use and enables the user to scroll through all published NTS or to search by country, title of project, EC NTS/RA identifier, keyword, species[7], purpose(s) of project[8], year of publication, and language. Combined searches can be performed, e.g., species by purpose of project (more than one can be selected). Searches can be downloaded as an Excel file.

There is no explanation of how to use ALURES on its website, and it is not clear how accurate a search of NTS by keyword is currently. When conducting a search, the results are provided with no summary information. For example, a search of species (dog selected) and purpose of project (all selected) would not give the split of the number of projects involving dogs for each purpose of project; the NTS are simply provided in a list. That way a user would not immediately see that, for example, there are no projects involving dogs with the purpose of "preservation of the species".

The way NTS are presented in a list does not completely match the available search criteria, i.e., the "purpose of project" and "species" fields are not displayed in the NTS list. This is possibly because NTS may have more than one entry for these. Similarly, there is no capacity to search for or see a list of NTS by "severity level" of the project or "total number of animals". These would also require a more sophisticated presentation of the NTS.

On 1 May 2023 there were 22,921 entries in the database, comprising NTS and RA. There were 11,871 NTS for 2022.

For 2022, there were NTS available from all 27 member states (Tab. 2). However, on 1 May 2023, no NTS were available from six member states (Hungary, Croatia, Luxembourg, Latvia, Cyprus and Malta) for the year 2023.

Most member states were publishing continually, i.e., as projects are authorized – 20 member states had deposited NTS within the last three months. However, publishing among the remaining

[4] E.g., NTS-AT-081832 v.2, 31-05-2022 = Austrian NTS, number of NTS, version number, date of publication.

[5] ALURES allows for NTS to be updated into a new version. When searching, previous versions will not appear.

[6] In order to reduce bureaucratic burden for member states by allowing them to submit NTS for projects that do not fall within the scope of Directive definitions but may be considered as projects under the national legislation, for example, killing animals for organs/tissue and purely observational studies in which none of the techniques reach the definition of a procedure in Article 3(1).

[7] As listed in the statistical reporting requirements under Commission Implementing Decision (EU) 2020/569.

[8] Purpose(s) of project is listed as in the statistical reporting and also goes down one further level, e.g., "Basic research-Respiratory system". Some NTS have more than one purpose.

Tab. 3: The percentage of 300 NTS from Germany for 2014 and 2022 that scored a yes, partial or no for the reporting of six elements in the predicted harms section (rounded to whole percentages)

Predicted harms	Year	Yes (%)	Partial (%)	No (%)	Chi-square result, p value
Procedures	2014	31	36	33	
	2022	60	30	10	65.1, $p < 0.001$
Frequency	2014	33	8	59	
	2022	46	9	45	12.8, $p < 0.01$
Duration	2014	15	4	81	
	2022	37	7	57	42.2, $p < 0.001$
Adverse effects	2014	39	27	34	
	2022	41	27	32	0.5, $p > 0.05$
Severity	2014	55	30	15	
	2022	98	1	1	154.3, $p < 0.001$
Fate	2014	69	3	28	
	2022	99	0	0	103.8, $p < 0.001$

Tab. 4: The percentage of 300 NTS from UK for 2013 and 200 for 2020 that scored a yes, partial or no for the reporting of six elements in the predicted harms section (rounded to whole percentages)

Predicted harms	Year	Yes (%)	Partial (%)	No (%)	Chi-square result, p value
Procedures	2013	31	55	14	
	2020	50	48	2	28.7, $p < 0.001$
Frequency	2013	8	10	82	
	2020	33	53	14	221.4, $p < 0.001$
Duration	2013	6	9	85	
	2020	54	14	32	164.4, $p < 0.001$
Adverse effects	2013	41	35	24	
	2020	48	49	3	38.9, $p < 0.001$
Severity	2013	61	4	35	
	2020	77	18	5	76.0, $p < 0.001$
Fate	2013	83	7	10	
	2020	98	1	1	27.6, $p < 0.001$

member states was more sporadic. For example, the last deposit by Italy was in February 2023 and the last one by Hungary was in November 2022.

3.2 Improvement in the quality of the "predicted harms" section: German and UK NTS

Germany

By 2022, there was near-complete reporting of the *severity* categories of the project and the *fate* of the animals in the German NTS (Tab. 3, Fig. 2).

60% of NTS reported the *procedures* adequately, although another 30% were considered to have done this only partially. There was less complete reporting of the *frequency* of these procedures (46% adequately and 9% partially) and the *duration* of these procedures (37% adequately and 7% partially). There was a statistically significant improvement in all these elements compared to 2014.

However, there was no significant improvement in the reporting of the expected *adverse effects*. Only 41% were considered to have adequately addressed this element, compared to 39% in 2014 (Tab. 3, Fig. 2).

UK

There was a similar pattern of improvement in the UK NTS as seen in Germany.

There was statistically significant improvement in all elements (see Tab. 4, particularly for frequency and duration). However, the improvement in reporting of adverse effects was smaller. By 2020, still only 48% of the NTS had adequately completed the adverse effects element of the section, compared to 41% in 2013, respectively. 23% of the NTS were still missing some information on the severity categories (Tab. 4).

Comparison between Germany and UK

There was a significant difference between the scores (yes, partial, no) between Germany (2022 NTS) and the UK (2020 NTS) for procedural information (chi-square 23.5, $p < 0.001$), frequency information (chi-square 124.7, $p < 0.001$), adverse effects (chi-square 63.9, $p < 0.001$), and severity (chi-square 57.0, $p < 0.001$). The difference for all but severity was that the UK NTS were more likely to provide more *partial* information (Fig. 3). German NTS provided more complete information on severity.

There was no significant difference between the two countries in their scores for reporting duration (chi-square 2.0, $p > 0.05$) or fate (chi-square 1.8, $p > 0.05$).

Evaluation of the current reporting of predicted harms in the NTS

While adequate reporting of the procedures in the German and UK NTS increased 20-30 percentage points in comparison to 2013/14, by 2020/22 still only 50-60% of NTS were considered to have done this satisfactorily.

There was still a tendency to use technical language and focus on irrelevant aspects such as:

- Overly detailed descriptions of surgical procedures, including drug regime used and where incisions are made
- Fate of the animals including method of killing (which belongs in the "fate" section)
- Techniques being used to measure the effect the researchers were interested in (that were not relevant to the animal's experience, e.g., what they were doing with tissues after dissection).

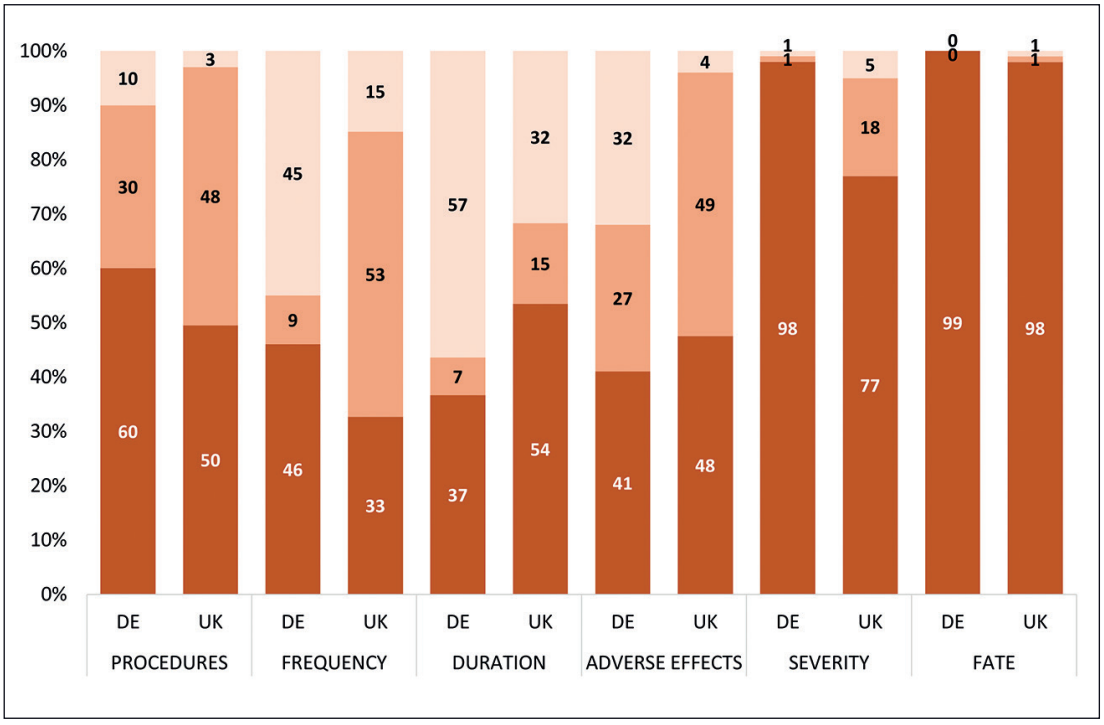

Fig. 3: Comparison of the percentage scoring of German NTS from 2022 (N = 300) and UK NTS from 2020 (N = 200) for each element of the "predicted harms" section Complete (dark orange), partially complete (medium orange) or incomplete (light orange).

A significant proportion scored only a partial. Partial scores in the procedural section were due to researchers:

- Failing to describe all major procedures (when this was apparent to us), including how an animal model had been created
- Failing to describe important aspects of those procedures, e.g., what is being injected (where this could be relevant to adverse effects), route of administration or a brief description of behavior tests
- Using very scientific or technical terms that were not subsequently explained, e.g., intravenous, intraperitoneal, cecal ligation and puncture, myocardial infarction, percutaneous instrumentation, midline laparotomy. This was compounded by the use of acronyms, e.g., IV, IP, CLP, etc.
- Conversely using very vague terms, e.g., "treated with", "administered", "received", "induced".

There seemed to be a particular issue with the reporting of the *duration* of the procedures. Only 37% of the German NTS and 54% of the UK NTS had properly addressed this element according to our expectations. NTS scored a "partial" if they had taken the question literally and given the length of injections (e.g., one minute) or surgery (e.g., one hour) but failed to provide the overall length of the experiment (e.g., 28 days).

There has been little improvement in the proportion of NTS fully answering the "adverse effects" section, particularly for German NTS. The most common reasons for NTS failing to score fully for adverse effects was if they had:

- Not considered the impacts of *all* of the major procedures described in the procedure subsection, i.e., considered the impact of injecting substances but failed to consider the impact of a cancerous growth if cancer models were being used or failed to consider the impact of *what* substances they were administering to the animal, focusing on the administration procedure only
- Used vague terms, e.g., "clinical signs of infection", "disease progression", "adverse effects"
- Used overly technical terms, e.g., "neurological deficits", "mild phenotypes", "leukopenia"
- Not considered the duration of the suffering, which is required in the section. This was more common when it was claimed that there would not be any suffering or that it would be minimal. In some cases, researchers also had included the point at which the animals may start to experience effects, e.g., from day 10, but then failed to mention when the experiment would end
- Described the adverse effects only in terms of the severity level the project was assigned, i.e., mild, moderate, and not what effects the animals would actually experience, such as weight loss, mobility problems, etc.
- Described only the humane endpoints, i.e., what signs they would use to decide when to kill an animal, rather than what they thought the animals may actually experience.

It was notable that researchers often struggled to consider and describe adverse effects more precisely than the classic terminology of "pain, suffering and distress". It was unusual to see more detailed symptoms such as diarrhea, nausea or fatigue to be considered nor the location, severity, type and duration of any pain.

It was common to see mention of regular monitoring, the provision of pain relief, and the implementation of humane endpoints in the "adverse effects" section. This was often in place of any description of the adverse effects.

We also saw examples where the description of the adverse effects appeared at odds with the severity level given for the project.

This was more common in the direction that the adverse effects were described as minimal even though the severity level was set at moderate or severe.

4 Discussion

4.1 Accessibility of the NTS

As a result of these legislative changes, all member states are now uploading their NTS into a centralized and searchable database. The NTS from across the EU are now available in one place, and this is a vast improvement to the accessibility for all those interested in the NTS. It should enable the NTS to be more easily found, explored, and read, which should be reassurance to those who have spent their time writing them. Whilst there are some countries lagging behind in their publication rate, only six have not submitted any NTS in the last three months, and with the exception of Hungary, these are countries that tend to use fewer animals.

The ALURES database is simple and easy to use. The search function is fairly rudimentary, however, and it is not yet clear if a search of keywords will indeed identify all relevant projects. If the NTS are to be mined to help "*understanding of different animal use areas amongst the public and non-governmental organisations (NGOs), …support the sharing of good practices in relation to the 3Rs …and support evidence-based policy making by competent authorities*." (Aims 2, 5 and 6 of the EU Guidance), then the search functionality needs to be more sophisticated. Being able to search by severity of the project or the total number of animals would, for example, help those seeking to prioritize those areas of animal use that cause the most suffering and/or use the highest number of animals. These enhancements would require alterations to both the website but also to the submission itself.

To date, the NTS have been used to, e.g.:

- Identify the scale of animal use in controversial research
  - Botulinum toxin testing (Taylor et al., 2019)
  - COVID-19 research (Schwedhelm et al., 2021)
  - Use in education and training (Zemanova et al., 2021)
- Identify fields of research in need of the development of new alternative methods (Bert et al., 2017; Bonassera et al., 2022)

But this was all prior to ALURES – using member states' NTS websites, and some of the authors were also hampered by lack of accessibility of the NTS and the quality of the information provided (Zemanova et al., 2021) as we were.

Whilst the purpose was not to directly compare the number of animals used against the number of NTS per country, it was of interest to see if there is any discrepancy in project size between countries as shown by a lower or higher number of NTS compared to (general) animal use. There was a variation in the ratios of NTS to animal use. Notably, countries that tended to use fewer animals had a lower ratio, while some of the heavier animal using countries like the Netherlands, had a higher ratio. This could be due to delay with the publication of their NTS (possible in Hungary's case for example) or having larger projects using more animals. For example, we know that Ireland is a center for European botulinum toxin testing where just a few projects are likely to involve many thousands of animals (Taylor et al., 2019). The fact that countries using fewer animals have a tendency to have lower ratios of NTS to animal use, i.e., smaller projects using fewer animals, might be expected from countries where the use of animals in science is not a priority. This is one example of how mining the ALURES database can shed light on Europe's use of animals in science.

4.2 Improvement in the quality of the "predicted harms" section: German and UK NTS

There is no question that the splitting out of the elements required to be dealt with in the "predicted harms" section has improved the completion rate of the NTS. Making it clear that an answer is required, especially in quantitative terms, helps ensure that it is answered. This is most evident in the questions on severity and fate for which there is now a close to 100% reporting rate. The lower complete reporting for severity in the UK is possibly explained by the fact that in their template the question is not required to be given in quantitative terms (number of animals per severity level), but more descriptive answers are permitted.

Whilst there has been improvement in the reporting of procedural elements including duration of the procedures and their frequency, complete reporting of any of these three elements rarely exceeded 50% in either the UK or German NTS. It is possible that this is due to these three elements still being within one single question, increasing the risk that some of them are not addressed. Whilst this certainly appeared to be the case, there were the same issues of the use of overly technical language as in the previous review. It has transpired that the UK NTS are currently being computer generated from the project application form (ASC, 2020), which would explain this problem for the UK.

The problem with reporting the duration of procedures seems to stem from the way the question is framed in the template: "*In what procedures will the animals typically be used (for example, injections, surgical procedures)? Indicate the number and* duration of these procedures" (our emphasis). The tendency was to complete this literally, i.e., by giving the length of an injection (one minute), omitting to provide the overall duration of the experiment. If the other opportunity to provide the overall duration of the experiment located in the "adverse effects" section was not taken, because it was considered that the animals would not suffer any adverse effects for example, then third parties would have no concept of how long the animals were being used for. In our view it is this aspect in which third parties would be more interested as it speaks to how long the animals are being held in captivity in the laboratory and potentially suffering from that as well as the effects of the procedures. The revised EU Guidance (EC, 2021) acknowledges this risk and explains on page 13 that particularly for short, multistep procedures the overall length of the experiments (e.g., in days) should be given. In our view it needs to be made clearer that the overall duration of the experiment(s) should be given, either through adjustment of the template or amended guidance. This is not to be confused with the overall duration of the project, which can be made up of several experiments of varying duration involving different groups of animals and which is given at the top of the template.

Most notably, and most worryingly, there has been no significant change in the quality of the reporting of the expected adverse ef-

Tab. 5: Non-technical project summary checklist (derived from EU Working Group Guidance)

Non-technical project summary	Items to be included
Title of the project	Contains all the elements to identify the project and gives scientists and lay persons a sense of its objective(s)
Project duration in months	Matches duration requested in the project application (1-60 months).
Keywords	1-5 (preferably at least 3). Summarizes the project. Sufficient to facilitate searches by lay persons and scientists. Includes where relevant: • Strain/GM model/animal model • Specific disease/organ of interest • Third level project purpose, where given in the statistics Should not include terms in the Title, Species or Purpose fields.
Purpose(s) of project	Selected from a (multiple choices) dropdown menu. Use more than one if necessary.
Objectives and predicted benefits of the project	
Describe the objectives of the project (for example, addressing certain scientific unknowns, or scientific or clinical needs).	**Overall goal** of the project is described in non-technical language. **Specific research questions** that are being addressed should be described explaining their relevance.
What are the potential benefits likely to derive from this project? Explain how science could be advanced, or humans, animals or environment may ultimately benefit from the project. Where applicable, differentiate between short-term benefits (within the duration of the project) and long-term benefits (which may accrue after the project is finished).	Potential benefits of the project should be **realistic**. Can include potential advances in scientific knowledge and the value of this, who will benefit and how. Must relate only to outcomes from **this** project; if other potential benefits need further projects in order to be realized (i.e., evaluating treatments), then this must be clearly stated.
Predicted harms	
In what procedures will the animals typically be used (for example, injections, surgical procedures)? Indicate the number and duration of these procedures.	Briefly describes **ALL** procedures including those to: • Create the model (including if genetically modified) • Administer treatments/substances • Assess any effects Includes route(s) of administration/sampling and substance, where relevant Includes **frequency**, where applicable, e.g., max 3 injections Includes **duration** of the procedures, where relevant, e.g., 30 min Includes **overall duration of experiment**, e.g., 28 days
What are the expected impacts/adverse effects on the animals, for example pain, weight loss, inactivity/reduced mobility, stress, abnormal behaviour, and the duration of those effects?	Addresses **ALL** possible impacts/adverse effects, including cumulated harms, if any, of each procedure. Considers, where relevant, the impact of: • Procedures to create model, surgical and non-surgical • Effects of any disease induced or bred • Effects of any treatment or other substance • Effects of any procedures to assess effects Considers, level and duration of restraint, withholding/provision of analgesia/anesthesia, novelty of model or procedure, housing and food/water restrictions, potential for stress/distress, impact of "below threshold" interventions such as behavior tests, frequency of procedures. Includes **duration** of these effects, e.g., 3 days Uses descriptive terms, not severity terminology, e.g., mild Uses non-technical language Considers **expected** effects, not just unlikely effects, or humane endpoints unless this is relevant to degree of suffering allowed.
What species and numbers of animals are expected to be used? What are the expected severities and the numbers of animals in each severity category (per species)?	Completed for **all** animals used Represents prospective, cumulative, maximum severities that each group of animals (of each species) is realistically expected to reach Matches procedures and expected adverse effects.

Non-technical project summary	Items to be included
What will happen to the animals kept alive at the end of the procedure?	Only animals kept alive after the completion of the project should be reported here.
Please provide reasons for the planned fate of the animals after the procedure.	Provides reasons for the planned fate of all animals, including those that are to be killed.
Application of the 3Rs	
1. Replacement State which non-animal alternatives are available in this field and why they cannot be used for the purposes of the project.	Explains what partial and/or full replacements were considered – or used – prior to deciding to use animals. These may include *in silico*, *in vitro* or *ex vivo* approaches. Explains why they were not (yet) suitable. Avoid absolute statements like "only possible in an animal model".
2. Reduction Explain how the numbers of animals for this project were determined. Describe steps that have been taken to reduce the number of animals to be used, and principles used to design studies. Where applicable, describe practices that will be used throughout the project to minimise the number of animals used consistent with scientific objectives. Those practices may include, e.g., pilot studies, computer modelling, sharing of tissue and reuse.	Demonstrates how the appropriate number of animals to be used was determined. Lists steps that were taken during design of the project to reduce the number of animals, considering control group sizes, optimizing study design to maximize statistical power, learnings from previous studies, re-use, sharing of information, etc. Include any steps to reduce the number of surplus animals related to the project.
3. Refinement Give examples of the specific measures (e.g., increased monitoring, post-operative care, pain management, training of animals) to be taken, in relation to the procedures, to minimise welfare costs (harms) to the animals. Describe the mechanisms to take up emerging refinement techniques during the lifetime of the project.	Explains choice of procedures and why these are maximally refined, and if not, why not. Clearly outlines all of the measures taken to alleviate expected adverse effects of procedure(s) (for example habituation, analgesia, anaesthesia, special diets, acute/intensive monitoring, etc.)
Explain the choice of species and the related life stages.	Explain why the species, the related life stage, and gender chosen is the most appropriate and refined to achieve the objectives.

Important points from the EU Working Group Guidance
Any potential benefits accruing from the project, as well as predicted harms to the animals, shall be consistent with the information in the project application.
The NTS shall be anonymous and shall not contain the names and addresses of the user and its personnel.
In general, it is not appropriate to describe provisions that are essential legislative requirements (e.g., environmental enrichment, daily monitoring, access to appropriate veterinary care, competency to perform procedures, etc.).

Additional points to avoid a poor quality NTS
- Does the text address the specific questions asked in each section? Is there text that belongs in other sections? E.g., Refinement in "predicted harms"? Objectives in "predicted harms"?
- Is the language too technical, copied from the project application, including excessively detailed surgical techniques and drug regimes, scientific terminology, and the use of abbreviations?
- Does the text contain sentences copied from the NTS examples in the initial or revised EU Guidance?
- Is it too long as a consequence of unnecessary information and a failure to summarize in lay person's terms?

fects on the animals. Researchers are still describing the potential effects in terms of severity levels (mild, moderate, severe) or using vague concepts such as distress and discomfort. They are failing to fully consider what the animals might *actually experience* by listing clinical signs. In this section, they often sought to reassure that any pain, distress and suffering would be minimized without describing how the animals might still yet suffer even though these mitigating factors are in place. The revised EU Guidance states that: "*In general, it is not appropriate to describe provisions that are essential legislative requirements (e.g. environmental enrichment, daily monitoring, access to appropriate veterinary care, competency to perform procedures etc.)*" (EC, 2021, page 18). Furthermore, whilst the description of humane endpoints can help show the limit of any suffering, and could be an important 3Rs aspect to share, they do not give the reader any sense whether these endpoints are likely to be met and by how many animals. Therefore, they, in themselves, do not give a sense of the expected adverse effects, which is the requirement in the template.

Tab. 6: Examples of terminology of administration and sampling procedures that should be used in the NTS

Scientific terminology	Suggested lay person's language
Administration, treated	
Gavage	Restrained by hand and a tube is carefully pushed down their throat to administer the substance directly into the stomach
Inhalation	Placed into a small individual chamber into which the gas is pumped or sedated and a mask is placed over their nose and mouth to inhale the gas
Intracerebral, IC	Injected directly into the brain under anesthesia
Intramuscular, IM	Injected into a leg muscle
Intranasal, IN	Placed into the animal's nose under sedation
Intraperitoneal, IP	Injected into the belly
Intratracheal, IT	Placed down the animal's throat under sedation
Intravenous, IV	Injected into a vein in the base of, e.g., the tail, neck, leg
IV catheter	Via an indwelling thin plastic tube temporarily held in place to allow access to a vein.
IV infusion	Injected into a vein of, e.g., the arm over a period of XX time
Mini pump	Small devices which are implanted under the skin to enable the substance to be slowly released into the blood system
Oral	Substance is placed in the animal's food or water
Subcutaneous, SC	Injected under the skin
Topical, dermal	(Skin is shaved) substance is placed onto their skin for XX time
Sampling, measured	
Biopsy	Small piece of tissue taken from, e.g., the ear
Blood sampling, (jugular) venipuncture	Blood sample taken from a vein in, e.g., the neck, leg, tail, base of the eye or blood sample taken using a small pin prick on the ear
Metabolism cages	Placed (on their own) in a cage so that their feces and urine can be collected for XX time
MRI/PET/CT scan, live imaging, *in vivo* imaging	Placed in an imaging machine (under sedation)
Telemetry, measurement of physiological parameters	Under surgery a device is implanted into XX to allow for the measurement of XX
Related procedures	
Analgesia	Pain relief
Diet/fluid restriction	Food or water withheld for XX hours
General anesthetic	Anesthesia
Light anesthesia	Sedated
Restrained	Placed in a tube, restrained by hand, strapped into a device
Sacrificed/euthanized	Killed

One of the obstacles for a more completed "adverse effects" section may be a reluctance to be honest for fear of drawing negative attention to the project. This is a very real concern as a draft NTS accompanies the project application form (Article 37 of the Directive). A workshop on the NTS organized by the UK Animals in Science Committee (ASC, 2020) noted that; "*The questions have been tricky for applicants where sometimes they may downplay harms or avoid answering the question directly, as if answering in full may hinder approval of their application*." When reviewing the NTS we saw several examples of where the description of adverse effects seemed at odds with the prospective severity level. Either the researchers are downplaying the adverse effects, or they have genuinely set severity levels that they do not expect many, if any, animals to experience as a worst-case scenario. The revised EU Guidance (EC, 2021), and the Directive, however, require that the prospective severity is the "*overall* maximum severities *that each animal/group of animals (of each species used) is* realistically anticipated or likely to experience." (our emphasis) (page 14).

Another reason for the absence of detailed information in NTS could be that it was not included in the full project application in the first place. A recent investigation in Berlin, Germany, reports

the authorization of project applications despite them lacking essential information (Rücker, 2023).

Our interpretation is that the responsibility for ensuring the NTS is satisfactory lies with the competent authority since a NTS must be included with the project application (Article 37) and project authorization is the responsibility of the competent authority (Article 36). But are competent authorities ensuring that NTS are at the very least complete? Are they checking – as noted in the EU Guidance (EC, 2021) – that the information in the NTS is consistent with that in the full project application?

To help competent authorities we provide here a checklist of what should be included in a complete NTS (Tab. 5). The checklist has been derived from our own methodology for reviewing the quality but, importantly, is also consistent with the points made in the revised EU Guidance (EC, 2021). Since the competent authorities submit the completed NTS onto ALURES directly using a web tool, this checklist could potentially be embedded into this.

Researchers need further help and support to ensure that they are properly describing procedures and adverse effects in terms that are intelligible for all. We wonder if a collective effort could be made to come up with a universal list of terminology that researchers could use to ensure they are using language that is generally understandable. We make some suggestions in Table 6 of terminology for administration and sampling procedures intelligible for lay persons that we saw routinely described using scientific terminology. In time it may also be possible to provide a list of potential adverse effects for standard procedures and animal models, noting that the EU Guidance on severity assessment also helps here (EC, 2012).

In a future review, it may be worth extending our analysis to include NTS published by other countries that use a significant number of animals (e.g., France and Spain).

5 Conclusions and recommendations

With the mandatory submission to the ALURES database under Regulation (EU) 2019/1010, there has been a significant improvement in the accessibility and availability of the NTS. This now facilitates the mining of information on the projects using animals being authorized in the European Union.

However, our update of the review on the quality of the information in the NTS, with a focus on the "predicted harms" section, has shown that researchers still need help to improve their reporting of the procedures and adverse effects on the animals. Unless NTS are more complete they will not be able to act as a tool to support the sharing of good practices in relation to the 3Rs or to support evidence-based policy, as was hoped.

We recommend that:

- The European Commission monitors the use of the ALURES database and implements more sophisticated search functionality to facilitate efforts to use it to inform research and policy-making
- Competent authorities endeavor to briefly check the quality of the NTS, ensuring it is consistent with the project application and avoids complex terminology
  - To help we include a check list that could be used to facilitate this
- Competent authorities and research associations consider working with researchers to:
  - Define lay person terminology for common words and procedures used in the NTS
  - Improve the reporting of adverse effects, including duration of and types of pain, suffering and distress more broadly.

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Conflict of interest

The authors state that they have no conflict of interest.

Data availability

Data on the number of NTS published by EU member states and the sample of NTS from Germany were downloaded from the ALURES EU Database on the Use of Animals for Scientific Purposes Under Directive 2010/63/EU[1]. The sample of NTS from the UK was downloaded from the UK Home Office website (Home Office, 2022). All results were transferred into an Excel spreadsheet for analysis. This spreadsheet is available upon request from the corresponding author.

Data on the total number of animal uses by EU MS was taken from (EC, 2023).

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