Review Article

Recommendations to Improve the EU Non-Technical Summaries of Animal Experiments

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Summary

Under the new Directive 2010/63/EU, member states have to publish non-technical summaries (NTS) of the projects involving animals that they authorise. These summaries must include information on the objectives of the project including the predicted harm and benefits and the number and types of animals to be used. Summaries should also demonstrate compliance with the 3Rs. The intention was that NTS would help increase the transparency of animal research in the EU. In this article, we review the status of the publication of NTS across member states and give some general observations on publication speed, identification, accessibility and quality. We also review in more detail the quality of reporting in a selection of NTS from Germany and the UK. We consistently found that NTS from Germany and the UK were deficient in their description of what is being done to the animals and what they might experience as a result. Using examples taken from specific NTS we highlight what we view to be good and bad examples to assist member states and researchers in producing better NTS in the future. The NTS can also be an important tool in sharing of best practice in the 3Rs and the avoidance of duplicative animal testing. For this to happen, however, member states need to publish timely, ensure that NTS are accurate and, ideally, there needs to be some centralisation of the NTS.

Keywords: Directive 2010/63, Europe, transparency, non-technical summaries, 3Rs

1 Introduction

There have been several recent opinion polls demonstrating the public desire for better access to information on animal experiments. A government-funded opinion poll in 2016 found that the majority of the British public do not feel well informed about the use of animals in research; only one third (34%) said they feel either very or fairly well informed (Ipsos Mori, 2016). 54% wanted to know more about what is being done to improve the welfare of the animals who are used in experiments. A survey of over 1,000 people in 2015 in the Czech Republic found that 75% felt that there is not enough information available about the living conditions of animals in laboratories (PORC, 2015). And, according to a survey of six EU countries (UK, France, Germany, Italy, Sweden and the Czech Republic) conducted by You Gov in 2009, just prior to the creation of Directive 2010/63 on the protection of animals used for scientific purposes (EC, 2010, "the Directive"), 80% agreed that all information about animal experiments should be publicly available, except information which is confidential or would identify researchers or where they work (You Gov, 2009).

Information on the experiments being licensed is not just of interest to the general public and interest groups. It is important that policy makers, who are not involved in the review and authorisation process, are aware of the types of experiments being authorised. It would also help those experimenting on animals to be aware of what others are doing in case there are opportunities to reduce animal numbers by avoiding duplication and improving collaboration. Given that scientific papers often do not include information on how the 3Rs have been applied in research projects (Taylor, 2010; Avey et al., 2016; Killkenny et al., 2009), it is important that this information is available somewhere else so that best practice can be shared.

Prior to the Directive, only limited statistical information was obligated to be published periodically by member states and provided in three-yearly reports to the European Commission. Some countries have been publishing more detailed

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Annex I

Template/Headings for a Non-Technical Summary

Project Title			
Duration of project			
Key Words (maximum of 5)			
Purpose of Project (as in Article 5)	Basic research	Yes	No
	Translational and applied research	Yes	No
	Regulatory use and routine production	Yes	No
	Protection of the natural environment in the interests of the health or welfare of human beings or animals	Yes	No
	Preservation of species	Yes	No
	Higher education or training	Yes	No
	Forensic enquiries	Yes	No
	Maintenance of colonies of genetically altered animals, not used in other procedures	Yes	No
Describe the Objectives of the Project (e.g the scientific unknowns or scientific or, clinical needs being addressed)			
What are the potential benefits likely to derive from this Project (how science could be advanced or humans or animals could benefit from the project)			
What species and approximate numbers of animals are expected to be used			
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?			
Application of the Three Rs			
1. Replacement State why animals need to be used and why non-animal alternatives cannot be used			
2. Reduction Explain how the use of minimum numbers can be assured			
3. Refinement Explain the choice of species and why the animal model(s) used are the most refined, having regard for the scientific objectives Explain the general measures to be taken to minimise welfare costs (harms) to the animals.			

Fig. 1: EU template for the non-technical summaries (NTS)
Reproduced from EC, 2013a.

annual statistics for many years and some countries even publish all or part of the project application or will release it upon request (Denmark, Sweden and Norway, pers. comm.). Other countries, for example France, have been historically very poor at providing information on animal experiments. In the UK and Germany, persons involved in the authorisation of experiments could be imprisoned if they pass on details of the applications to others.

One of the improvements to this variable picture that came with the Directive, in our view, was the requirement for every member state to publish summaries of the experiments they authorise. Whilst most animal protection organisations do not

consider summaries to be a sufficient or the only method for improving transparency on animal experiments, they did recognise that they would at least provide some harmonised level of information across the entire EU.

Article 43 of the Directive requires member states to publish "non-technical summaries" (NTS) of each project authorised. The requirement for NTS came into effect for all projects authorised after January 1, 2013 (Article 64), except those authorised under a simplified administrative procedure (Article 42).

> **Article 43 of Directive 2010/63/EU**
> **Non-technical project summaries**
> *1. Subject to safeguarding intellectual property and confidential information, the nontechnical project summary shall provide the following: (a)* information on the objectives of the project*, including the* predicted harm and benefits *and the* number and types of animals *to be used; (b) a* demonstration of compliance with the requirement of replacement, reduction and refinement*. The non-technical project summary shall be anonymous and shall not contain the names and addresses of the user and its personnel.*
> *2. Member States may require the non-technical project summary to specify whether a project is to undergo a retrospective assessment and by what deadline. In such a case, Member States shall ensure that the non-technical project summary is updated with the results of any retrospective assessment.*
> *3.* Member States shall publish the non-technical project summaries of authorised projects *and any updates thereto.*

Recital (41) explains the rationale for the requirement of NTSs:

> *"To ensure that the public is informed, it is important that objective information concerning projects using live animals is made publicly available. This should not violate proprietary rights or expose confidential information. Therefore, users should provide anonymous non-technical summaries of those projects, which Member States should publish. The published details should not breach the anonymity of the users".*

Some member states had already been publishing similar, summary-style information of the projects being authorised. For example, the UK competent authority for animal experiments had been publishing one or two-page summaries of each project licensed since 2005, although this was voluntary for the researchers. Denmark had already been publishing the (anonymised) project application and authorisation decision since 2003. However, for many countries this was a new requirement that carried some administrative burden on the part of the researchers (to write) and the competent authority (to review and publish).

To assist member states, the European Commission formed an expert working group in 2012 to draft guidance on what to include in the NTS. In fact, the working group was able to agree on some guidance and a template that member states could choose to use if they so wished (EC, 2013a). This is replicated in Figure 1 and is referred to as "the EU template".

As animal protection organisations, we have a particular interest in the NTS. We hope they will give us more information on the types of animal experiments that are being conducted across Europe, the levels of suffering involved, and the efforts being made to replace, reduce and refine them. Our immediate concern, however, is that the NTS are easily accessible and complete; otherwise the information of interest will not be available. We therefore undertook a survey to find out which member countries were publishing their NTS, how quickly NTS were being uploaded following authorisation and the quality of the information contained in them. In order to provide a more comprehensive review of the quality of the NTS, we also reviewed in more detail a selection of NTS from Germany and the UK. We chose these two countries as they are two of the top three users of animals in experiments in Europe (Taylor and Rego, 2016) and both use the EU template, so a direct comparison between them would be possible. This paper summarises the findings of our two reviews and includes what we consider to be good and bad examples with the aim that this may help member states and researchers provide better NTS in the future.

2 Methods

Publication of NTS by EU members

We approached the members of the European Coalition to End Animal Experiments (ECEAE) to assist in locating the NTS for their country. The ECEAE is a coalition of 24 animal protection organizations across 22 EU member and applicant states that campaigns peacefully on behalf of animals in laboratories. Where we had no ECEAE member or they could not locate the NTS, we supplemented this with our own search for the NTS on the websites of the competent authority for animal experiments. The initial review was conducted in June 2015 and then repeated in May 2017. Several websites had changed during that time.

Analysis of the quality of individual NTS from the UK and Germany

We then performed a more detailed, objective review of the quality of the NTS published by Germany and the UK. Both countries had adopted the EU template for their NTS.

By 1 April 2016, the UK had only published NTS in the EU template for 2013[1]. By 1 April 2016, Germany had published over 5,000 NTS of the years 2014, 2015 and the start of 2016[2].

We decided to survey the first complete year of publication for both countries; for the UK this was 2013 (577 NTS) and for Germany 2014 (1,735 NTS).

1 https://www.gov.uk/government/collections/non-technical-summaries-granted-during-2013
2 http://www.animaltestinfo.de/

A sample size generator[3] indicated that for Germany we would need a sample of approximately 300 NTS to have 95% confidence that our sample was representative of the NTS for the whole year. We chose to also look at 300 NTS from the UK, greater than the sample size needed, but for ease of presenting the results. A list of the NTS for the chosen year was put into a spreadsheet and a random number generator was used to select the NTS for review.

The "Adverse effects" or "*Schäden*" (damage) section was then reviewed for each selected NTS. This is the section where the applicant must describe what is being done to the animals and how they might suffer as a result. We considered that this section (only) could be reviewed objectively in terms of whether specific information was there. However, because we did not have access to the project application itself, it would not be possible to assess if the information provided was accurate. According to the EU template, the "adverse effects" section is 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?"*

We decided that in order to satisfy "what is being done to the animals", three elements needed to be satisfied:

- *Type of procedure* (Are the main interventions described? E.g., method of giving disease, method of administration, type of surgery, etc.?)
- *Frequency of interventions* (Is the number of interventions given, e.g., number of surgeries, injections, etc.?)
- *Duration of procedure* (Is the length of time the animal is subjected to the procedure given and/or the overall length of time the animal will be held?)

Note, according to the Directive, "a *project* is a programme of work having a defined scientific objective and involving one or more *procedures*" (Article 3(2)). A procedure can be made up of one or more *interventions* (see Annex VIII).

Furthermore, according to the EU template, the adverse effects section also needs to include:

- *Description of expected adverse effects* (Is there a description of what ill effects animals might experience, e.g., weight loss, death, infections, etc., or a specific note that no ill effects are expected?)
- *Expected level of severity* (Is the suffering quantified into "below threshold", "non-recovery", "mild", "moderate" and/or "severe"?)
- *Fate of the animals* (Does it say what happens to all the animals at the end of the experiment?)

NTS scored a yes for each element if there was text answering the question in brackets. NTS scored a "partial" if the element was only partially addressed, the text was vague, was obviously incomplete or only referred to some of the animals. For example, "animals will be given a treatment to induce disease" (too vague), "most animals will suffer mildly" (incomplete). NTS scored a "no" if there was no discernible text at all addressing that element. Rego (native English speaker, science degree) reviewed the UK NTS and Weber (native German speaker, science degree) reviewed the German NTS. Following training we assessed the agreement between them on the scoring of elements using a small sample of NTS that were not included in the final review.

The reviewers also agreed on a selection of particularly good and bad examples of text in the "Potential benefits" and the "Replacement", "Reduction" and "Refinement" sections of the NTS, see Figure 1. Examples of German NTS reproduced here were translated by Weber. Very minor spelling or grammatical edits were made to both the UK and German NTS reproduced here and irrelevant sentences were omitted using (…) for brevity.

3 Results

3.1 Publication of NTS by EU members

3.1.1 Speed of publication

At the time of the initial review in June 2015 only NTS from 13 member states could be found. By May 2017, however, the NTS for several more member states had been located and to date, 24 out of 28 member states appear to be publishing NTS. No NTS could be found on the relevant competent authority website for Cyprus, Greece, Malta and Portugal. Table 1 lists some key features of the NTS from each member state. A list of the websites where the NTS can be found is given in the supplementary file[4].

The speed of upload of an NTS following authorisation was not determinable for most countries because most do not give both a date of project authorisation and a date of upload of the NTS. Most countries provide some sort of date indication by grouping the NTS by the year or month, but whether this corresponds to the year in which they were authorised is not always clear. France and Spain are notable in not presenting the NTS in any kind of date order so that there is no indication of when the project was authorised or uploaded. Eight of the 24 member states have NTS described as falling within 2017 (plus previous years), nine have NTS up to and including the year 2016. Even without being able to assume that the year of publication is the same as the year of authorisation, at the time of this review therefore seven member states were at the very least 18 months behind in their publication of NTS. These were Belgium, Croatia, Estonia, Hungary, Italy, Sweden and the UK.

Based on a combination of the date of authorisation and date of upload, where provided, and the date on which this review was undertaken, it could be discerned that the Czech Republic, Denmark, the Netherlands and Poland appear to be publishing within 3 months of authorisation, sometimes sooner. It is possible that other countries are also publishing at similar speeds.

[3] http://www.raosoft.com/samplesize.html
[4] doi:10.14573/altex.1708111s

Tab. 1: Details of the Non-Technical Summaries being published in EU member states

Country	Started publishing	Years available	Frequency of uploading	Current delay in publishing, months	ID no.?	Format	Arranged by	Search function	EU format used?	Average length, pages	Comments
Austria	2013	2013-2016	Quarterly	Min. 6	No	Grouped pdf (4 per year)	Year	No	Yes	2	Missing sections: Project title, Duration of project, Key words, Objectives, Potential benefits and adverse effects merged into a single section, 3Rs sections merged into a single section
Belgium	2014 (regionally in 2013)	2014-2015	Yearly	Min. 18	Numbered within the year	Grouped pdf (1 per year)	Year	No	Yes	1	
Bulgaria	2015	2014-2016	Yearly	Min. 12	Numbered within the year	Individual pdf	Year	No	Yes	2	
Croatia	2016	2014-2015	??	Min. 18	Yes	Individual pdf	Year	No	Yes	1.5	Duration of project can include from-to dates
Cyprus											No NTS could be found
Czech Republic	2013	2013-2017	??	Max. 3	Numbered within the year	Individual pdf	Year	No	Yes	1	Duration of project gives end date of the project
Denmark	2003	2003-2017	??	Approx. 3	Yes	Individual webpage	Month	General search box	No	Several	Publishes application and decisions incl. on amendments, incl. dates. Application covers same elements as EU template but more detail is requested on the description of the experiment as well as duration, severity and adverse effects
Estonia	2015	2013-2015	??	Min. 18	No	Grouped pdf (1 per year)	Year	No	No	0.5	No clear template, summary tends to cover objectives, adverse effects and 3Rs
Finland	2013	2013-2016	??	Min. 6	Numbered within the year	Grouped webpage (approx. 20)	Year	General search box	Yes	1.5	Severity level is clearly identified
France	2015	2013-2016	??	Min. 6	Numbered in order of publication	Grouped pdf (100 per pdf)	–	No	No	0.5	No dates given, no title, no clear template, summary tends to cover objectives, adverse effects and 3Rs

Country	Started publishing	Years available	Frequency of uploading	Current delay in publishing, months	ID no.?	Format	Arranged by	Search function	EU format used?	Average length, pages	Comments
Germany	2014	2013-2017	??	Min. 3 (Up to 15 is permitted in their processes)	No, although can be discerned from weblink	Individual webpage or pdf	Year	Searchable by Species, Year of publication, Purpose, Keyword, No. animals used	Yes	1	The sections of the objectives and potential benefits are combined
Greece											No NTS could be found
Ireland	2013	2013-2016	Quarterly	Min. 6	Numbered within the year	Grouped webpage (4 per year) with links to individual pdf	Quarter	No	Yes	2	
Hungary	2015?	2013-2015	??	Min. 18	No	Individual pdf	Year	No	No	0.5	No clear template, summary tends to cover objectives, adverse effects and 3Rs
Italy	2016	2014-2015	??	Min. 18 (although 3 is foreseen in their processes)	No	Grouped .swf file (1 per year)	Year	No	Yes	1.5	.swf files are not easily opened
Latvia	2015	2013-2017	??	Min. 3	No	Individual pdf or word doc	Year	No	No	1.5	No clear template, summary tends to cover objectives, adverse effects and 3Rs
Lithuania	2013	2013-2016	??	Min. 6	No	Grouped pdf (1 per year)	Year	No	Yes	2	Duration of project gives from-to dates
Luxembourg	2016	2016	Yearly	Min. 6	No	Grouped	Year webpage (3 per year) with links to individual pdf	No	Yes	2	
Malta											No NTS could be found (but no animal experiments since 2014)

Country	Started publishing	Years available	Frequency of uploading	Current delay in publishing, months	ID no.?	Format	Arranged by	Search function	EU format used?	Average length, pages	Comments
The Netherlands	2015	2015-2017	Daily	Days	Yes	Individual webpage and pdf	Purpose	By keyword	Yes	4	Can only look at NTS within "purpose" categories, so cannot. see how many per year. Duration of project can include from-to dates. Adverse effects section split into adverse effects, severity level, fate. Refinement section split into choice of species and efforts to reduce suffering
Poland	2016	2016-2017	Monthly	Max. 1	No	Grouped zip file (by month) including individual pdfs	Month	No	Yes	3	Duration of project includes from-to dates Objectives and potential benefits merged into a single section (description of experiment). Adverse effects and 3Rs merged into a single section.
Portugal											No NTS could be found
Romania	2016	2016-2017	Every 2 months	Min. 2	No	Individual pdf	Date	No	Yes	2	
Slovakia	2015?	2013-2016	??	Min. 6	Yes	Grouped pdf (covering 2 months)	2 months	No	Yes	3	Severity limit separated out
Slovenia	2015?	2013-2016	??	Min. 6	Numbered within the year	Individual pdf	Year	No	Yes	2	Missing sections: Duration of Project, Key words. Objectives, potential benefits and adverse effects sections merged into single section
Spain	2014	2014-2017	??	??	No	Individual pdf	–	By keyword in title and by purpose	Yes	1	No grouping by year and no ID number or date so no indication when project was approved
Sweden	2016	2013	??	Min. 41	Numbered within the year	Individual pdf	Year	No	Yes	1	Publication seems to be delayed by moving to electronic format for project applications
UK	2005 (from 2014 in new template)	2005-2015	Yearly	Min. 18	No	Grouped pdf (by sub-purpose within each year)	Sub-purpose within each year	No	Yes	3	Northern Ireland NTS not being publishing. Publication seems to be delayed by moving to electronic format for project applications

3.1.2 Identification of an NTS

Most countries identify the projects being summarised by title. The titles often include specific scientific terms. Austria and France however do not provide any title and therefore for these countries, aside from being assigned a number in the list (France), there is no way to identify a specific NTS. Only four countries give an identification number to the NTS (Croatia, Denmark, Netherlands, Slovakia), however seven provide a number that corresponds to the NTS's position within the year (Belgium, Bulgaria, Czech Republic, Finland, Ireland, Slovenia and Sweden). The NTS from Croatia, the Czech Republic, Denmark, Lithuania, the Netherlands and Poland often had the dates of the project within the NTS in the "Duration of project" field, which provides further identification.

3.1.3 Accessibility of the NTS

Most countries are presenting the NTS in .pdf format (20 countries). Seven of these are including more than one NTS in a single pdf with the number of NTS within each pdf tending to be quite high (covering either all or a significant part of the NTS for each year). Denmark is the only country to consistently provide the NTS as individual webpages; Germany still has some NTS as pdfs on its website, although the majority are presented as individual webpages. Only Denmark, Finland, Germany and the Netherlands provide a search function, although Spain provides the option to search by keywords in the title of the pdfs.

3.1.4 Quality

Most countries are using the EU template, or a slight modification of it. Latvia, Hungary, France and Estonia do not appear to be using any template. Denmark is providing what appears to be most of the project application (anonymised), which includes the same elements as the EU template but has more subheadings for the description of the experiment, severity and adverse effects. The decision by the authority and any amendments to the project are also published. Of the 19 countries using the EU template, four appear to have missed out sections or combined sections in the template. These were Austria, Germany, Poland and Slovenia, see Table 1 for more details.

The length of the NTS varies from approximately half a page to four pages. The NTS from member states not using any template are consistently shorter than those using the EU template, approximately only half a page in length. However, the format of the NTS used affects the length, such that, irrespective of the amount of text, the form would be a minimum of two pages (e.g., Lithuania, UK).

In providing us with the information on the NTS in their country, our ECEAE members were consistent in criticizing the tone and incompleteness of the NTS. Many of them also noted that the NTS had a tendency to overexaggerate the benefits of

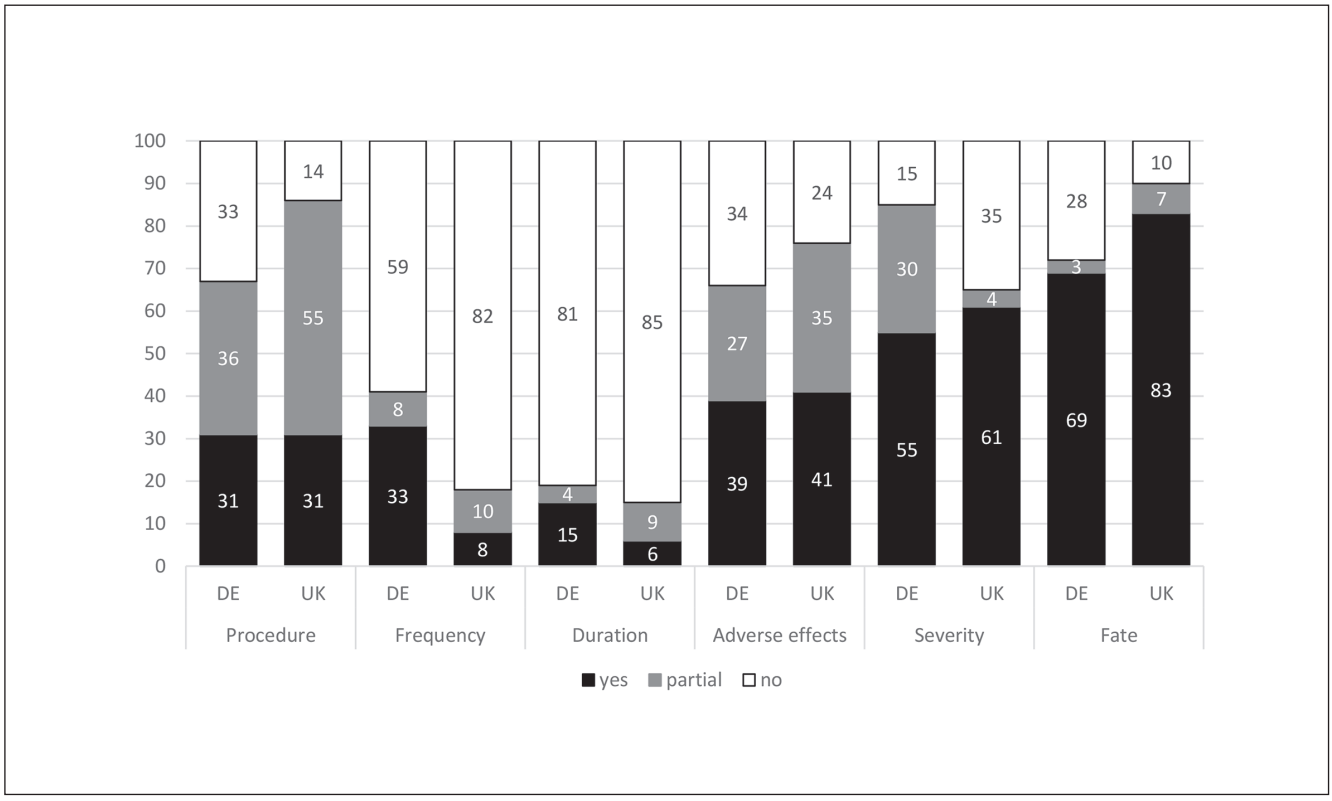

Fig. 2: Reporting of elements relevant to "adverse effects" in German and UK non-technical summaries (%, N = 300, from 2014 and 2013, respectively)

the research, downplay the suffering of the animals and provide only vague statements about adherence to the 3Rs.

3.2 Analysis of the quality of individual NTS from the UK and Germany

3.2.1 Adverse effects section

The NTS from both Germany and the UK scored moderately for providing information on the severity category of the experiment (55% and 61%, respectively), see Figure 2. However, 35% of UK NTS did not provide the severity limit (15% of the German NTS). Adequate text for the severity would simply have been, e.g., "*the severity of the procedure is expected to be moderate*". Several examples mentioned that animals would experience "mild distress" or "moderate effects" but did not actually specify that this equated to the severity level of the procedure (this would have scored a partial). German NTS were more likely to do this, with 30% giving a vague impression of the severity, i.e., "low stress", without specifying the actual severity level.

The NTS also scored moderately for providing information on the fate of the animals, with the UK NTS scoring higher than Germany (83% compared to 69%). 28% of the German NTS (10% of the UK) did not provide any information related to the fate of the animals. A simple statement such as "*The animals will be humanely killed at the end of the experiments*" scored positively. However, it was rare to see more detail of the method of killing, with researchers preferring to use descriptive terms such as "without pain" or "humanely". Some examples mentioned that animals would be killed if they appeared to be suffering, but did not state whether they would all be killed at the end regardless; these scored a partial.

The NTS were less consistent in 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 of the type of procedure applied to the animals. 14% of the UK and 33% of the German NTS did not appear to provide any real information in this regard. NTS mentioning surgeries rarely described the type of surgery and those mentioning "dosing" or "administering" substances often did not say what the route of administration was, e.g., injection, oral, inhalation, etc. (would have scored a partial). Even where "injected" was used (which would have scored a "yes"), it was very rare that the route of injection was given, e.g., intravenous, subcutaneous, etc. Complete description of the frequency of interventions (33% of German and 8% of UK) or duration for which animals were being experimented upon (15% of German and 6% of UK) was rare.

Only 41% of the UK NTS described the adverse effects the animals may experience and 35% gave a partial description (e.g., effects were described for some procedures but not for all). A similar pattern was found in the German NTS, with 39% describing the adverse effects and 27% only partially.

Poor examples

An example of no information being provided on the type of procedure (or much else apart from the severity level) in a German NTS:

> *The severity levels for the animals are evaluated to be moderate at maximum. The animals are constantly monitored and immediately removed from the experiment upon the occurrence of harm and/or suffering. (Germany ID1028)*

This NTS gives no information on the type of procedure except for the suggestion that some of it might be carried out under anaesthesia. It is not possible to understand what is actually being done to the animals based on this NTS:

> *All of the studies to be performed will maintain animals under anaesthesia throughout the study. While it is possible that some of the treatments might result in hypoglycaemic events of some kind of unexpected toxicity, the animals will not experience any of these issues. At the termination of each study, the animal will be euthanized without regaining consciousness. (UK vol 35.1)*

Some examples mentioned that animals would be induced with a disease or condition but did not describe how the animals would be induced. For example, this NTS actually gives no information at all:

> *As we are modelling disease our animals they will progressively demonstrate symptoms of the disease. However, we closely manage these symptoms to ensure that the animals do not undergo any undue suffering. (UK vol 17.10)*

This NTS scored badly for most of the elements (except severity level) including a complete absence of a description of the procedures and adverse effects, providing instead reassurances that actually suffering would be kept to a minimum, with no explanation for what that minimum is:

> *Great care and attention has gone into refining the techniques used to monitor animal responses to the treatments used in order to reduce the degree and duration of any suffering incurred to a minimum. Work with mice and cattle is not expected to be of greater than moderate severity. Experienced observers, with access to veterinary advice and care at all times, monitor clinical signs of all experimental animals at regular intervals in order to identify quickly any animal requiring veterinary treatment. Any animal failing to respond to treatment is killed humanely. By necessity, experimental animals will be humanely killed at the end of procedures. (UK vol 14.4)*

This NTS preferred to describe what appeared not to be a regulated experiment for some of the animals and failed to describe what was being done to those that were being experimented upon:

> *The majority of the animals will not have any regulated procedures that will cause them distress undertaken on them, as we will cull the mice then we will be isolating cells. The likely severity will be mild... (UK vol 44.4)*

Good examples

This NTS clearly describes the procedure in lay person terms. There is also information on frequency and duration of the experiment, adverse effects, severity and fate:

> *Each animal used in this project will have a small operation under general anaesthetic, where two small pieces of*

human ovarian tissue will be transplanted onto the inner lining of the abdomen. We do not anticipate anything more than some minor bleeding from the skin and abdominal wall which will be stopped immediately during the operation. The animals may experience some post-operative pain which will be controlled by the use of pain-killing agents. After 5 months, the animals will receive a total of six injections of human hormones on alternate days. The injection sites will be alternated, and we expect that these injections will only cause momentary needle-stick pain. The likely severity level of these interventions is mild. All animals will be killed humanely at the end of the study. (UK vol 18.9)

This NTS provides a clear description of the procedure, although it uses scientific terminology. It also includes elements of duration, length, severity and partial information on adverse effects. This shows that NTS need not be long:

The basis of the experiment is a surgical closure of the middle cerebral artery under anaesthesia. This results in a stroke for the mice, which manifests itself in hemiplegia, which constitutes the main factor and is classified as a medium severity. Animals will still eat. The observation time is at 90% of the animals for 24 h, at 10% for 72 hours. Pain plays a lesser role, as pre- and 6-8 h postoperatively analgesics are administered. (Germany ID 517)

This is an example of a German NTS scoring well for frequency, as well as duration of procedure, severity and fate, but not description of adverse effects. It is notable that performing three surgeries on pigs was considered to cause only "slight" severity:

Overall, the test animals will undergo surgery under general anaesthesia three times within one year. In the first operation, all premolars are removed. The implants are inserted in three-monthly intervals. The inserting of the implant abutments and bone augmentation takes place another three months later. The injection of fluorochromes into forehead and jaw for the detection of bone remodelling takes place in two-weekly intervals. The duration of the procedure for all groups is 55 weeks. All animals are killed painlessly at the end of the study. A slight severity level in this study is expected due to experience from previous studies. (Germany ID 1656)

This NTS gave an admission that the researchers did not know if the animals would suffer pain in this experiment and covered all elements except for frequency:

During general anaesthesia cancer cells are injected into one of the mouse's leg nerves and their gait is observed for 4 weeks. A decrease in strength is observed in the affected leg after about 7-10 days. It is not yet known whether the animals even suffer pain thereby. All animals are killed at the end of the study painlessly. In this study a moderate severity level is expected. (Germany ID 1778)

This NTS describes the interventions, duration, adverse effects and fate; however it appears to downplay the suffering:

Killed bacteria are injected into the hindpaw of the mouse (inflammation). The paw inflames and swells. In other animals the sciatic nerve is constricted by ligation (neuropathy). The sutured wound heals after a few days. The animals keep the inflamed or nerve-injured paw protectively underneath the body. In both cases, the animals eat and drink normally and increase in weight. They behave basically unremarkably in comparison to untreated animals (they move and climb, e.g., around the cage lid). There are no indications of suffering. The animals are killed painlessly by an anaesthetic after 2 days (inflammation) or after 2 or 14 days (neuropathy). The cells are isolated and examined in vitro. *(Germany ID 768)*

This NTS gave a good description of the expected adverse effects:

All studies require that lung injury is induced which leads to inflammation and lung fibrosis. Previous experience suggests that all animals developing lung injury, inflammation or lung fibrosis, lose weight, get increased breathing rates and some hair standing up on end. However, overall the level of discomfort is moderate and their progress will be carefully monitored to ensure the well being of all animals during the course of these studies. All mice are humanely killed at the end of these studies (UK vol 41.3)

This NTS was considered to have covered all elements except for duration:

Acute pneumonia in rat lungs is caused via injection of hydrochloric acid into the trachea or via X-ray radiation. During this the animals are under general anaesthesia. Some animals are given artificial respiration under continued general anaesthesia and subsequently killed. The severity level for these animals is mild. For other animals the change from acute pneumonia into a chronic pneumonia is expected. These animals can experience a moderate severity level due to dyspnoea or respiratory pain. The pain is treated by medication. The rats with chronic pneumonia are also given artificial respiration under general anaesthesia and subsequently killed in deep anaesthesia. (Germany ID 1676)

3.2.2 Potential benefits section

This section asks researchers: "*What are the potential benefits likely to derive from this project (how science could be advanced or humans or animals could benefit from the project)*".

Bad examples of answers include those that contain little information about how the project is contributing to scientific knowledge, justify the benefit (solely) in terms of the severity of the disease under investigation, or make exaggerated claims as to the likely outcome of that particular research project.

For example, this NTS focuses on the severity of Huntingdon's disease but does not explain how the proposed project contributes to alleviating it, nor the likelihood of success:

We want to develop a safe effective human therapy for a disease that causes a slow and unpleasant death. Huntington's disease is inherited and devastates affected families, with 100% of carriers developing the disease. (UK vol 27.10)

This NTS describes a basic research project using mouse models to investigate the role of the immune system in experimental autoimmune encephalomyelitis. Based on other information within the NTS, it is clear that the purpose of the project is not to test or identify novel compounds and yet this is claimed. Fur-

thermore, the NTS claims that the quality of life of patients is expected to improve as a result:

> *The project will advance our knowledge of the mechanisms of disease in MS. The programme of work is also expected to clarify how some of the currently used medicines used in MS work and to lead to the identification of novel compounds which will then be taken to clinical trials. Thus it is expected to make a difference in the quality of life of patients who suffer from MS by providing new treatment options. (UK vol 39.5)*

This German NTS uses complex terminology and makes a claim that better understanding of a specific mechanism will directly lead to improving the quality of life of patients:

> *The aim of this study is to investigate the receptor-ligand interaction, to develop a better understanding of the intracellular processes and signalling cascades. In cardiological research many regeneration and repair processes are promoted by receptor-ligand interaction. The results lead to a better understanding of the processes so that different treatments and drugs can be developed, improving the life of affected persons. (Germany ID 1757)*

Good examples include those that talk about the overall aim in the context of what the research project is designed to accomplish and the likely outcome of the work:

> *This project is designed to increase the evidence base in order to assist in any future TB eradication strategy. Badgers are implicated in the spread of bovine TB and gathering ecological measurements for badger contact, badger movements and badger social organisation will provide data that could be used to shape bio security measures to minimise cattle badger contact. (UK vol 49.9)*

Whilst containing too much experimental information (omitted here), this German NTS does explain the purpose of the project and how it might contribute to the treatment of obesity:

> *The prevalence of overweight and obese individuals has increased continuously worldwide in recent years. In contrast, the possibilities to deal with this problem are limited. The so-called "brown fat" represents a promising target tissue for the prevention and treatment of obesity. Through its ability to release energy in the form of heat, it could be activated through specific treatments and contribute therefore to a healthy body weight. Currently, there are no suitable side-effect free treatments, though. It is shown in a study on high-fat fed mice that supplementation with bile acids can counteract obesity. However, the underlying mechanism is not yet completely clarified. Thus, this experimental project should apply suitable methods to discover these mechanisms; ... (Germany ID 1507)*

3.2.3 3Rs sections

Replacement

This section asks researchers to "*State why animals have to be used and why non-animal alternatives could not be used*".

Bad examples of answers give generic statements that animals have to be used, or that the aspect under investigation has to be demonstrated in a whole organism, without explaining why. Bad examples do not demonstrate that they have considered replacements and do not provide good reasons as to why they are inappropriate. For example, this NTS just gives a generic statement:

> *These studies require the use of living animals due to the complexity of the cellular and tissue responses. (UK vol 44.3)*

This NTS makes a generic statement that studies in humans would not be ethical and includes information about the validity of using mice rather than really justifying why they have to be used:

> *We have to use animals in order to be able to study behaviour and cannot use humans because appropriate drugs and other relevant procedures are either not available or are ethically unacceptable. We shall use rodents, mainly mice, because such tasks are easy to implement and because the general details of brain structure and function are already well understood and are sufficiently similar to humans to allow extrapolation. (UK vol 34.9)*

Good answers for this section, in our view, explain the scientific problems with the available alternatives (in a simple way). An even better answer in our view, although not strictly necessary according to the EU template, would be a demonstration of how the researchers look for alternatives or are working on improving them.

This example clearly explains the limitations of *in vitro* methods (maintaining them for the required length of time) and provides some evidence that the researchers are trying to look for replacements:

> *... In our laboratory, we are currently using human specimen (biopsies) from the local hospital to establish* in vitro *organ culture using human biopsies. However, the intrinsic difficulties in maintaining the intestinal tissue viable in culture for long time prevent us for using this approach for a variety of experiments... (UK vol 42.5)*

Similarly, this one describes the limitations of 3-D tumour models in their view:

> *We have already performed extensive* in vitro *studies that showed that AMF intensely stimulates the migration of glioblastoma cells. However, there is no* in vitro *model, where a growing three-dimensional tumour can be inserted into a surrounding environment that corresponds to the complexity of an* in vivo *tissue. Tumour cell invasion in particular, which occurs along blood vessels in the brain, as well as tumour angiogenesis cannot be mimicked adequately reproducibly* in vitro*. Therefore, the success of anti-invasive and anti-angiogenic tumour therapies (either separately or in combination) cannot be investigated* in vitro*. Therefore, there is a dependency in the research of such complex mechanism on animal models which pave the way to subsequent clinical studies. (Germany ID 882)*

Reduction

This section asks researchers to "*Explain how the use of minimum numbers can be assured*".

Bad examples, in our view, give blanket reassurances that the number of animals used is the lowest possible without providing evidence of this. Indicating that statistics or statisticians

will be employed to ensure the "right" number of animals are used should be assumed to be common practice in any scientific experiment. So, whilst this is an answer, it is not particularly informative or progressive:

> *The number of animals to be used in the project has been calculated by power analysis to provide the minimum number of mice sufficient to support robust statistical analysis by standard methods such as Analysis of Variance, Students t-test and linear regression. (UK vol 36.3)*
>
> *We identified the minimum number of animals through biometric analysis. There will be used just as few animals as necessary for the statistical analysis. (Germany ID 2255)*

Good examples, in our view, provide details of steps that have either recently been taken to reduce animal numbers and/or practices that are used throughout the project to keep numbers down.

This example gives evidence that the numbers of animals per experiment are already the lowest they can be and demonstrates that the researchers are aware of other ways to avoid experimentation:

> *A minimum number of animals will be used for each antigen. Initially, we typically immunise 3 mice, though many other researchers use more than this. The 3 mice often show different immune responses. Occasionally, only one mouse will produce antibodies of the required kind. By experience we have found the initial immunisation of 3 mice with each antigen is a good compromise in that animal numbers are kept low, but there is a good chance of getting at least one animal with the required response within the time frame of the initial series of immunisations. If a satisfactory mAb is already available commercially or on free distribution, we would not make new mAbs to duplicate it. (UK vol 11.18)*

This NTS gives some specific examples of how the numbers are reduced:

> *We reduce the number of mice used by a variety of methods: 1. Using appropriate experimental design (e.g., transplanting appropriate numbers of cells such that engraftments give useful information, and performing statistical tests in advance in order to identify the minimal number of mice required for the experiment). 2. Transplanting multiple grafts per mouse. Transplanting multiple grafts in a mouse often does not increase the severity of the adverse effects that mouse will experience, but it can drastically reduce the number of mice required. 3. Performing cell culture experiments beforehand in order to see if an experiment is worth continuing in an animal model. (UK vol 25.8)*

This NTS also gives specific examples of how reduction is assured:

> *We will try to reduce the number of test animals by gentle methods of diagnosis (blood analysis with a device that uses minimal blood quantities, repeated blood draw of the same animal) and pooling of the researched questions. It is possible to pool the researched questions: With the blood of a single mouse we perform several experiments simultaneously (mobilization efficiency, stem cell assay,* in vitro *analyses). Several experiments (homing, engraftment, stem cell assay,* in vitro *analyses) are carried out with the bone marrow as well. (Germany ID 1587).*

This example gives a good demonstration of recent reductions that have been made, albeit via the use of alternatives:

> *Attempts are in progress to establish cultures of a pig macrophage cell line in sufficient quantities to reduce the requirement for primary pig cell cultures for replication of ASFV. The number of pigs used has been reduced by 50% from 500 to 250 in the last two years already. The Culicoides and mosquito colonies are to date fully maintained through blood feeding on artificial membrane systems and feeding on live mice will only have to be considered in the imminent threat of colony collapse. Overall this achievement has reduced the requirement for mice dramatically from 10000/ 5 years on the last licence down to 500/ 5 years in this licence. Attempts will continue to develop a method allowing reliable feeding of tick colonies on an artificial blood- membrane system. (UK vol 18.11)*

Refinement

This section asks researchers to "*Explain the choice of species and why the animal model(s) used are the most refined, having regard for the scientific objectives. Explain the general measures to be taken to minimise welfare costs (harms) to the animals*."

Blanket statements such as "*The health and welfare of the animals will be maintained by dedicated professional animal technologists and care staff*" are not informative as this should be assumed anyway. This is an example of an NTS with generalised statements for refinement:

> *Sheep are the only suitable species for such studies since they are the only species of seasonal mammal with a sequenced genome. The husbandry conditions at the facility where the animals are maintained are outstanding, and the staff highly experienced, thus allowing us to minimise harm to the animals during periods of housing in artificial photoperiods. (UK vol 44.3)*

This example took many words to simply describe what is standard practice:

> *In order to reduce the severity of the animals to a minimum, they are kept in groups from an early stage on until the beginning of the experiment. To protect the animals' health, they are accommodated under the highest hygienic conditions up to the beginning of the experiment. To avoid stress for the animals, they are nursed by only one animal keeper, who will only choose animals with a normal behaviour for the experiment. Afterwards, the animals are further handled by one person only (the experimenter). The experimental duration is limited to an absolute minimum (4 hours at the utmost). The killing is only done by special trained personnel and not in the presence of conspecifics. (Germany ID 2155)*

Good answers, in our view, provide examples of where the animal's welfare is improved both during the procedure and in the housing and care. Examples should describe efforts that go beyond the legislative minimum requirements. Furthermore, it is important that statements about care and monitor-

ing are explained; "frequent monitoring" for example, could mean daily monitoring, which is a standard requirement of the Directive.

For example, this NTS (whilst too long and including some generalised statements) mentions procedural efforts to minimise harm (reduced number and volume of injections, reduced number of blood samples) and application of humane endpoints (although the frequency of monitoring is not given) and housing improvements (enrichment, nesting materials and refuges as well as noting that the animals are group-housed):

> *We use mice because they respond well to antigen injection and the donor cells used to fuse to the spleen cells are of mouse origin .... We have reduced the number of injections and the volumes to be injected to the minimum. We have the reduced the number of test bleeds ... Adjuvants are only used when they are essential to generate an adequate immunological response. Only the smallest blood sample required will be taken for serum analysis. We will minimise suffering to the mice by regular and frequent monitoring and immediately killing any mice that are unexpectedly ill or showing signs of poor health... [mentions standard requirements] ... Wherever possible, we will strive to go beyond minimum housing guidelines, for example by providing refuges, nesting material and chew blocks. Animals are housed together at a young age usually in groups of 4-5 of the same sex per cage and they remain together until the procedure has completed. (UK vol 23.10)*

This German example includes three procedural refinements:

> *A catheter implantation enables animal blood sampling without multiple puncturing of the veins. Analgesics for venous catheterization are applied post-surgery as well. Furthermore, the health status of the animals will be observed daily. The total withdrawn amount of blood will not exceed 10% of the total blood volume within 24h, thus no impairment of the animal's normal physiology is expected. (Germany ID 619)*

This NTS also includes various procedural refinements and details of humane endpoints:

> *The study of mammary gland function requires the use of mammals. In all protocols, mice are the most appropriate species for genetic analyses using conditional-null gene deletion ... Following surgery, soft water gel pads will be provided to keep mice hydrated, and mice will be monitored closely over the first 48 hours ... Mice will be checked routinely for the appearance of mammary or other tumours and killed if lesions become greater than 1 cm diameter (UKCCCR guidelines) ... (UK vol 44.5)*

4 Discussion

4.1 Publication of NTS by EU members

Table 2 provides a list of the best and worst performing countries for speed of publication, identification, accessibility and quality. It was interesting that it was not always the most animal-using countries who were the best at publishing NTS in terms of speed and presentation. For example, France, Italy and the UK scored consistently badly in these areas. Some former Eastern bloc countries, who have had less experience with specific animal testing legislation, scored very well for some aspects, e.g., Czech Republic, Poland and Romania.

The initial problem of failure to publish NTS seems to have been resolved and although four countries may still be not compliant, two of these (Cyprus and Malta) conduct few, if any, animal experiments. During our survey, the website addresses of previously identified NTS had changed. Other countries do not have clear links to the NTS from their competent authority webpages so considerable detective work was required to find them, see supplementary data for member states' current URLs[5]. So, whilst the picture now looks quite good in terms of some levels of publishing for most countries, it has taken some four years from implementation of the Directive for this to be resolved.

However, issues remain with the irregular and slow speed of publication for most countries. Although at least four countries are publishing within three months of authorisation, seven countries are more than one year behind in publishing their NTS and a further two do not appear to be intending to publish more regularly than annually. Sweden and the UK are particularly behind in their publication, currently over three and two years respectively, which is apparently due to transitioning from paper to electronic project applications (pers. comm.). It was, however, very difficult to ascertain what the specific time delay from authorisation to publication was for most countries due to a failure to provide this information.

The stated purpose of the NTS is to enhance transparency about animal experiments (Recital 41), so that there can be informed public debate and accountability of regulators' decisions. It is self-evident that debate and accountability cannot take place about particular animal research projects until the relevant NTS are published. Similarly, the public cannot build a picture about what sorts of experiments are licensed in particular member states and for what reason until information is made public. The Directive is unfortunately silent on how quickly NTS should be published following authorisation, although the Guidance states that "NTS should be published when the project is authorised" (EC, 2013a). NTS are part of the application process and therefore should be available for publication as soon as an application is granted. It may be reasonable to publish in batches, but we believe that there should not be a delay of more than three months from authorisation if the goal of transparency is to be properly met.

Finally, it was good to note that so far, no member state appears to have taken down any NTS, and all published years are still available. The Guidance on the NTS says that they should be accessible for at least five years, longer if a retrospective assessment is indicated (EC, 2013a). It is our view that the NTS

[5] doi:10.14573/altex.1708111s

Tab. 2: Best and worst countries in their publication of the non-technical summaries

	Best (runners up)	**Worst** (runners up)
Speed of publishing	**The Netherlands** (Czech Republic, Denmark, Poland)	**Cyprus, Greece, (Malta) and Portugal** – none to date (Belgium, Croatia, Estonia, Hungary, Italy, Sweden, UK)
Identification	**Poland, Romania** (Croatia, Denmark, The Netherlands, Slovakia, Czech Republic, Lithuania)	**France, Spain** (Estonia, Germany, Hungary, Italy, Latvia, Luxembourg, UK)
Accessibility	**Denmark** (Germany, The Netherlands)	**France, Italy** (Belgium, Austria, Estonia, France, Lithuania, Slovakia, UK)
Quality	**Denmark** (The Netherlands)	**Latvia, Hungary, France and Estonia**

should be available for longer than this. This is so that the information is not lost to the public and so that third parties can look at trends over time.

Providing an identification number, even a rudimentary one, helps the reader to identify the NTS. This helps when discussing the project with third parties, including the competent authority. Aside from identification by (often complex) titles, only four countries give a specific identification number to the NTS. This is unfortunate, particularly for those countries collating NTS into larger files, as it makes identifying and describing the NTS difficult. Others have also suggested that being able to identify projects is an important element of transparency (Varga et al., 2010).

The heavy use of pdf by most of the member states is problematic for a number of reasons. It makes searching for, accessing, using and storing the information within documents extremely cumbersome, if not impossible. Grouping more than one NTS within a pdf document reduces the accessibility and usability of the NTS even further.

Only those countries using webpages to publish the NTS are able to provide a search function. The European Commission Guidance says that the NTS should be searchable by keyword (EC, 2013a), so it is unfortunate that only five countries have made this possible. Germany provides the best search function given that it has put the NTS on an online database which is searchable by species, year of publication, purpose, keyword and number of animals used (Schönfelder, 2015).

The use of paper-based project applications may partly explain why the majority of the countries are publishing NTS in pdf format, sometimes as scanned documents. As countries update their licensing systems the situation should hopefully improve. Currently, it is fair to say the NTS system is losing its transparency because of the format in which the NTS are being published.

It is interesting that the majority of countries have chosen to adopt the EU template. This will help in the consistency of reporting and make comparisons much easier between countries in terms of both quality of reporting and the details of the actual projects. Subjectively, it does seem to improve the quality of the information, as those countries not using any template were much more likely to produce shorter and more variable NTS. However, members of the ECEAE consistently reported poor tone and content of the NTS, even from those using the EU template.

The best country in terms of tone and clarity of information was Denmark. Because they publish the relevant parts of the project application, there is less burden on the researcher to write a separate summary and, apparently, more chance that the tone will be neutral. The documents were several pages long; however, since they were in a single webpage, it was relatively easy to scroll down to the elements of interest.

4.2 Analysis of the quality of individual NTS from the UK and Germany

Our organisations, like many animal protection organisations, do not think that the NTS are a sufficient or the only method for improving the transparency of animal experiments. This position, however, should not affect our ability to objectively review whether the NTS are performing the role they were designed for. By their nature, the NTS are not meant to be a substitute for the project application. However, they should be a summary of the purpose of the project, the main procedures being applied to the animals, a description of how this might affect them and the extent to which the researchers have addressed the 3Rs. What is clear from our analysis is that NTS need not be lengthy to do this.

Any review of the quality of the NTS is likely to run into difficulties with assessing the accuracy of the statements if access to the project application is not also available. We could, however, make a judgement as to whether items required by the EU template had been included in the NTS, which was easiest to do for the "adverse effects" section. Unfortunately, our review found that the level of information in this section was fair to poor in the NTS from both Germany and the UK. Only about two-thirds of NTS reviewed had at least partial information on important elements describing the procedure and the expected adverse effects. Reporting briefly on the frequency and duration of procedures performed on the animals, we believe, is integral to describing "what is being done to the animals" and yet was very poor, particularly in the UK NTS. Even elements that were specified in the EU template, such as the severity level and the

fate of the animals, were not included in approximately a quarter of NTS from either country.

The potential benefits sections tended to contain more text than the other sections and yet suffered from a failure to describe the likelihood of the project achieving its aims. There was also a tendency to present the benefits in terms of the severity of human disease rather than the actual intended outcomes of the project. It would be beneficial for competent authorities to refer researchers to the Bateson cube for considering harms and benefits in the EU guidance on project evaluation to help them with this section (EC, 2013b).

The 3Rs sections were generally of low quality from both countries, although we perceived the German NTS as being worse out of the two. There was a tendency for NTS from both countries to have a relatively high proportion of generic statements providing reassurances that the 3Rs were being applied, with no evidence provided to allow the reader to assess the veracity of this claim. Worryingly, Weber reported that approximately 10% of the NTS reviewed had cut and pasted text from the example given in the German template (BfR, 2013) for the Reduction section.

Common errors in the 3Rs sections were: (1) for reduction, to just talk about the use of appropriate statistics and, (2) for refinement and replacement, to focus only on justification of the use of animals, specific species or models and not advancements in these areas and, (3) for text appropriate to other sections to be included in the wrong section. We found rare examples that provided details of how the researchers were taking further steps to reduce suffering or look for replacements. This may constitute a difference of opinion between us and the researchers as to what applying the 3Rs means. In our view, it is going beyond standard practice, even if standard practice constitutes an improvement on practice 20 years previously. In effect, the 3Rs is a moving target. Therefore, in our view, references to frequent monitoring, keeping harms to a minimum, providing social housing, having trained staff, etc. are all standard under the Directive and do not, any longer constitute applying the 3Rs. We note that reviewing these sections is complicated by the difficulty in separating out a complete and honest answer with demonstration of applying the 3Rs. The refinement section, for example, asks what is being done to minimise harms. If the researcher supplies information that represents standard practice (only), then they have completed the section, but are indirectly informing the educated reader that they are doing very little to advance the 3Rs. It is important that researchers are made aware of this distinction. There may be circumstances where they cannot refine the experiment or housing any further, within the restrictions of the laboratory environment, of course.

Although there was quite a lot of consistency in the results of the review from Germany and the UK, there were differences. German NTS tended to describe procedural elements in more detail, but not with greater length. The UK NTS tended to describe more generalised, complex projects with more focus on the potential benefits and some consideration for the 3Rs. These observations perhaps reflect the differences in approach to authorisation between the two countries. The annual number of German NTS is approximately three times that of the UK and yet the scale of animal use is similar (see Tab. 1), suggesting that smaller, more defined projects are authorised in Germany. This may explain why the German NTS were more likely to give greater information on the procedure, including the frequency and duration, than the UK NTS. The German NTS were also more likely to include complex scientific terminology including strains of mice, drug names, acronyms, abbreviations and physiological terms. Nonetheless, in general the German NTS were briefer than the UK ones and it was common for each section to be completed with only one or two sentences. We also noted that there may be a potential discrepancy between the two countries in the assessment of severity, with some German NTS reporting procedures as causing mild suffering that would be considered moderate in the UK and also according to the EU guidance on assessment of severity (EC, 2012). Potential under-estimation of severity in the German NTS has also recently been reported by others (Strittmatter, 2017).

Although the dates of the NTS we reviewed in detail are now a few years old (2013 and 2014), this was because at the time of the review these were the most complete years available for each country. We have no reason to believe the quality has necessarily improved since then as there have been no specific initiatives by either country to improve them and the EU template has not changed. At the end of 2016 the UK government added more information about how to prepare an NTS in their project application template (Home Office, 2016). However, since they have not published the NTS from 2017 (or indeed 2016) it is not possible to see if this has helped improve compliance.

Our analysis clearly shows that there is a need for competent authorities to ensure that NTS are clear and complete. Competent authorities should also ensure the tone of the NTS is neutral and not biased or misleading. It is important that the potential benefits are not over-exaggerated, and the adverse effects downplayed. It is our view that it is a legal requirement under the Directive that competent authorities must ensure that (i) NTS are included with a project application; and (ii) that they comply with Article 43. Article 43 (shown above) includes the requirement that the NTS must include: (a) information on the objectives of the project, including the predicted harm and benefits and the number and types of animals to be used; (b) a demonstration of compliance with the requirement of replacement, reduction and refinement.

There appear to be conflicting views amongst member states as to their obligations: Germany appears to consider that the content is the responsibility of the applicant[6] (only), however this may only be in terms of completing the information, not whether it is complete. On the contrary, Sweden states that the ethical committee shall check that the content is correct[7]. It would be helpful if the European Commission would reiterate to the member states that it is their responsibility to check the

6 https://www.animaltestinfo.de/faq.cfm
7 http://bit.ly/2A3sWS9

Tab. 3: Suggested changes to the EU template

Section	Current description	Suggested description
Project number[a]		
Duration of project	*No advice provided*	Include dates from and until the work is authorised
Procedures[a]		Describe briefly the procedures to be applied to the animals including types of intervention, frequency of application and typical duration of the experiment
Adverse effects	*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?*	Describe the expected adverse effects on the animals
Severity level[a]		List the severity categories for the procedures in the project
Fate[a]		Provide the fate of the animals and the method of killing, where relevant
Replacement	*State why animals have to be used and why non-animal alternatives could not be used*	Give explicit reasons why non-animal methods are not adequate to address the Objectives and provide evidence of steps you are taking to address this, if any
Reduction	*Explain how the use of minimum numbers can be assured*	Provide steps that have either recently been taken to reduce animal numbers and/or practices that are used throughout the project to keep numbers down
Refinement	*Explain the choice of species and why the animal models(s) used are the most refined, having regard for the scientific objectives. Explain the general measures to be taken to minimise welfare costs* (harms) to the animals	Give recent examples of improvements to your procedure and husbandry systems that reduce the harms to the animals. Include consideration of pain and distress and the need to express natural behaviours

[a] new sections to be added to the template

NTS briefly for accuracy and completeness and provide more guidance if necessary.

4.3 Recommendations to improve the NTS

The EU template has shown to already be very useful in facilitating both consistency within and between countries in the level of information provided in the NTS. However, the guidance associated with the template is quite brief (EC, 2013a) and, in light of this review, could now be revisited, including the template itself. Table 3 lists some sections in the template that could be amended to encourage better reporting. Particular consideration should be given to splitting the "adverse effects" section so that the procedures, severity level and fate are described separately to the adverse effects. This will ensure that these elements are always addressed. Four countries are already clearly specifying the severity limit. The new "procedure" section should be viewed as a neutral section relating neither to harms nor benefits but simply outlining what is being done to the animals. It is surprising that there is no section for this important element, which will surely be of primary interest to any lay person reading the summaries. Currently, "in the context of what is being done to the animals" is too nebulous and, as can be seen in our analysis, often does not result in the procedures themselves being described.

Currently the 3Rs questions are worded so as to not produce particularly useful answers; replacement and refinement both ask two questions within each section with the risk that only one will be addressed. The Netherlands has recognised this by splitting up the refinement section into "choice of species" and "efforts to reduce suffering". It should be made clearer, in our view, that the refinement section covers elements that go above standard practice to reduce suffering. It would also provide more transparency, and assist in identifying projects of interest, if a project number was provided (that corresponds to the authority's records for ease of tracking) and the dates for which the project is authorised are given in the "duration of project" section. Six countries already do this.

Finally, the NTS could potentially provide a more useful role if they were located centrally. This would enable researchers in particular to search for similar work being done in other countries, which would enable them to avoid duplication. It could also help them look for 3Rs improvements that they could make to their own research. It would also enable third parties to review practices across member states more easily. Heed would need to be paid to language barriers, but species and key words could be in English at least. In the very short term, the Commission could assist by providing the links to the NTS on their website[8] (they already do this for the national statistical reports and national efforts to promote the 3Rs).

[8] http://ec.europa.eu/environment/chemicals/lab_animals/index_en.htm

Box 1: Recommendations for member states and researchers on non-technical summaries

Simple recommendations for Member States publishing NTS:

- Publish soon after authorisation, ideally within three months
- Ensure the location of the NTS is on a permanent website that can be located easily
- Provide a template for the NTS and guidance on what information has to be provided
- Avoid grouping several NTS into one pdf
- Ensure the NTS are fully searchable, ideally by keyword, species, purpose
- Provide a date of authorisation *and* publication
- Provide an identification number for the NTS that links it to the project
- Review each NTS prior to authorisation to ensure it is clear, balanced and complete, ensuring that technical terms are avoided and reporting of benefits and severity matches the project application
- Encourage researchers to search the NTS prior to applying for projects to identify potentially duplicative work or opportunities for collaboration
- Maintain the NTS on the website for as long as possible, enabling access to an archive if necessary

Simple recommendations for researchers drafting NTS:

- Avoid the use of technical words and terminology, including acronyms, names of drugs, receptors and mouse strains, scientific terms for diseases and body parts
- Avoid the use of unjustified reassurances and general statements
- Make sure the information is in the appropriate section
- Make sure you have answered all elements required in that section
- Potential benefits section:
  - Be careful to ensure the potential benefits are a fair representation of the intended outcomes of the project, e.g., do not make claims as to application of the research when the research is basic
  - Include an assessment of the likelihood that the project will achieve its aims
  - Include an assessment of the validity of the animal models used
- Adverse effects section:
  - Try to cover all elements in the adverse effects section (procedure, frequency, duration, adverse effects, severity and fate)
  - Adverse effects are not rare events that might not happen – it is a description of what the animals are likely to experience as a result of the procedure
- 3Rs sections:
  - Demonstration of application of refinements requires more than a statement of legal compliance or industry standards
  - Refinement considerations should include both procedural and husbandry, including consideration, where relevant, of humane endpoints, pain relief, anaesthesia, procedural refinements to limit duration and intensity of suffering, monitoring frequency, positive reinforcement, housing enrichment, social housing, space, etc.

We have collated simple recommendations for member states publishing NTS as well as for researchers drafting NTS (Box 1).

5 Conclusion

The NTS have the potential to improve the transparency of animal experiments across the EU. They can also be an important tool to help in sharing of best practice in the 3Rs and the avoidance of duplicative animal testing. However, for this to happen NTS must be published regularly and be more easily accessible and searchable. It is important that the information contained within them is clear, complete and unbiased. Our review shows that 24 of 28 member states are publishing their NTS and some are doing this well. There are significant improvements in speed of update and accessibility that need to be addressed, particularly by the heaviest animal-using countries. Until these are addressed it is our view that the system is not yet providing the intended transparency.

Based on a review of the NTS from Germany and the UK, the quality of the information contained within the NTS also needs significant improvement. We consistently found that NTS were deficient in their description of what is actually being done to the animals and what they might experience as a result. This perhaps reflects a natural difficulty that researchers have in describing their experiments in simple terms and admitting that their work can cause harm to the animals. Competent authorities have a role to play in improving their guidance to researchers and ultimately ensuring that the NTS they produce is a fair representation of the project being authorised. The European Commission can also help by improving the EU template and by providing further simple advice on what sort of information is expected in the various sections.

NTS are not the only tool to improve the transparency of animal experiments in Europe. There are other ways in which the public can be informed and empowered with information on the projects that are often being funded with their taxes. Entire project applications could be published as in Denmark; in Norway and Sweden they are available upon request. This could potentially avoid the need for any kind of summary to be made. Aspects of the authorisation process could also be published, such as the harm benefit assessment conducted by the competent authority (Varga et al., 2010; Pound and Blaug, 2016) and "conditions" imposed on licenses to monitor and reduce suffering as in Denmark. Establishments could allow access to and CCTV surveillance of their laboratories.

Follow up projects could now start to look at the actual information in the NTS and not just the quality of reporting. It would be useful to review several member states to see if there are any interesting patterns with the use of animals, use of refinements and reporting of severity. Policy makers may be interested in the areas in which animals are being used and the reported barriers to the use of replacements. From our perspective, it would also be interesting to see if there is consistency in the types of experiment being licensed or if there are opportunities to further harmonise to improve the welfare of animals across Europe.

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Conflict of interest

We declare there are no conflicts of interest.

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