Title

**Reporting of animal research studies in concordance with ARRIVE guidelines in Indian medical journals: A retrospective study**

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**Reporting of animal research studies in concordance with ARRIVE guidelines in Indian medical journals: A retrospective study**

**Abstract**

**Background:** Inappropriate reporting of animal studies have been a serious issue. ARRIVE guidelines were published to improve design, analysis and reporting of animal studies.

**Methods:** The present study was a retrospective observational study in which original research using small laboratory animals published between the year 2014 to 2019 in Indian Journal of Medical Research (IJMR), Indian Journal of Pharmacology (IJP), Indian Journal of Experimental Biology (IJEB), and Journal of Pharmacology and Pharmacotherapeutics (JPP) were reviewed in accordance with ARRIVE guidelines.

**Results:** 377 articles (JPP n= 15, IJMR n=37, 157 IJEB n=157 & IJP n=167) were analyzed. A statement regarding ethics approval was reported in 90.2 % of articles. Information regarding randomization and blinding was reported in 20.4% and 0.53% of studies respectively. Only 9 articles mentioned sample size calculation. Macro environmental information like room temperature/humidity was detailed in 87.5% and light and dark cycle in 96.5% articles. Concerning micro environmental conditions, access to food and water was reported in 75% of studies. Only 6.3% studies gave the details of adverse events. Information regarding humane endpoint was missing in all studies.

**Conclusion:** Inappropriate and inadequate reporting in some areas of animal research need to be curbed by adhering to ARRIVE guidelines.

Key words: ARRIVE guidelines, Animal research, Animal Ethics, Preclinical studies

**Introduction**

Preclinical studies provide the preliminary validation of the safety and efficacy of interventions. These studies are also important in determining the entry of new interventions into the clinical research phase. The validation of animal studies must be based on design of the study, standardized experimental procedures, and transparent reporting. Several studies have been conducted which highlighted the issue of poor reporting of animal studies published in different journals. 1-3

In order to assess the quality of experimental design, statistical analysis and reporting of Animal research, a systematic survey was carried out by the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), in which 271 published articles were included and assessed. In this study, authors observed that hypothesis or objective of the study was mentioned in only 59% of studies. Also, total number of animals used and their characteristics like strain, age, species etc. were missing in 41% of studies4. Most of the papers failed to report randomization (87%) or blinding (86%). Statistical methods used in the study was not mentioned in 30% of the publications. This survey has highlighted various issues related to the reporting of animal studies and also stressed on the importance of developing reporting standard specifically for animal research. 4

To improve the quality of reporting, in 2010, ARRIVE(The Animals in Research: Reporting in Vivo Experiments) guidelines were released i.e. 5 These guidelines were drawn up by National Centre for the Replacement, Refinement and Reduction of Animals in Research in UK with main objective to improve the design, analysis, and reporting of research. The ARRIVE guidelines is a 20 items checklist that intended to improve the reporting of animal research. This checklist include all the vital information that can also act as a guide in planning and conduct of study.5

ARRIVE guidelines which were developed to improve the design, analysis, and reporting of research were partially being adhered too.6-8A study done in 2014 reported that 86%–87% of papers reporting animal studies did not describe randomization and blinding methods, and more than 95% of them did not comment on the statistical power of the studies to detect a difference between experimental group.9

A complete and systematic description of objectives , methodology, statistical analysis etc may avoid unnecessary repetition and facilitate data integration from different studies. The problem of poor quality of reporting of preclinical studies is not limited to one region; it has become a global issue. Reporting of Animal Studies in leading Indian medical journals have been inconsistent and non-uniform as no guidelines were being followed with regard to standard pattern of reporting a research study.10 It is pertinent not only to conduct the research ethically but also to present the research systematically so as to maximize the output from that research possible.

The Quality of reporting animal research studies on the basis of ARRIVE so far has not been studied in Indian subcontinent in context to ARRIVE guideline. Hence, we thought of taking up this study where we can comment upon quality of publications with regard to animal studies in Indian medical journals.

**Material and Methods**

The present study was a retrospective observational study carried out in the Department of Pharmacology, Maulana Azad Medical College, New Delhi.

**Screening and selection of animal studies**

Animal studies using small laboratory animals were retrieved from four selected leading journals like Indian Journal of Medical Research (IJMR), Indian Journal of Pharmacology (IJP), Indian Journal of Experimental Biology (IJEB), and Journal of Pharmacology and Pharmacotherapeutics (JPP).

Animal studies included for review 1) were published during the period 2014–2019. 2) were original research articles. Exclusion criteria were 1) papers categorized as *in vitro studies* 2) review articles 3) correspondence 4) short communications.Articles were retrieved using search engines like Pubmed, Ermed, Google scholar, journal’s website etc. Two independent reviewers screened and reviewed a total of 409 studies. Subsequently, authors performed critical review of all publications to determine the eligibility of each of the articles. (Figure 1)

**Measurement of concordance with ARRIVE guidelines**

Selected articles were rated according to the checklist of 20 items mentioned in the ARRIVE guidelines using a dichotomous scale (described=0, not described=1). Sub items were added to the checklist that we felt deserved specific attention.

List of sub items added5

1. Item 2 of checklist (abstract): background, research objective, details of species or strain of animal used were considered as separate sub items
2. Item 6 b (study design): randomization and blinding were considered as separate sub items
3. Item 7 (Experimental procedures): method of euthanasia considered as separate point
4. Item 8 (experimental animals): Species, strain, sex, development stage and weight were considered as separate sub items

**Data Analysis**

Descriptive statistics were performed and data was expressed as number (percentage). Each paper was assessed against the 20 items of the ARRIVE guidelines, generating percentages of fully reported items. Mean percentages of items were calculated for each journal.

**Results**

Among the total 409 articles screened, 377 articles were included in the study.(Figure 1)

**Reporting of title and abstract section**

Concise and accurate title was observed in 91.2 % of the reviewed articles. We observed that in abstract of the assessed articles, research objective (99.2%), key methods (98.9%), principal findings (98.4%) and conclusion (95.7%) were adequately reported. Howsoever, background (58.3%) and details of animal species and model used (77.9%) were missing . (Table 1)

**Reporting of introduction section**

Study background, including primary and secondary objectives, were well reported. However, only 19.2% of the studies clearly described rationale for specific animal model used and how that model can address the scientific objectives of the study. (Figure 2)

**Reporting of Methods section**

A statement regarding ethics approval was reported in 92.7% of the reviewed publications. There were several key items in study design that were poorly reported. Information regarding randomization was mentioned only in 20.4 % of reviewed papers. Blinding was reported in only two publications. Details of sample size calculation were given in 2.3% of the studies. Information regarding how animals were allocated to experimental groups was detailed in 9.7% of the studies. Two third of the reviewed papers failed to mention euthanasia methods (37.9%). (Table 2). Basic details about the animals used like species (96%), strain (88.5%), age (85.9%), weight (67.6%) and source of animals (99.2%) was mentioned in most of the papers. (Table 2)

Macro environmental information such as room temperature and humidity were detailed in 87.5% of articles and light and dark cycle in 96.5% of studies. Concerning micro environmental conditions, access to food and water (mostly ad libitum), was reported in 75% in published papers. Housing conditions was mentioned in most of the reviewed papers but information with regard to type of cage, bedding material and number of animals in each cage was not properly addressed. Details of statistical method used for each analysis and unit of analysis were mentioned in 96% of studies. (Table 2)

**Assessment of reporting of results and discussion section**

Baseline data was mentioned in 80.6% of assessed articles (57.8% IJMR, 71.3% IJEB, 92.6% IJMR and 100% JPP). Only in 6.3% of studies details of all important adverse events were mentioned.(Table 3) Only 14% of the studies commented on the limitation of their study. Implication of the3Rs was mentioned only in 6 articles of IJMR out of all 377 articles that were included in the present study. (Table 4). List of funding sources was mentioned in 75% articles. (Table 4)

**Discussion**

In our study, we observed inadequacies in reporting of animal studies predominantly with regard to Method section. Many papers failed to report complete methodology, results, and other vital information that is important for effective communication.4,11,12

Several steps have been taken to standardize the reporting of in vivo experiment, one such step is ARRIVE guidelines. Studies were conducted globally to measure the impact of ARRIVE guidelines but the results were not very encouraging. In India, the information regarding the quality of published animal studies is inadequate and there is paucity of data about the impact of ARRIVE guidelines.

We observed inadequacies in Abstract section as information with regard to background and animal species and strain used were missing in more than 50% of the studies. The information regarding the animal species or strain used for a particular study was available in 77% of articles. Our study results are in contrast to previous published study, where none of the studies reviewed mentioned the animal strain or species.13 In our point of view, information about animal species and strain is vital in assessing suitability of animal model to address the research question.

Animal models plays a critical role in finding new drug targets, exploration of disease pathophysiology, and in testing new chemical entities. Concern with animal model is the validity which means to what extent an animal model measures what it purports to measure.14 Genetic variations within each species or between closely related genetic species can alter the study results. For example, some mouse strains are fully resistant to Ebola virus, others die without specific symptoms and others develop fatal hemorrhagic fever15.

Statement regarding Ethics approval was mentioned in 90% of the articles which was comparable with the study published in the Indian Journal of Pharmacology (IJP) which reported it to be 97%10. Another study compared the reporting of Ethics statement in two Indian medical journal in comparison to British Journal of Pharmacology (BJP). In this study, 79% of animal studies published in the Indian journals included ethics committee approval statement. In contrast, it was reported only in 62% of animals studies published in BJP16. Similarly, in a systematic review, it was observed that 78% of articles included the approval from Animal Ethic Committee statement.3

We also observed that, there was insufficient information in the methodology section. The two important indicators of good study design; randomization and blinding were reported in 20.4% and 0.53 % (2 articles) respectively. In a study, where quality of reporting of intervention animal studies were assessed using the ARRIVE guidelines, randomization and blinding was reported in 17.1% and 29.3%, respectively3. Another retrospective study, also revealed poor reporting of study design in animal studies17. The poor reporting of methodologies is one area which needs maximum focus. Inadequate reporting of methodology will make it impossible for researchers to reproduce the model in a new study. Preregistration of animal studies can be more effective tool in solving the problem of poor reporting of methodology, it can tackle the issue at early stage of planning of any animal study. Preregistration as being undertaken for clinical trials (clinical trial registry of India) could improve quality of protocol making as researcher has to register the study and describe all the statistical test/ experimental procedure before starting any study.

We also observed that, details of the anesthesia, analgesia or the time of drug administration schedule was reported inadequately. In a systematic review accessing quality of reporting of published international animal studies, detailed information regarding anesthesia was mentioned only in 33% and information regarding preanesthetic medication was mentioned in 24.9% and post interventional analgesia in 12.2% of articles18. Animal welfare guidelines recommend minimal harm to be inflicted to animals during research. As a result, adequate anaesthesia and analgesia should be administered if not contraindicated. Post intervention analgesia is also recommended after completion of intervention to prevent post operative pain.

Different methods of euthanasia for killing animals may affect outcomes of the study. It was observed in a study, that different method of euthanasia in rodent model influence the level of inflammatory mediators19. It was observed that information regarding method of euthanasia was mentioned in 61.4% of articles published in Indian journals in comparison to 44.4% of BJP articles20. In our study, information regarding method of euthanasia was mentioned only in 37.9% of the articles. In ARRIVE guidelines euthanasia is a part of experimental procedure and not a separate item. We suggest that method of euthanasia must be a separate item in checklist to improve the quality of reporting.

Although all species, strain and weight of the animal was mentioned in majority of articles, only half of the studies mentioned the development stage of the animals (53.8%). Some investigators believe that age of the rodent can be calculated from the body weight curves. The correlation of body weight and age is highly dependent on life stage, stock and stage of animal. Moreover, nutritional and environmental factors also affect the weight of the animal. Thus, reporting of age of animal in a particular research is important. Diseases like Alzheimer’s and osteoarthritis are age related and testing or screening new drug in young animals can give misleading result. 19 Information regarding health or immune status of the animal was missing in most of the studies. The findings of present study echoed with other studies where the relevant characteristics of animal were inadequate and incomplete in the most of the articles13,21.

A study was conducted to find out the effect of physical and social environmental enrichment on growth and behavior of adolescent male rats. The results revealed that physiologic and behavioral differences are evident soon after differential housing of the rats22. We observed that details of husbandry conditions was mentioned in most of the assessed articles but failed to mention information regarding enrichment (1.3%) and welfare related assessment (10.8%).

We found that only few studies (1.5%) provided a statement regarding the implication of replacement, refinement or reduction procedures in animal welfare. These 3R’s are being globally practiced to replace animal models with other in vivo alternatives, refine the techniques to minimize pain/ suffering and reducing the number of animals in research study to the extent of statistical significance only. This can only be improved by appropriate training of researchers. Education and training are needed to raise awareness and courses in Laboratory animal sciences can be helpful in improving the present scenario.

**Limitations**

Since in our study sample size was not uniform across four journals, we opted for descriptive analysis. Also, our objective was to bring out quality of reporting with regard to ARRIVE guidelines. We restrained from commenting on editorial process of a journal.

**Conclusion**

Overall analysis of articles revealed inadequate and non uniform reporting of the animal experiments in all four Indian journals. Studies failed to elaborate study design, experimental procedures and details of husbandry conditions. To standardized the reporting of animal studies and to improve the quality: ARRIVE guidelines are an important tool. It gives a basic frame work for better planning of animal experiments and also for effective communication to solve the issue of reproducibility and transparency. Every journal should implement these guidelines for appraisal and publication of manuscript. Preregistration of animal studies like clinical trial registry may be helpful tool in improving the standard of reporting of animal studies.

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Table 1: Assessment of Title and Abstract on the basis of ARRIVE guidelines

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Items | Recommendations | IJMR  N (%) | IJEB  N (%) | IJP  N (%) | JPP  N (%) | Total  N (%) |
| Title | Provide accurate and concise description of the content | 31 (81.5) | 136 (86.6) | 162 (97) | 15 (100) | 344 (91.2) |
| Abstract | Provide an accurate summary of- | | | | | |
|  | Background | 37 (97.3) | 132 (84) | 46 (27.5) | 5 (33.3) | 220 (58.3) |
|  | Research objective | 38 (100) | 154 (98) | 167 (100) | 15 (100) | 374 (99.2) |
|  | Details of species or strain of animal used | 33 (86.8) | 138 (87.8) | 108 (64.6) | 15 (100) | 294 (77.9) |
|  | key methods | 38 (100) | 154 (98) | 166 (99.4) | 15 (100) | 373 (98.9) |
|  | Principal findings | 38 (100) | 151 (96.1 | 167 (100) | 15 (100) | 371 (98.4) |
|  | Conclusion | 38 (100) | 141 (89.8) | 167 (100) | 15 (100) | 361 (95.7) |

For assessment of abstract background, research objective, details of species used, key methods, principal findings and conclusion take as separate identities. (Item 2 of ARRIVE guidelines)

Table 2: Evaluation of reporting of Methods on the basis of ARRIVE guidelines

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Items | Recommendations | IJMR  N (%) | IJEB  N (%) | IJP  N (%) | JPP  N (%) | Total  N (%) |
| Ethical Statement | Ethical Statement | 35 (92.1) | 131 (83.4) | 163(97.6) | 13 (86.6) | 342 (90.7) |
| Study design | Number of experimental and control groups | 34 (89.4) | 157 (100) | 156 (93.4) | 15 (100) | 362 (96) |
| Randomization | 4 (10.5) | 12 (7.6) | 60 (35.9) | 1 (6.6) | 77 (20.4) |
| Blinding | 1 (2.6) | 0 (00) | 0 (0) | 1 (6.6) | 2 (0.53) |
| Experimental unit | 34 (89.4) | 154 (98) | 157 (94) | 15 (100) | 360 (95.4) |
| Experimental procedure | Details of all procedure | 37 (97.3) | 157 (100) | 164 (98.2) | 15 (100) | 373 (98.9) |
| Method of euthanasia | 10 (26.3) | 39 (24.8) | 91 (54.4) | 3 (20) | 143 (37.9) |
| Experimental animal | Provides details of animal used including | | | | | |
| Species | 36 (94.7) | 153 (97.4) | 158 (94.6) | 15 (100) | 362 (96) |
| Strain | 30 (78.9) | 136 (86.6) | 153 (91.6) | 15 (100) | 334 (88.5) |
| Sex | 23 (60.5) | 76 (48.4) | 97 (58) | 7 (46.6) | 203 (53.8) |
| Developmental stage | 29 (76.3) | 126 (80.2) | 154 (92.2) | 15 (100) | 324(85.9) |
| Weight | 15 (39.4) | 130 (82.8) | 97 (58) | 13 (86.6) | 255 (67.6) |
| Source of animals | 38 (100) | 157 (100) | 164 (98.2) | 15 (100) | 374 (99.2) |
| Housing & Husbandry | Housing | 29 (76.3) | 146 (92.9) | 158 (94.6) | 15 (100) | 348 (92.3) |
| Husbandry conditions | 26 (68.4) | 139 (88.5) | 161 (96.4) | 15 (100) | 341 (90.4) |
| Welfare related assessments and interventions that were carried | 3 (7.8) | 27 (17.1) | 0 (00) | 11 (73.3) | 41 (10.8) |
| Specify no. of animals used in each experiment, and no. of animals in each group | 33 (86.8) | 157 (100) | 156 (93.4) | 15 (100) | 361 (95.7) |
| Details of sample size calculations | 00 (0) | 9 (5.7) | 0 (00) | 0 (00) | 9 (2.3) |
| Indicate the no. of independent replications of each experiment if relevant | 3 (7.8) | 12 (7.6) | 5 (2.9) | 0 (00) | 20 (5.3) |
| Allocating of animals to experimental groups | Full Details how animals were allocated included randomization or matching | 3 (7.8) | 24 (15.2) | 10 (5.9) | 0 (00) | 37 (9.7) |
| Describe the order in which the animals in the different experimental groups were treated and assessed | 36 (94.7) | 157 (100) | 144 (86.2) | 15 (100) | 352 (93.3) |
| Experimental outcomes | Primary and secondary experimental outcomes | 37 (97.3) | 157 (100) | 160 (95.8) | 15 (100) | 369 (97.8) |
| Statistical Methods | Details of statistical method used for each analysis | 36 (94.7) | 156 (99.3) | 158 (94.6) | 15 (100) | 365 (96.8) |
| Unit of analysis for each dataset (eg. Single animal or group of animals) | 32 (84.2) | 157 (100) | 158 (94.6) | 15 (100) | 362 (96) |
| Any methods used to assess whether the data met the assumptions of the statistical approach | 00 (0) | 16 (10.1) | 0 (00) | 0 (00) | 16 (4.2) |

For the assessment randomization and blinding were considered as separate sub-items (study design item 6b of ARRIVE guidelines. Information regarding method of euthanasia was also taken as separate identity. Information related to experimental animal (item 8a of ARRIVE guidelines) like species, strain, sex, development stage and weight were taken as separate sub-items.

Table 3: Assessment of reporting of Results on the basis of ARRIVE guidelines

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Items | Recommendations | IJMR  N (%) | IJEB  N (%) | IJP  N (%) | JPP  N (%) | Total  N (%) |
| Baseline data | Report relevant characteristic and health status of animal\* | 22 (57.8) | 112 (71.3) | 155 (92.8) | 15 (100) | 304 (80.6) |
| Numbers analysed | Report the number of animals in each group included in each analysis | 29 (76.3) | 145 (92.3) | 156 (93.4) | 15 (100) | 345 (91.5) |
| If any data were not included, explain why | 2 (5.2) | 3 (1.9) | 3 (1.7) | 0 (00) | 8 (2.1) |
| Outcomes and estimation | Report results for each analysis carried out with a measure of precision | 38 (100) | 157 (100) | 155 (92.8) | 15 (100) | 365 (96.8) |
| Adverse event | Details of all Adverse event in each group | 7 (18.4) | 17 (10.8) | 0 (00) | 0 (00) | 24 (6.3) |
| Any modification in experimental protocol to reduce ADR | 1 (2.6) | 8 (5) | 0 (00) | 0 (00) | 9 (2.3) |

\*Reporting of relevant characteristics and health status of animals include weight, microbiological status and drug or test naïve) prior to treatment or testing (item 14 of ARRIVE guidelines

Table 4: Evaluation of Discussion on the basis of ARRIVE guidelines

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Items | Recommendations | IJMR  N (%) | IJEB  N (%) | IJP  N (%) | JPP  N (%) | Total  N (%) |
| Interpretation/  Scientific implication | Interpretation of results | 38 (100) | 157 (100) | 164 (98.2) | 15 (100) | 374 (99.2) |
| Comment on study limitation | 6 (15.7) | 4 (2.5) | 43 (25.7) | 0 (00) | 53 (14) |
| Describe any implications of your finding for 3 Rs\* | 6 (15.7) | 0 (0) | 0 (00) | 0 (00) | 6 (1.5) |
| Generalisability/translation | Comment on finding of the study are likely to translate on other species or system | 30 (78.9) | 145 (92.3) | 88 (52.6) | 15 (100) | 278 (73.7) |
| Funding | All funding sources | 30 (78.9) | 117 (74.5) | 123 (46) | 13 (86.6) | 283 (75) |

\*3 Rs Include Replacement, refinement and reduction.

Figure1: Flow chart depicting number of articles included in the study for analysis

N= 409 articles were screened for the study

A total of n=22 studies were excluded which were:

Short communications n=8

Studies on large animals n=6

In vitro studies n=6

Review articles n=2

Articles included in the study after applying inclusion and exclusion criteria n=377

JPP (n=15)

IJP (n=167)

IJEB (n=157)

IJMR (n=38)

Figure 2: Assessment of Introduction of articles on the basis of ARRIVE guidelines