Global cross-company data-sharing on the housing of non-rodents during the recording of cardiovascular telemetry data on safety pharmacology and toxicology studies

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The surveys were developed by an international working group consisting of representatives from eight Pharmaceutical companies, six Contract Research Organisations, the NC3Rs and the Safety Pharmacology Society.

Introduction

- A cardiovascular assessment of all new chemical entities and some biologics is required in a non-rodent species prior to first administration in humans; this is generally performed as a separate safety pharmacology study and/or combined within a toxicology study.
- Although most facilities group-house their non-rodents (generally dogs, minipigs and non-human primates (NHPs)) before studies and in between recording sessions, during the cardiovascular telemetry recording the animals are often individually housed (for around 24 hours on multiple occasions during the study).
- Individual housing of the animals during the recording session may be due to concerns about pen size, limitations of the hardware (signal strength and transmission on the same frequency) and/or behavioural impacts (e.g. increased activity of individual animals or destruction of equipment if jacketed telemetry used) of group housing on data quality. However, separation during recording periods may introduce additional stress to the animals, even when an individual is within sight/touch of another animal which impacts animal welfare and potentially data quality.
- There is therefore an opportunity to review and refine the current practices used for this data recording to improve animal welfare and scientific data quality.

Data collection and results

- Data was collected by questionnaire. Questions focused on current housing conditions of dogs, minipigs and NHPs during safety pharmacology and toxicology studies. The data presented here is specifically on recordings for cardiovascular endpoints included in safety pharmacology studies. Questions were also asked to investigate opinions on the risks and benefits of group-housing during the cardiovascular recordings.
- Data from 28 dog, 16 minipig and 30 NHP safety pharmacology respondents were shared by 33 different facilities worldwide.
- Most companies use 4 animals in the study however, some use 6 or 8 animals. Most companies use one sex only, whilst some companies do use both sexes within the study. 82% of respondents currently use a latin-square study design.
- Companies generally pair/group-house animals on safety pharmacology studies on non-recording days, however, most companies individually house the animals during the telemetry recordings (FIGURE 1).
- The major reason stated for not group-housing during recordings was limitations of the recording equipment. Many other reasons were also stated (TABLE 1).
- Some companies do successfully group or partially group house dogs and/or NHPs on recording days, demonstrating that this can be done in practice.
- Additionally, some companies are actively considering changing procedures/equipment to allow for group-housing of animals over the next two years (FIGURE 2).

Figure 1: Housing method on telemetry recording and non-recording days

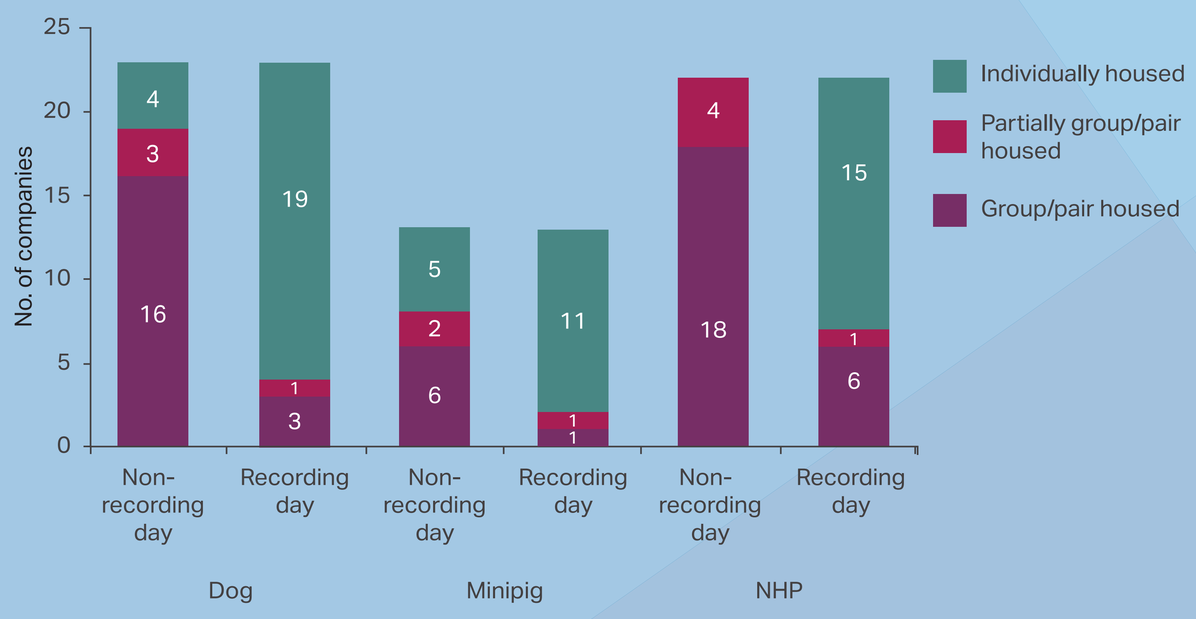


Figure 2: Do you have plans to increase availability of group housing?

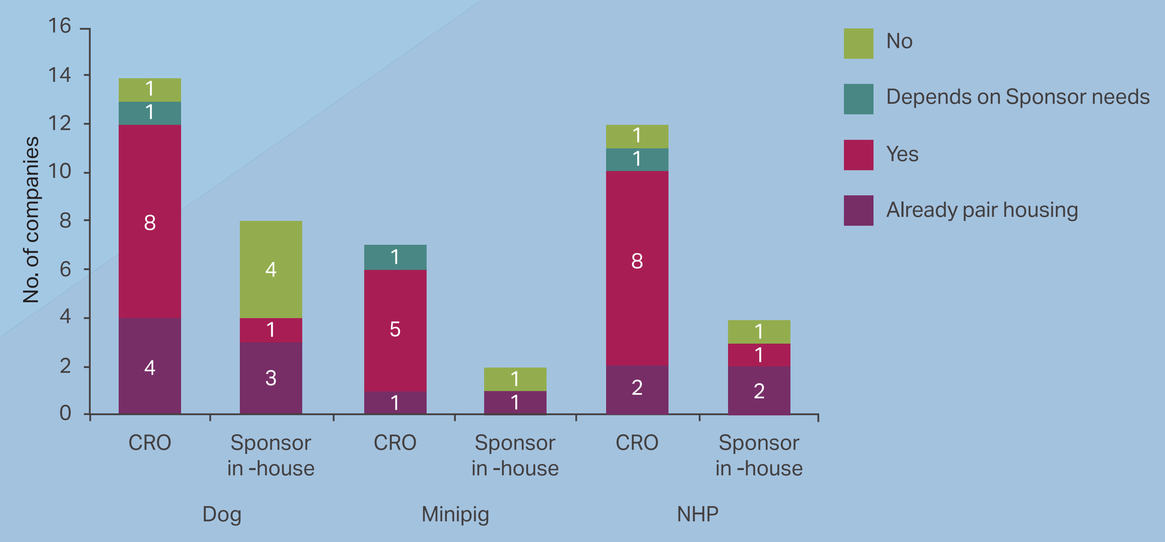


Table 1: Reasons for not group housing during recordings in safety pharmacology studies

	Dog	Minipig	NHP
Limitations of recording equipment	76	64	91
Study design	68	71	64
Temperament of animals	56	43	50
Clinical signs monitoring	48	21	27
Increased/abnormal activity	40	29	32
Quality of data	36	21	23
Food consumption recording	32	14	23
Size of cage/no. of cages available	28	29	32
Sponsor requirement	28	29	27
Validation of process	28	14	23
Recording room set up	28	0	27
Colony management	24	29	50
Housing options available at CRO	16	7	18

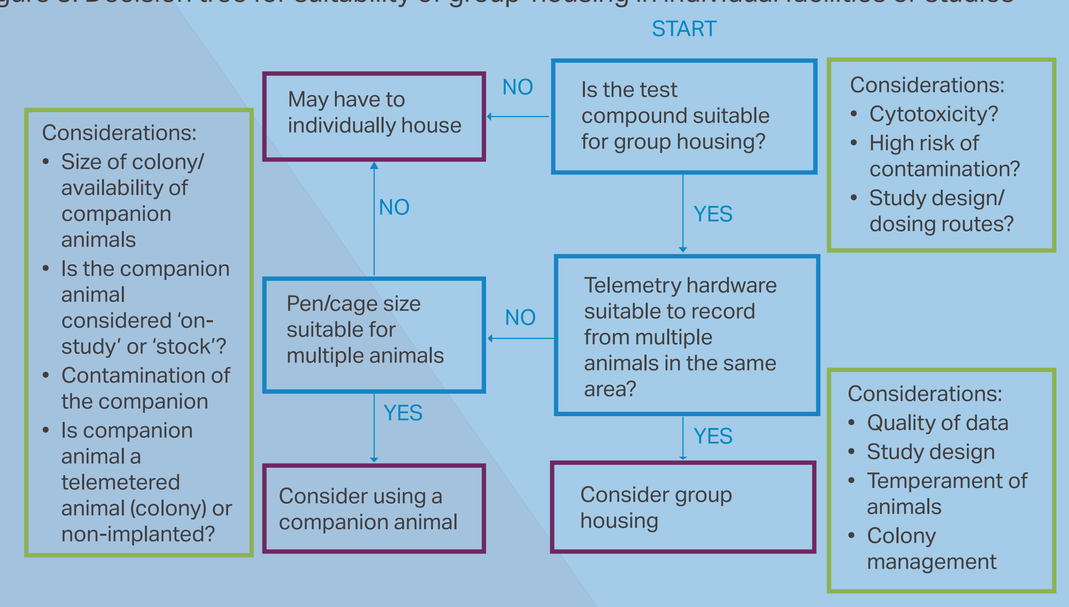
Table 2: Perceived barriers to group housing on safety pharmacology studies and potential resolutions

Perceived barriers	Potential resolutions with available information
Limitations of recording equipment	• Advances in technology will allow recording from multiple animals in the same pen/cage • Consider using an unrecorded companion animal
Quality of data and increased/abnormal activity	• Publications indicate that group housing does not impact the quality of data in both dogs and NHPs e.g. Klumpp et al, 2006; Prior et al 2015 • In companies that had experience of group housing 7/7 dog, 2/2 minipig and 7/8 NHP indicated that the data was the same or better than individually housed animals
Study design (i.e. latin square, one animal one dose)	• Use partial latin square or ascending dose • Ascending dose design • Dose animals different dose levels within a pen/cage (risk of cross contamination, but how often does contamination actually occur?) • If using double latin-square (ie, 8 animals), pairs of animals can receive the same dose
Temperament of animals / colony management	• Acclimatisation period to the recording day housing/animals • Close observations and knowledge of individual animals within the colony • May have to remove 'unruly/disruptive' animals from colony • Larger colony groups allow more options for smaller groups on-study
Clinical signs and/or food consumption recording	• Expected effects of test compound (indications from previous work e.g. MTD studies) • Use of CCTV (but may be hard to identify individuals) • Are individual food consumptions required, or a nice-to-have?
Sponsor requirement/CRO availability	• Publications indicating that group housing does not affect the scientific integrity of the data will increase the uptake which will in turn increase the CRO availability of this type of housing
Regulatory acceptance of group housed data	• Publications indicating that group housing does not affect the scientific integrity of the data will support acceptance • Precedence with biologicals, where SP data included within tox studies which may already utilise group-housing, and data is accepted

Recommendations

- 5/24 respondents indicated that they successfully group/partially group-house dogs and 7/22 successfully group/partially group-house NHPs during telemetry recordings for cardiovascular data during safety pharmacology studies. Sharing of best-practices and publication of validation datasets may encourage others to adopt group housing during recording.
- TABLE 2 indicates the current perceived barriers to adoption of this refinement, along with some potential resolutions.
- FIGURE 3 shows a decision tree which could be used for individual studies or facilities to ascertain whether group housing is a suitable option.

Figure 3: Decision tree for suitability of group-housing in individual facilities or studies



3Rs impact

Potential to refine the housing conditions of thousands of non-rodents during telemetry recordings within safety pharmacology studies worldwide.

Conclusions

- There are opportunities to increase the group-housing of non-rodents during telemetry recordings within safety pharmacology studies.
- Data sharing (best practice processes and validation data) could lead to further adoption of this refinement worldwide.