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

Anna Bottomley[1], Helen Prior[1] and Jason Cordes[2]
[1]National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs), London, UK; [2]Pfizer, Inc, Groton, CT, USA.

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 with a toxicology study.
- Although most facilities group-house their non-rodents (generally dogs, mini-pigs and non-human primates (NHPs)) before studies and in between recording sessions, during the cardiovascular telemetry recordings, the animals are often individually housed (for approximately 24 hours on multiple occasions throughout 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 were collected by questionnaire. Questions focused on current housing conditions of dogs, mini-pigs and NHPs during safety pharmacology and toxicology studies. The data presented here are specific to cardiovascular telemetry recordings included in toxicology studies. Questions were also asked to investigate opinions on the risks and benefits of group-housing during the cardiovascular recordings.
- Data from 20 dog, eight mini-pig and 22 NHP toxicology respondents were shared by 25 different facilities worldwide (FIGURE 1).
- Most companies obtain cardiovascular data from jacketed/implanted telemetry devices however, many still obtain this data via 'snap-shot' recordings (FIGURE 2).
- Companies generally pair/group-house animals on toxicology studies on non-recording days, however, most companies individually house the animals during the telemetry recordings (FIGURE 3). All respondents indicated this was for periods of greater than 16h per session.
- The major reason stated for not group-housing during recordings was the potential damage to the equipment (jackets/leads) by cagemates, leading to potential loss of data. 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 1: Number of respondents for each species

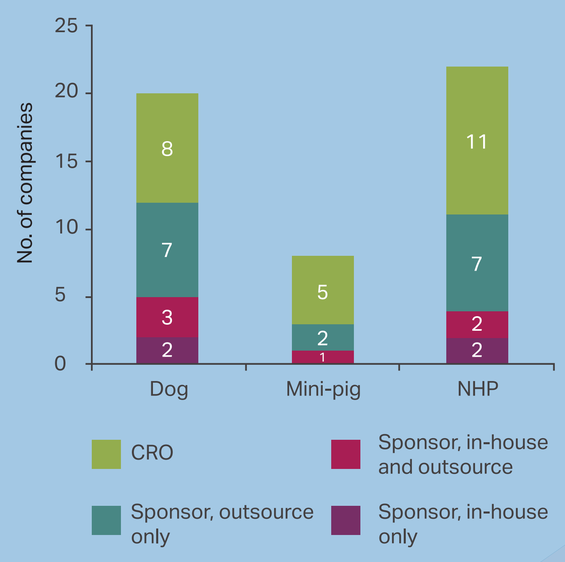


Figure 2: Method of telemetry recording used for each species

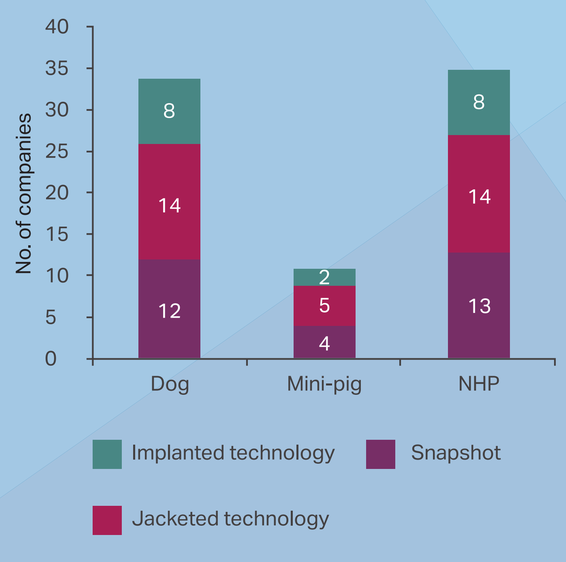
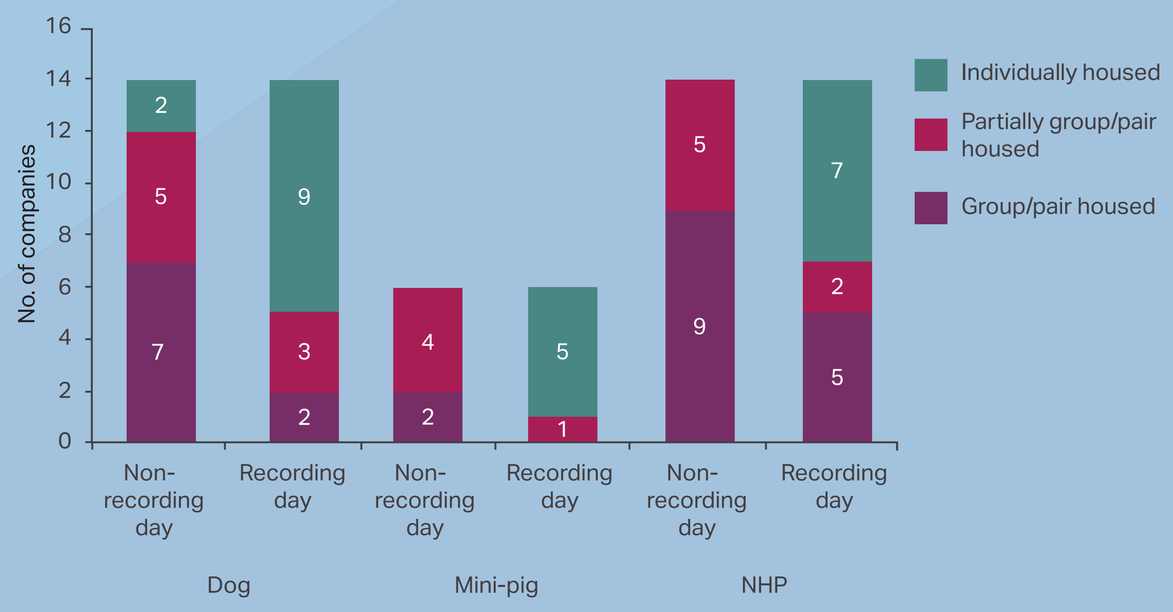


Figure 3: Housing method on telemetry recording and non-recording days



Recommendations

- 5/14 respondents indicated that they successfully group/partially group-house dogs and 7/14 successfully group/partially group-house NHPs during cardiovascular telemetry recordings on toxicology 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.

Table 1: Reasons for not group-housing during telemetry recordings (data is presented as the percentage of respondents)

	Dog	Minipig	NHP
Damage to the equipment	80	50	67
Food consumption recording	73	67	60
Limitations of recording equipment	53	67	60
Temperament of animals	53	67	40
Validation of process	47	50	47
Increased/abnormal activity	47	33	47
Quality of data	47	33	40
Clinical signs monitoring	53	33	47
Size of cage/no. of cages available	27	50	27
Recording room set up	27	17	33
Sponsor requirement	27	17	20
Size of animals	7	17	27
No. of respondents	**n=15**	**n=6**	**n=15**

Table 2: Perceived barriers and potential resolutions with available information

Perceived barriers	Potential resolutions with available information
Damage to the equipment	• Acclimatisation period to the jackets, before study and before sessions • Double-jacket the animals (body temperature?) • Use implanted telemetry devices instead • Publication indicating no increase in incidence of equipment damage in NHP pair vs single housed (Kaiser et al 2015)
Food consumption recording	• Impact of food consumption recording would be similar as on non-recording days of the study • Consider short-term individual housing for food consumption
Limitations of recording equipment	• Using alternative technology or collection methods
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. Kaiser et al 2015, Sadekova et al 2015 and Xing et al 2015 • In companies that had experience of group housing 4/5 dog, 1/1 minipig and 4/5 NHP indicated that the data was the same or better than individually housed animals • If animals group housed for the majority of the study, individual housing may disturb the animals more
Temperament of animals	• Acclimatisation period prior to the start of study investigations • Species considerations (e.g., NHP hierarchies/dominance) • Age of animals being used
Validation of process	• Safety pharmacology studies publishing data on pair/group housing Klumpp et al, 2006; Prior et al 2015
Size of animals	• Age of animals being used • Grouping used for the rest of the study • Acclimatisation to grouping prior to start of investigations
Sponsor requirement	• 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
Clinical signs monitoring	• Expected effects of test compound (indications from previous work e.g. MTD studies) • Use of CCTV (but may be hard to identify individuals)

Conclusions

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

3Rs impact

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

References

- Klumpp et al (2006) Optimizing the experimental environment for dog telemetry studies. *J Pharm Tox Meth* 54:141-149
- Prior et al (2015) pair-housed dog telemetry: Animal welfare refinement with early indications of similar study sensitivity. *J Pharm Tox Meth* 74 (in press)
- Kaiser et al (2015) Telemetric assessment of social and single housing: Evaluation of electrocardiographic intervals in jacketed cynomolgus monkeys. *J Pharm Tox Meth* 74 (in press)
- Sadekova et al (2015) Effect of Moxifloxacin Hydrochloride on cardiovascular parameters assessed via jacketed external telemetry (JET) in the male beagle dog co-housed in european caging. SOT poster
- Xing et al (2015) Effects of group housing on ECG assessment in conscious cynomolgus monkeys. *J Pharm Tox Meth* 74 (in press)