

Background

- 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 socially house their non-rodents (generally dogs, minipigs 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 social housing on data quality. However, separation during recording periods may introduce additional stress (increase in heart rate) 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.

Figure 1: Number of responses.



Figure 2: How do you record CVS data on toxicology studies?

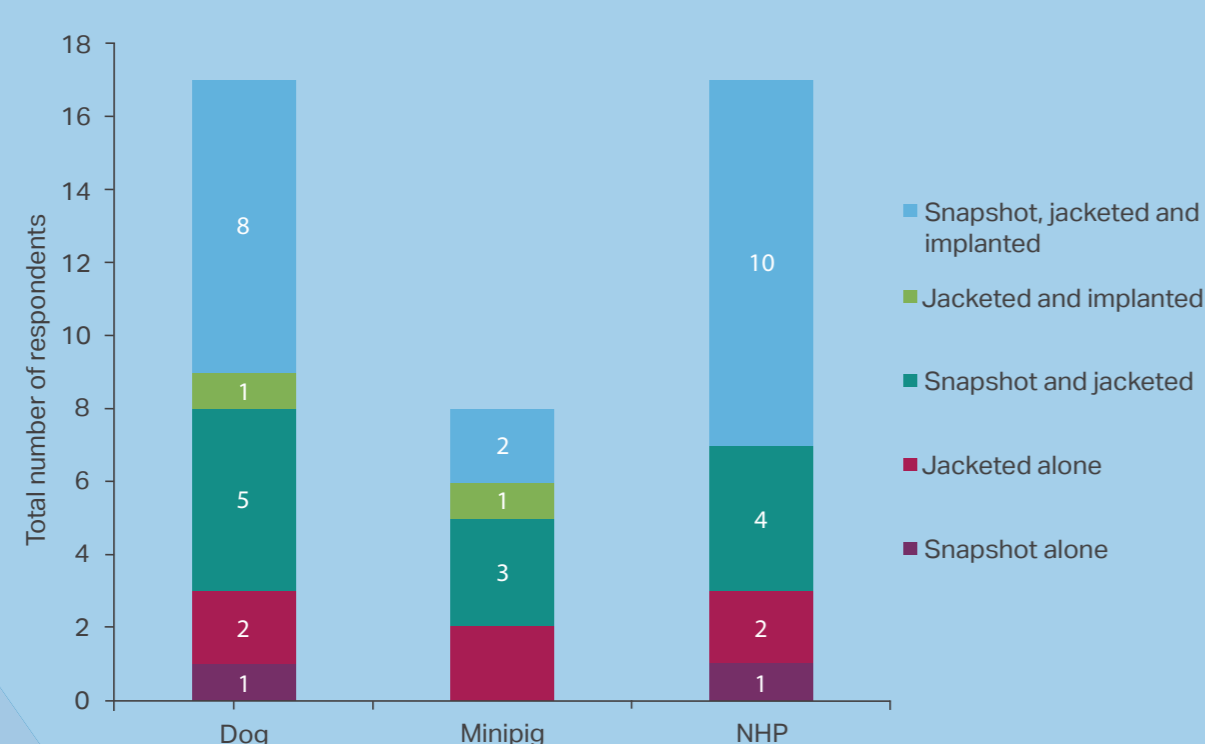
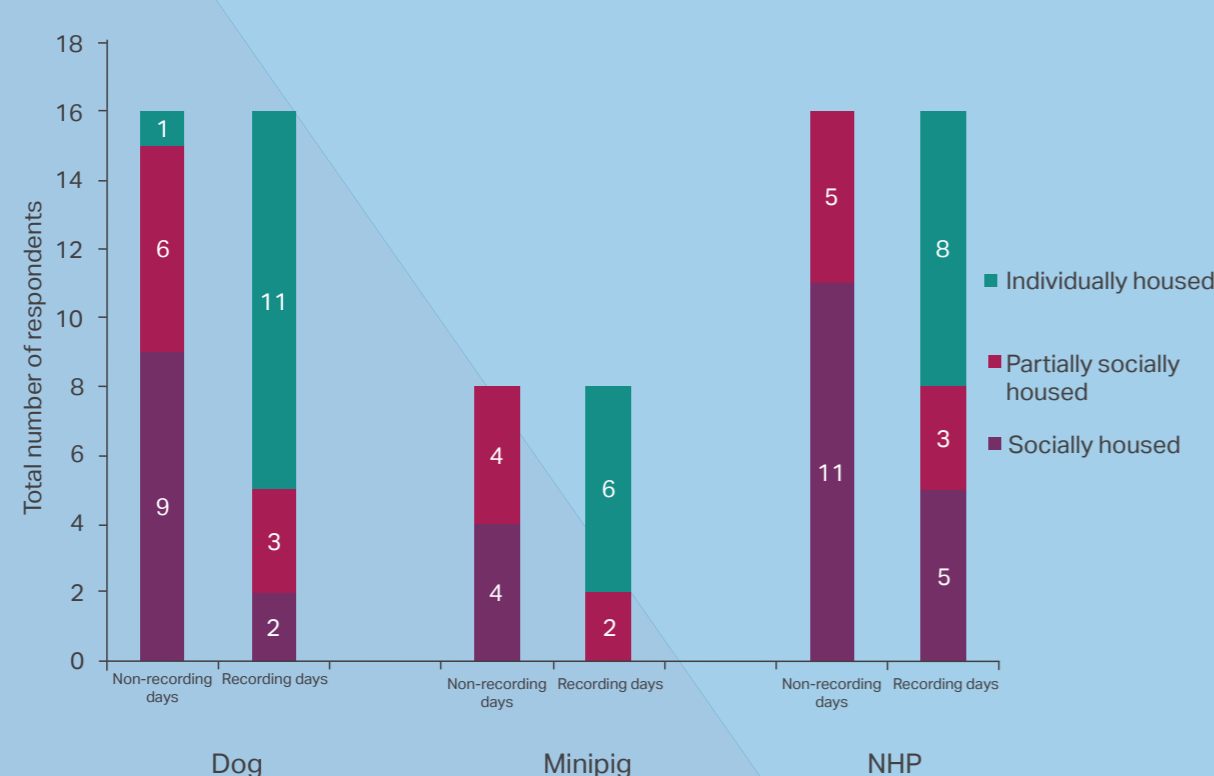


Figure 3: Housing of dogs, minipig or NHPs on recording and non-recording days in toxicology studies.



Conclusions

- There are opportunities to increase the social 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.

Data collection and results

- Data was collected by questionnaire. Questions focused on current housing conditions of dogs, minipigs and NHPs (cynomolgus macaque) during jacketed telemetry recording on toxicology studies. Questions were also asked to investigate opinions on the risks and benefits of social-housing during the cardiovascular recordings.
- Data from 24 dog, 13 minipig and 25 NHP toxicology respondents were shared by 29 different facilities worldwide.
- Most companies obtain cardiovascular data from jacketed/implanted telemetry devices. However, many still obtain this data via 'snap-shot' recordings.
- Companies generally socially house animals on toxicology studies on non-recording days, however, most companies individually house the animals during the telemetry recordings. All respondents indicated this was for periods of greater than 16h per session.
- The major reason stated for not socially housing during recordings was the potential damage to the equipment (jackets/leads) by pen/cagemates, leading to potential loss of data. Many other reasons were also stated (Table 1).
- Some companies do successfully socially or partially social-house dogs, minipigs 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 social housing of animals during recordings over the next two years.

Table 1: Reasons stated for not social-housing during recordings in toxicology studies.

	Dog (22)	Minipig (11)	NHP (21)
Damage to the equipment	64	55	48
Food consumption recording	59	55	48
Limitations of recording equipment	50	62	52
Temperament of individual animals	41	45	38
Validation of processes required	36	45	38
Increased/abnormal activity	32	27	33
Quality of data obtained	36	36	29
Clinical signs monitoring	41	27	38
Size of pen/cage/no. of pen/cages available	27	36	19
How the recording room is set up	23	18	24
Sponsor requirement/expectation ^a	63 (8)	20 (5)	50 (8)
Size of animals	9	18	18

Data represented is % of respondents (the number in parenthesis next to species indicates the number of replies received for that species and subset of the survey).

^aThis questions was only asked of the CROs and therefore the total number of respondents is different than the other replies and is stated in brackets next to the percentage.

Recommendations

- 5/16 respondents indicated that they successfully socially/partially social house dogs and 8/16 successfully socially/partially social house NHPs during telemetry recordings for cardiovascular data during toxicology studies. Sharing of best-practices and publication of validation datasets may encourage others to adopt social housing during recording.
- Table 2 indicates the current barriers to adoption of this refinement, along with some potential resolutions.

Table 2: Potential considerations/recommendations for social housing on toxicology studies.

Major barriers identified in the survey and possible resolutions	
Damage to the equipment by pen/cage mates:	<ul style="list-style-type: none"> Consider the amount of acclimatisation to the jackets prior to the study start and if further acclimatisation/refreshing should be performed before each recording session during the study. Consider using a second jacket or T-shirt under the outer jacket, to cover the ECG leads. Consider using implanted technology. Kaiser <i>et al</i> (2015) indicates that there was no increase in incidence of equipment damage in paired NHPs vs single housed animals.
Limitation of the recording equipment currently being used (e.g. signal cross-talk):	<ul style="list-style-type: none"> Consider using alternative technologies which allow for multiple signals to be recorded.
Quality of data obtained:	<ul style="list-style-type: none"> Publications indicate that social housing does not impact the quality of data in both dogs and NHPs (e.g. Kaiser <i>et al</i> 2015; Sadekova <i>et al</i> 2015; Xing <i>et al</i> 2015). In companies that had experience of social housing 8/9 dog, 3/3 minipig and 8/9 NHP respondents indicated that the data obtained was the same or better than from individually housed animals.
Temperament of individual animals:	<ul style="list-style-type: none"> Consider the acclimatisation period prior to the start of study investigations. Species considerations (e.g. NHP hierarchies/dominance). Age of animals being used. Consider working with the supplier to assess compatibility of animals prior to arrival.
Validation of processes required for social housing:	<ul style="list-style-type: none"> Safety pharmacology studies are publishing data on social housing (Klumpp <i>et al</i> 2006; Prior <i>et al</i> 2015). Consider investigating the implications of social housing during the pretreatment phase of studies to build up data on processes and impact.
Monitoring of clinical signs observed in individual animals:	<ul style="list-style-type: none"> Consider the expected effects of test compound (indications from previous work e.g. MTD studies). Consider the use of CCTV cameras and methods of identifying individual animals (e.g. colour coded jackets).
Size of animals:	<ul style="list-style-type: none"> Consider the age of the animals being used. Consider the introduction procedures utilised when the animals first arrive at the site. Consider the acclimatisation to the social groups prior to the start of any investigations.