Challenge 3: Rodent Big Brother: automated recording of rodent activity and temperature in the home cage

Surgery Questions and Answers

Study design and current system:

Q. What size are the studies?
A. They range in size and duration. The shortest is a safety pharmacology study lasting 24 hours, and comprising four treatment groups of six rats per treatment group. The largest is a one month repeat-dose toxicity study, which can contain 10M and 10F per group (three dose levels and a control) and recovery animals of 5 per sex per group on the high dose level and control. Therefore we need to study about 100 animals for a month.

Q. Do the standard cages need to be in a standard racking system or could the cages be in different racks? For example, could monitoring be done only for the cages at the four corners of the rack?
A. Ideally, all the cages in a standard rack would be monitored; just using the 4 corners of a rack would not be an efficient use of space.

Q. Are the cages stacked?
A. Yes, in a movable racking system (e.g., 5 x 5).

Q. Is the lighting for each cage individual or room lighting?
A. Room lighting, controlled automatically on a 12 h light-dark cycle.

Q. Do mice have access to activity wheels?
A. No

Q. How many rats are in a cage?
A. 3-5/cage.

Q. Are all cages currently videoed?
A. No, only on extremely rare occasions.

Specification:

Q. How long do you need to record on the same animal?
A. Ideally for the length of the study, sampled throughout the light-dark cycle, for one month of dosing plus one month recovery.

Q. What are the details of the Radio Frequency Identification (RFID) tag currently used?
A. It is a standard tag used for pet cats and dogs. The specifications are IPLEXX IPTT-300. A hypodermic injector is used to introduce it subcutaneously into rats or mice.

Q. Is video tracking a possibility?
A. There are issues with video tracking such as the use of opaque cages by some laboratories, and the optimal positioning of cameras, but it is not a definite no if the application overcomes these limitations.

Q. Do the devices have to be subcutaneous?
A. No, but the interscapular subcutaneous temperature is close to core temperature, due to thermogenesis in the interscapular brown adipose tissue, and it is very easy and quick to inject an Radio Frequency Identification (RFID) chip subcutaneously in this region of a rat or mouse.

Q. Is size very important, the chips will have to be smaller for mice than rats?
A. The priority is a device for rats, if it works for mice as well then that would be advantageous but not essential. We currently use the same RFID chip in mice and rats.

Q. How precise does the tracking need to be?
A. The important parameter is the quantity of locomotor activity rather than exact tracking. It is also essential to distinguish between individuals.

Q. Is there a preference for an external device?
A. Any internal device must be injectable, and not require surgery. Any external device cannot be at risk of being chewed at by cagemates.

Q. Is it an absolute prerequisite that the software is GLP compliant?
A. Yes

Q. Is it OK for the software to be compliant within the three years?
A. The applicant would need to describe when the software was likely to be compliant and the process to get there would need to be defined. However, it would be preferable to begin the software development with GLP-compliance in mind.

Q. What type of device are you looking for to perform data capture and analysis? Could it be similar to the chips already available?
A. Yes, but automatic detectors would have to be used: the current system uses a hand-held 'wand'.

Types of measurement:

Q. If we need to measure convulsions, what do the convulsions actually look like? For instance, it might be hard to distinguish between convulsions and seizures.
A. Convulsions (usually loss of posture with abnormal, involuntary, repetitive muscle contractions, etc.) are distinct from seizures, a term which embraces both convulsions and seizure events that do not translate into motor events (e.g., absence seizures, involving a brief 'trance-like state'). Detection of convulsions is considered a feasible goal; automated detection of 'absence seizures' in rodents without EEG recordings is considered too challenging. If using a video approach, events such as tonic-clonic convulsions could be flagged-up as 'abnormal motor event' in a cage; the experimenter could then review the footage before, during and after the event, decide whether indeed it was a convulsion, and identify the individual animal involved. If using a non-video approach (e.g., injectable accelerometer), the detection method would have to be rigorously validated, as there would be no video footage to fall back on.

Convulsions sometimes occur in toxicology studies, as higher dose levels are explored in these studies. They generally occur within a couple of hours of dosing, but can happen at any time of the day or night. As they are brief in duration, even if they occur during working hours, they may be missed. We currently have no method of monitoring for convulsions in rodents over 24 h periods, other than by surgically implanting EEG electrodes.

Q. What would be the priorities after temperature and activity?
A. Detecting convulsions, and measuring food and water consumption.

Q. What does pattern of activity mean in practice?
A. We need a rough idea of what the animals are doing, and where they are in the cage, but masses of detail on parameters on motor paths (e.g., angle of directional changes) are of limited value for our primary applications.

Q. How is this monitored at the minute?
A. It is carried out very infrequently and when it is we would use video tracking. We have to watch the video back and it can be difficult to distinguish between individuals during the dark phase using infrared.

Q. What behaviours are you trying to distinguish?
A. Ideally, ambulatory activity, rearing, eating, drinking, grooming, scratching, inactivity, and convulsions. As a minimum, ambulatory activity. The next level up would include detection of convulsions, eating and drinking.

Data Collection:

Q. Is continuous data needed? Do you need to monitor in real time or batch mode?
A. Sampling, for example, every 5 minutes would be sufficient for temperature; locomotor activity could be captured, for example, as 'zone crossings'. Convulsions may last less than 30 seconds or so, therefore this monitoring would have to be continuous.

Q. Would real time alerts be advantageous?
A. They would be useful during work hours but not essential as it is unlikely that most alerts would be acted on in the middle of the night.

Q. Is remote access to data needed?
A. Not necessarily: 'nice-to-have', but not essential.

Q. How often do you need to analyse? Daily, weekly, monthly?
A. In terms of analysis (as opposed to acquisition), a daily 'read-out' would be ideal.

Q. Does the data need to be timestamped with other data? For example, do you need to mark when an intervention happened etc?
A. Yes – this is essential (e.g., presence of technical staff in the room; cage lid off; rat removed from cage; light sensor indicating lighting levels transitioning between light and dark cycles; etc.). Events such as time of dosing are recorded elsewhere.

More detail on what is needed:

Q. It was noted that implantable chips which measure temperature, heartbeat and movement exist for one mouse per cage. Is it worth someone thinking of something novel, or better for expert manufacturers to change what already exists? What would score more highly on an application?
A. Both types of applications will be welcomed and the idea of the TSB SBRI scheme is to stimulate innovation. However, this is not a basic research scheme so there needs to be a product and clear process for validation in the application. There are some existing products that are 'part-way there', and we would encourage the manufacturer to try to bridge these to fulfil the challenge, whether alone or in collaboration with others.

Cost:

Q. What price would make a novel approach too expensive for a company to invest in?
A. This would be difficult to put a number on because if the solution could measure a lot of different things, the company would pay more than if looking at temperature and activity only. Some of the considerations for financial implications are whether chips can be reused or not. Additionally, more widespread use may bring the cost down.

One approach could be to price this as a modular system. For example, the 'entry-level' system could comprise measurements of individual locomotor activity and temperature. Subsequent levels could incorporate measurements of individual food and water consumption. The top specification might include automatic detection of convulsions, and even specific behaviours such as rearing and grooming.

Other:

Q. This is a brief for one company, any business would want to see more success than that. Is there a possibility to broaden the brief?
A. There is also responsibility on the applicant to make their solution as wide reaching as possible so it has the broadest business impact.

Q. How far does the winning bid need to be along development?
A. In the application there needs to be clear ideas at each stage with defined deliverables. The applicant must also clarify what is needed from the industrial sponsor and at what stage in the project. The Review and Challenge Panel will look at criteria such as novelty, cost, likelihood of success, robustness of the solution, and user-friendliness of the software.

Q. Would the applicant be working with only one cage manufacturer that AZ uses?
A. In the first instance, yes. However, a bid that was more widely applicable would be more competitive.

The specifications for the cages we currently use are:

Rat: Techniplast 2000P cages, with a flat lid: L610 mm; W435 mm; H 215 mm
Mouse: For group-housing we use Techniplast 1284 cages: L365 mm; W207 mm; H140 mm
Some mouse strains require single-housing of males (due to inter-male aggression); for this we use Techniplast 1144B cages: L332 mm; W150 mm; H 130 mm.

Validation:

Q. How will the device be tested/validated?
A. AstraZeneca's in kind-contribution will be to test the winning ideas in their laboratories. The applicant must describe the process that they think will be needed to assess, optimise and validate their device.