The Impact of the Functional Observational Battery and Irwin Tests in CNS Safety Pharmacology: Results of an Industry Survey

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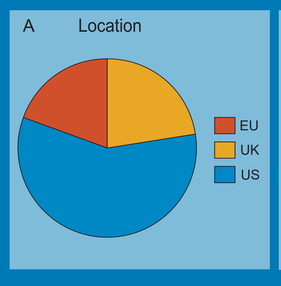
*This poster was the product of a working group convened by the NC3Rs to examine the use of the neurofunctional assessment. The working group consists of representatives from 11 pharmaceutical companies, 5 contract research organisations and 3 regulatory bodies. We thank them for time spent analysing and discussing the data.

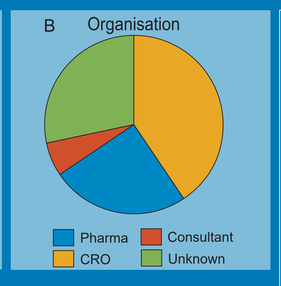
National Centre for the Replacement Refinement & Reduction of Animals in Research

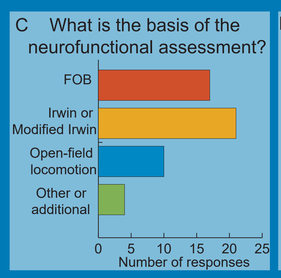
Introduction

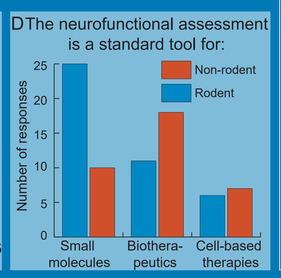
- The functional observational battery (FOB) and Irwin test battery (together called the 'neurofunctional assessment') are required during early drug development to assess the safety of a test substance on the central nervous system (CNS), as defined in ICH S7A regulatory guidance.
- CNS effects and adverse events account for a significant proportion of drug attrition during Phase I, II and III clinical trials and post-approval, and may have labelling implications[1]. This has been attributed to a lack of translational validity from animal models to humans, CNS side effects not being captured by the neurofunctional assessment, patient and disease context and differences in duration of treatment/dose regimen in animals and patients.
- In this study, an international working group formulated and distributed a detailed survey to gather information on how the neurofunctional assessment is used within organisations, how the data inform decision making, and opinions on the impact of individual measures.

Survey Respondent Demographics







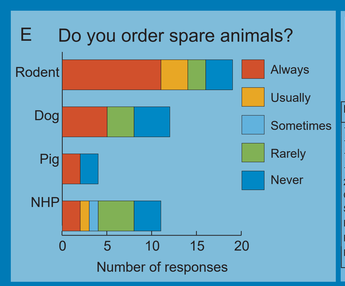


A. In which country do you work?
B. What kind of organisation do you work for?
C. What is the basis of the neurofunctional assessment used at your organisation?
D. Is the neurofunctional assessment used as a standard tool to assess safety in small molecules, biotherapeutics and cell-based therapies?

- Responses were received from 32 individuals working at more than 11 separate organisations
- These data represent the viewpoints of the individual respondent, and not necessarily the organisation which employs them.

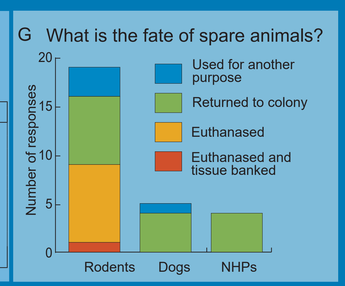
Spare Animals in the Neurofunctional Assessment

E. Do you order spare animals in case replacements are needed on the study?
F How often they are used? (Individual free-text responses.)
G. If yes, please describe the fate of the animals.

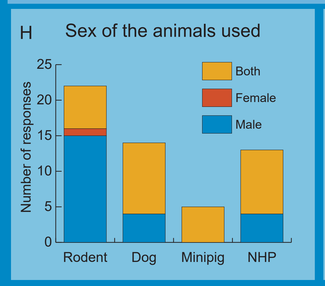


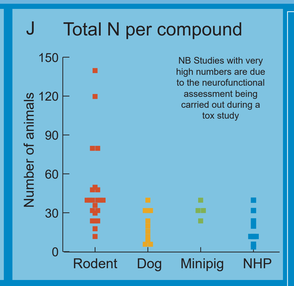
F How often are spare animals used on a study?

Rodents	Dogs	NHPs
10%	5%	25%
10%	25%	
10%	Rarely	
10%		
25%		
Occasionally		
Sometimes		
Rarely used		
Rarely used		
Rarely used		

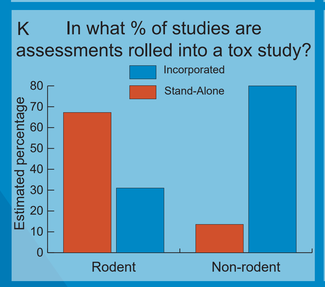


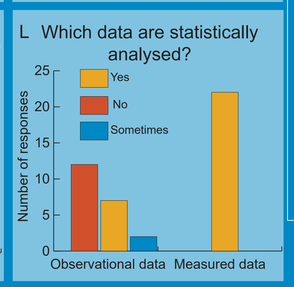
Experimental Design in the Neurofunctional Assessment



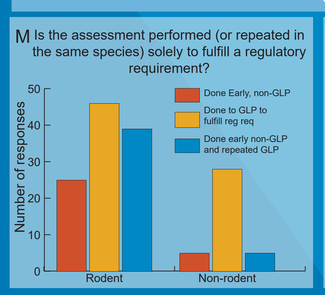


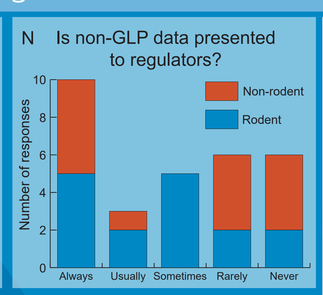
H. Which sex of animal are routinely used in studies?
J. How many animals are used for each compound tested in the neurofunctional assessment?
K. Are observational or measured data subjected to statistical analysis?
L. In what percentage of studies is the neurofunctional assessment incorporated into a toxicology study?



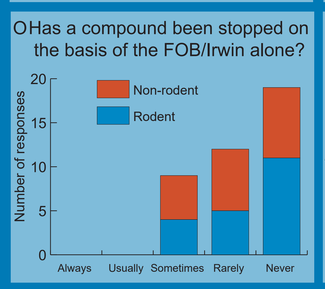


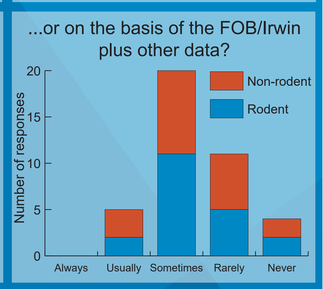
The Impact of the Neurofunctional Assessment on Decision-Making

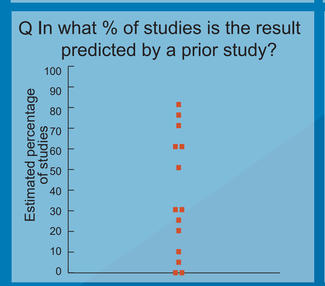


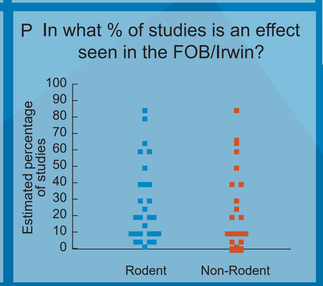


M. Is the assessment repeated in the same species to fulfill regulatory requirements?
N. Is non-GLP data presented to regulators?
O. How often does the assessment contribute to a decision to stop a compound?
P. In what percentage of studies has an effect been seen in the last 5 years?
Q. What percentage of assessments are predicted by a prior study?









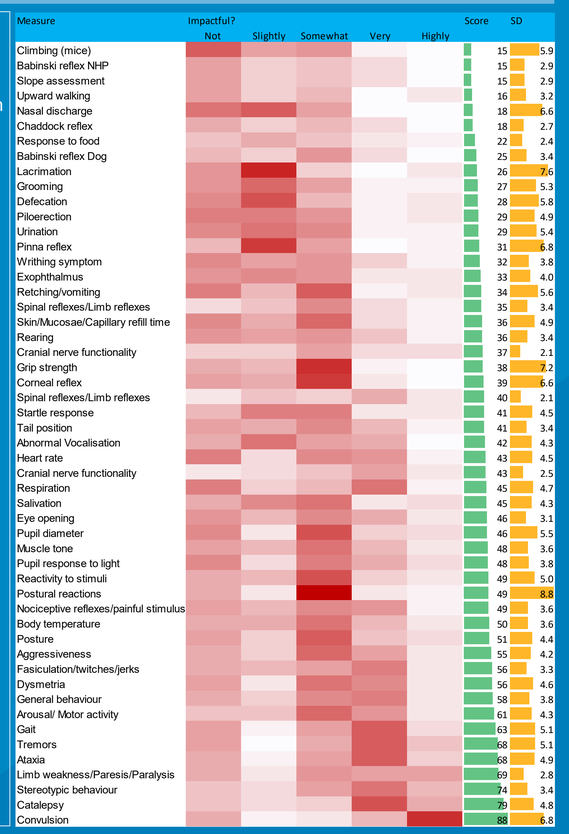
Analysis and Ranking of Individual Measures in the Neurofunctional Battery

Individual measures heatmap:

- A composite list of measures used in the neurofunctional assessment was created from published information[2-4].
- Respondents were asked to indicate how 'Impactful' each measure is on decision-making during drug development. Terms were defined as:
- **'Impactful':** the impact of the measures alone or in combination on decision making in drug development or candidate selection when using data from the neurofunctional assessment.
- **'Effect':** a compound-related effect which is of note in the neurofunctional battery.
- The number of people responding to each category was then weighted:

Category	
Not Impactful	-1
Slightly impactful	1
Somewhat impactful	2
Very impactful	3
Highly impactful	4

- The 'Score' and Standard Deviation (SD) were calculated for each measure



The heatmap illustrates that different measures are relied upon variably in the neurofunctional assessment, and paves the way for a discussion about automation of the critical measures.

Key Messages and Next Steps

- These results provide information on how the neurofunctional assessments are being used in drug discovery and early drug development, and present opinion from a cross-section of the community on how impactful individual measures are on the decision making process.
- There is wide variability in the conduct of neurofunctional assessments across the industry and the impact of individual measures within these tests. It should be noted that, although defined in the survey, the term 'Impactful' may have different interpretations.
- The neurofunctional assessment was designed to detect overt safety signs, but it's efficacy at detecting less severe adverse or non-adverse effects has not been characterised.
- Some 3Rs opportunities have been highlighted through this data, including variable and large group sizes, the use of spare animals and repeating studies for regulatory submission.
- These results will be further discussed in a Sponsored session on 3 November at the SPS Annual Meeting 2018

References

1 - Waring MJ 2015 An analysis of the attrition of drug candidates from four major pharmaceutical companies. Nat Rev Drug Discov.14(7):475-86.
2 - Gauvin DV 2008 A functional observational battery in non-human primates for regulatory-required neurobehavioral assessments. JPTM 58(2):88-93.
3 - Gad SC A 2003 functional observational battery for use in canine toxicity studies: development and validation. Int J Toxicol. 22(6):415-22.
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