Institution: University of Glasgow
Unit of Assessment: 10 – Mathematical Sciences
Title of case study: Quantifying animal pain

1. Summary of the impact

Statistical research has played a leading role in the creation of two pain measurement tools for dogs and a welfare tool for farm animals. The Glasgow Composite Measure Pain Scale (CMPS) was the first validated, multidimensional tool for assessing acute pain in domestic animals in surgical and clinical settings, leading to improved treatment. The tool is based on a statistical model and is unique in providing an intervention threshold for pain relief. Since its launch in 2008, it has been downloaded by over 3,000 users from both veterinary practice and industry and it has been used by several companies for regulatory approval of novel analgesics. A second pain measurement tool (GUVQuest) was developed for chronic pain in dogs, enabling its impact on quality of life to be assessed. This tool is suitable for animal owners and is being exploited commercially in web-based form. A welfare tool for pigs has also been developed using the same statistical principles and work is underway on the development of similar tools for cows and cats.

2. Underpinning research

Measurement is fundamental to the application of scientific methods in almost any context and statistical methodology provides a principled basis for dealing with the variation, analysis and interpretation of measurement data. However, in some settings observed data are only indirectly related to the underlying attributes of interest and so the construction of meaningful measurements of the underlying process is the fundamental problem. An important example is the phenomenon of pain - an experience with a strong subjective component which makes quantitative measurement problematic. In human medicine, this has been tackled through structured self-reporting questionnaires, which have provided valid, reliable and responsive tools for the measurement of pain and quality of life, developed using psychometric methods and with a central role played by statistical models. By contrast, in animal care where direct communication is impossible, the absence of a valid, reliable means of quantifying pain presents a major challenge. Traditional approaches based on observer ratings on a one-dimensional scale such as the Numerical Rating Scale have been shown to be unreliable for animals. Without a means of measuring pain, it is difficult to assess the effects of analgesic strategies and therapeutic agents, and so animal welfare is hard to guarantee. The process of developing suitable measurement scales is therefore fundamental to progress.

Collaborative research began in the University of Glasgow in 1997 to develop, for the first time, a validated pain scale for the measurement of acute pain in dogs, using sound statistical principles. The project was led by Prof. Marian Scott of the School of Mathematics & Statistics and by Profs. Andrea Nolan and Jackie Reid, then of the School of Veterinary Medicine. The research was interdisciplinary from the beginning, requiring levels of communication and co-operation between the partners which were sufficiently deep to allow the nature of the veterinary issues to be understood clearly and to allow the imaginative and innovative application of statistical methods in reaching an effective solution. The key role of Prof. Scott in this interdisciplinary collaboration is reflected in her role as a principal author of all the scientific papers and a major grantholder.

The starting point for the new research was the development of a novel veterinary language of pain, beginning with the generation of a large set of descriptors based on simple words or phrases used by human observers of animal behaviour. These were grouped into seven behavioural categories (vocalisation, attention to painful area, mobility, response to touch, demeanour, posture, activity) by an innovative combination of cluster analysis and Cronbach's alpha as a measure of within-category consistency [1]. In order to generate data on an interval level measurement scale, a sophisticated and powerful framework based on latent class analysis was developed in a University of Glasgow Statistics PhD thesis [2]. In combination with clinical and practical considerations, this led to the selection of a particular form of Thurstone-Rasch pairwise-

comparison model [3]. The resulting measurement scale was then validated in different medical and surgical conditions, using statistical methods for optimal design and analysis [3]. These studies demonstrated that the scores produced by the tool corresponded appropriately to independent clinical assessment and quantified the level of inter-observer variation. Multi-centre trials [5] were subsequently designed to identify a suitable intervention level at which pain relief should be administered, using discriminant analysis.

This was the first time that such models had been applied in, and adapted to, veterinary pain assessment and the resulting tool became known as the Glasgow Composite Measure Pain Scale (CMPS). A short form (CMPS-SF) was subsequently developed for widespread clinical use [5]. After addressing these issues in acute pain, attention moved to the assessment of chronic pain in dogs and its impact on quality of life, including both intensity and affect. This led to one of the first validated quality-of-life tools in veterinary science (GUVQuest), supported by funding from Pfizer Animal Health (£166k, 2000) and the BVA Animal Welfare Trust (£195k, 2004). The development of GUVQuest was based on adaptation of the statistical methods used in the earlier CMPS tool. This involved the design of interviews, focus groups, and online surveys whose subsequent analysis allowed a language of chronic pain to be identified, using over 100 descriptors. A study to provide data for a scoring model was then designed and executed. Statistical modelling based on factor analysis allowed a small number of factors to be identified, producing an informative multivariate profile for each animal [4]. Subsequent research has allowed a short form of the GUVQuest to be developed, based on modelling the contribution of each item to the overall score and characterising the performance of each item as evaluative or discriminatory.

3. References to the research

1. Holton, L., Reid, J., Scott, E.M., Pawson, P., and Nolan, A.M. (2001) Development of a behaviour-based scale to measure acute pain in dogs. *Veterinary Record*, 148 (17). pp. 525-531. ISSN 0042-4900 (doi:10.1136/vr.148.17.525)
2. Burnell, M. (2004). *The scaling of acute pain in dogs.* University of Glasgow PhD thesis in Statistics. [available from HEI]
3. Morton, C.M., Reid, J., Scott, E.M., Holton, L.L., and Nolan, A.M. (2005) Application of a scaling model to establish and validate an interval level pain scale for assessment of acute pain in dogs. American Journal of Veterinary Research, 66(12). pp. 2154-2166. (doi:10.2460/ajvr.2005.66.2154) *
4. Wiseman-Orr M.L., Scott E.M., Reid J. and Nolan A.M. (2006) Validation of a structured questionnaire as an instrument to measure chronic pain in dogs on the basis of effects on health-related quality of life. *American Journal of Veterinary Research* 67(11): 1826-1836. (doi:10.2460/ajvr.67.11.1826) *
5. Reid, J., Nolan, A.M., Hughes, J.M.L., Lascelles, D., Pawson, P., and Scott, E.M. (2007) Development of the short-form Glasgow Composite Measure Pain Scale (CMPS-SF) and derivation of an analgesic intervention score. *Animal Welfare*, 16. pp. 97-104. ISSN 0962-7286. [available from HEI] *

* best indicators of research quality

Key Grants

- 2000: J. Reid, A. Nolan, E.M. Scott. £166k, Pfizer Animal Health. Pain scales for dogs.
- 2001: J. Fitzpatrick, E.M. Scott, A.Nolan, C. Nicol. £258k, BBSRC, A welfare index for dairy cows.
- 2004: A. Nolan, J. Fitzpatrick, E.M. Scott, J. Reid: £195k, BVA Animal Welfare Trust. Lectureship.
- 2006: S. Fleetwood Walker, A. Nolan, J. Russell, A. Lawrence. [Scott, Glasgow CI]. £2.5m, BBSRC; Perinatal programming of stress responses, nociceptive mechanisms and the welfare consequences in pigs. With University of Edinburgh and Scottish Agricultural Colleges.
- 2011: A. Nolan, E.M. Scott. £59k, Pfizer Animal Health, an acute pain scale for cats.

4. Details of the impact

- **Reach:** Benefits veterinarians, dog owners and companion dogs in the UK and Europe; animal drug development industry R&D.
- **Significance:** Offers the first set of validated tools for vets and dog owners to assess acute and chronic pain, allowing more timely, appropriate and compassionate treatment.

Pain assessment in animals presents a challenge for clinicians because of the inherent communication difficulties but also because different animals and species respond differently to pain. The CMPS was the first statistically constructed and validated acute pain scale for dogs in surgical and clinical settings, incorporating a structured and objective approach to pain assessment. It has been used in clinical trials, was subsequently streamlined into the CMPS Short Form (CMPS-SF), and includes an intervention level for the administration of analgesic relief. The CMPS was first circulated through a comprehensive programme of CPD conducted by Reid and Nolan, but was later made available as an online tool. The CMPS acute pain scale is available for open-access download from the University of Glasgow website [a]. Since 2008, the CMPS has been downloaded by 3266 non-academic users worldwide. Once downloaded the CMPS can be copied (thus download data are likely to underestimate usage by this route). It has been translated into Italian (2010) for use in clinical trials, as validated pain measurement methods are required for the development and licensing of new animal analgesic drugs.

The unique means by which the CMPS can define an intervention threshold for administering pain relief has resulted in its inclusion in a number of textbooks, establishing it as a standard reference for measuring pain for both teaching and veterinary practice. It has also featured in key pain management handbooks for practitioners such as the *Handbook of Veterinary Pain Management* (2008) and *Anaesthesia for Veterinary Technicians* (2010) [b]. In 2009, the Glasgow Pain and Welfare Research Group (Scott, Nolan and Reid) won the Universities Federation for Animal Welfare inaugural Companion Animal Welfare Award [c], which recognises 'significant innovations or advances for the welfare of companion animals'.

The CMPS acute pain scale has been used by many of the market-leading veterinary healthcare companies in clinical trials and regulatory application for novel analgesics. This included Merial, Novartis Animal Health Inc., Vetoquinol, Dechra and Animalcare. The following applications have gained regulatory approval based on data obtained with the CMPS:

- 2008, Merial Ltd.– approval from the US Food and Drug Administration (FDA) for 'previcox' in dogs following orthopaedic surgery.
- 2011 – approval from the European Medicines Agency for 'Recuvyra' in dogs following orthopaedic surgery.
- 2011 Novartis Animal Health US Inc. – approval from the FDA for 'DERAMAXX' in dogs following dental surgery.
- 2012, Nexcyon Pharmaceuticals Inc. – approval from the FDA for 'Recuvyra' in dogs following general surgery.

Details are provided in [d].

Vetoquinol is the 10th largest veterinary pharmaceutical company in the world. Since mid-2012, its UK subsidiary has been using the CMPS acute pain scale as marketing support for their range of pain medications, including *Cimalgex*®. Vetoquinol specifically chose the CMPS acute pain scale because:

> *it is scientifically validated and well known in the UK whilst being simple to use….it was recommended to us by various veterinary surgeons throughout the UK.*

The Vetoquinol CMPS acute pain scale marketing support materials were a major focus of their *Cimalgex*® promotional activities at the London Vet Show (November 2012) and British Small Animal Veterinary Association Congress exhibition (April 2013).

The success of CMPS is reflected in its use as a standard tool in wider developments. CMPS itself is now being used in a wider range of disease conditions, including obesity [A] and cancer (publication in preparation). It has now also led to the creation of similar practical tools for welfare

assessment in farm animals (cows and pigs), for use by owners or stockmen [B]. New research, funded by Pfizer, has also created an acute pain instrument for cats which, for the first time in this species, includes facial shape and expression, based on an in-depth landmark study of cats' faces.

The GUVQuest tool for the assessment of chronic pain in dogs can be used by non-clinicians such as animal owners and is informing decisions on euthanasia, treatment or cancer therapy. It has been exploited commercially by Newmetrica Ltd, through a University of Glasgow Easy Access IP agreement, for provision as an online tool which provides users with automated output. This online version of the tool has been licensed to a number of individuals and companies for use in obesity, cancer and arthritis clinical trials.

5. Sources to corroborate the impact

A. German AJ, Holden SL, Wiseman-Orr ML, Reid J, Nolan AM, Biourge V, Morris PJ, Scott EM (2012) Quality of Life is Reduced in Obese Dogs, but Improves After Successful Weight Loss. *The Veterinary Journal* 192 (3). pp. 428-434. ISSN 1090-0233 (doi:10.1016/j.tvjl.2011.09.015) Corroborates use of CMPS as standard tool in wider developments (disease conditions).

B. Wiseman-Orr, M.L., Scott, E.M., and Nolan, A.M. (2011). Development and testing of a novel instrument to measure health-related quality of life (HRQL) of farmed pigs and promote welfare enhancement (parts 1 and 2). *Animal Welfare*, 20. pp. 535-558. ISSN 0962-7286 [available from HEI] Corroborates use of CMPS as standard tool in wider developments (other animals).

a. University of Glasgow website to download CMPS [link]

b. Textbooks reproducing CMPS:
- Wiseman-Orr ML, Reid JA, Nolan AM and Scott EM (2008) Quality of life issues. In *Handbook of Veterinary Pain Management, 2nd Edition*. Eds James S. Gaynor and William W. Muir, III. St Louis: Mosby Elsevier. ISBN 978-0-323-04679-4 and
- Bryant S (2010) Pain Assessment. In *Anesthesia for Veterinary Technicians*, Wiley-Blackwell. ISBN 978-0-8138-0586-3

c. Animal Welfare Award: [link]

d. Regulatory approval:
- Merial Ltd., FDA approval for 'previcox' [PDF link, or available from HEI]
- EMA approval for 'Recuvyra' [PDF link, or available from HEI]
- Novartis Animal Health US Inc., FDA approval for 'DERAMAXX' [PDF link, or available from HEI]
- Nexcyon Pharmaceuticals Inc., FDA approval for 'Recuvyra' [PDF link, or available from HEI]

e. Information from Vetoquinol is available on request