Institution: University of Glasgow (UofG)		
Unit of Assessment: UoA 10 Mathematical Sciences		
Title of case study: Veterinary tools to assess pain and quality of life in dogs and cats		
Period when the underpinning research was undertaken: 2000−2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Prof. Marian Scott	Professor of Environmental Statistics	1983−present
Prof Jacky Reid	Professor of Anaesthesiology	1983−2011
Prof. Andrea Nolan	Professor of Veterinary Pharmacology	1998−2013
Period when the claimed impact occurred: 2014–2020		
Is this case study continued from a case study submitted in 2014? Y		

1. Summary of the impact

Assessment of animal pain and quality of life is critical to veterinary practice. UofG statistical research underpinned the development of robust, psychometrically valid tools to measure acute pain, chronic pain and health-related impacts on quality of life in dogs and cats. The SME Newmetrica Ltd. was formed in Nov 2013 to commercialise these UofG tools, changing veterinary practice in both assessment of pain and quality of life, and support for decision-making by owners and veterinarians. Animal healthcare companies also use the tools to support regulatory approvals for new products and markets. The Glasgow Composite Measure Pain Scale (CMPS) is considered the gold standard for assessing acute pain in dogs in clinical settings as recommended in World Small Animal Veterinary Association (WSAVA) pain guidelines.

2. Underpinning research

The assessment of pain and quality of life for companion animals is strongly subjective and the need for psychometrically valid statistically designed tools has been long recognised. These tools are essential in facilitating assessment of analgesic strategies and therapeutic agents to improve animal welfare. Statistical models and experimental design principles were developed by Prof. Marian Scott (Mathematics and Statistics) in collaboration with Prof. Jacky Reid, Prof. Andrea Nolan and Lesley Wiseman Orr (Veterinary Science) and have underpinned 2 clinical tools to assess acute pain and 2 owner-centred tools to assess chronic pain and health-related impacts on quality of life in dogs and cats.

Acute pain tools for dogs and cats

UofG statistical research led the development of structured questionnaires, designed and implemented surveys, and formulated psychometrically valid scoring models (using item response theory, principal components and factor analysis). Together, these underpin the creation of the tools. Statistical research has been instrumental in demonstrating the tools' validity and reliability, essential properties for any tool used in clinical practice and in joint decision making between owners and veterinarians. The original Glasgow Composite Measure Pain Scale (CMPS; 2001) measured acute pain in dogs using psychometric methodology to a level of precision suitable for clinical trials. Statistical measurement theory was used to analyse the six behavioural categories associated with vocalisation, attention to wound, mobility, response to touch, demeanour and posture/activity.

For routine clinical use, where the emphasis is on speed, ease of use, and guidance for analgesia provision, a short form (CMPS-SF) was developed (2007) [3.1]. Subsequently, the acute pain cat tool (CMPS-Feline) was developed in 2014, initially using the same statistical approach as for the CMPS (for dogs) but also incorporating analysis of facial expressions around the eyes, ears and mouth. UofG statistical research used spatial, shape and landmark analysis to identify anatomical landmarks that discriminate between pain-free cats and cats in pain to deliver the simplified facial elements of the tool [3.2-3.4]. UofG research, with a focus on the communication and interpretability of the tool outputs, led in 2017 to the development and quantification of intervention using discriminant analysis techniques, to inform clinical decision-making [3.4]. The resulting measurement scales (for both dogs and cats) have been validated in different medical and surgical conditions (surgery, cancer, osteoarthritis, obesity), using statistical methods for optimal design

and analysis and are now being used to validate the analgesic efficacy of pharmaceutical products in clinical trials.

Chronic pain and health related quality of life (HRQL) tools for dogs and cats
The original Health Related Quality of Life (HRQL) tool for dogs was a paper-based assessment with 109 different questions and was too long for owners to easily and routinely use. In 2013 UofG statistical research led to the shortening of the tool to first 46 and then 22 items, and demonstrated the validity of a refined shortened assessment, VetMetrica Canine [3.5], which is superior to the original instrument in its ability to distinguish between healthy and unwell animals. The shortened tool was then validated in different medical and surgical conditions (cancer, osteoarthritis, obesity), using statistical methods for optimal design and analysis (including time trend analysis and mixed effect analysis of variance). Both canine and feline tools can be accessed via a mobile phone app for UK/Europe-based veterinary surgeons and pet owners. Subsequent statistical work in 2019 focussed on the creation of population norms for the HRQL dog and cat tools, and in providing alerts for vets and pet owners [3.6]. The feline generic quality-of-life tool was developed in 2018 (HRQL-Feline/VetMetrica Feline), co-funded by Newmetrica and a SMART grant from Scottish Enterprise. Subsequently, disease-specific HRQL tools have been developed as bolt-on modules for clinical assessment (the first disease being osteoarthritis) [3.7].

3. References to the research

3.1 Reid, J., et al., Development of the short-form Glasgow Composite Measure Pain Scale (CMPS-SF) and derivation of an analgesic intervention score. Vol. 1. Animal Welfare, 2007. 16, pp97−104 [PDF link].
3.2 Holden, E., et al., Evaluation of facial expression in acute pain in cats. Journal of Small Animal Practice, 2014. 55(12): pp. 615−621. doi:10.1111/jsap.12283
3.3 * Calvo, G., et al., Development of a behaviour-based measurement tool with defined intervention level for assessing acute pain in cats. Journal of Small Animal Practice, 2014. 55(12): pp. 622−9. doi:10.1111/jsap.12280
3.4 Reid, J., et al., Definitive Glasgow acute pain scale for cats: validation and intervention level. Veterinary Record, 2017. doi:10.1136/vr.104208
3.5 Reid, J., et al., Development, validation and reliability of a web-based questionnaire to measure health-related quality of life in dogs. Journal of Small Animal Practice, 2013. 54(5): pp. 227−33. doi:10.1111/jsap.12059
3.6 * Davies, V. , Reid, J., Wiseman-Orr, M. L. and Scott, E. M. (2019) Optimising outputs from a validated online instrument to measure health-related quality of life (HRQL) in dogs. PLoS ONE, 14(9),e0221869. doi:10.1371/journal.pone.0221869
3.7 Noble, C.E., et al., Development, initial validation and reliability testing of a web-based, generic feline health-related quality-of-life instrument. Journal of Feline Medicine and Surgery, 2018: p. 1098612x18758176. doi:10.1177/1098612x18758176

* = best indicators of research quality

4. Details of the impact

Pain is a vital sign and veterinarians widely recognise its central role in animal care and welfare. However, pain assessment in companion animals is challenging due to the inherent barriers to communication, and the species-specific response to and presentation of pain. The UK companion animal population included an estimated 10.9 million cats and 9.9 million dogs in 2019, many of which at some point in their lives may encounter pain through injury, chronic disease or surgery.

Commercialisation
In November 2013, Prof. Reid founded NewMetrica Ltd. (newmetrica.com) to promote the commercialisation and wider adoption of the UofG pain assessment tools within the veterinary community. UofG research knowledge was acquired by NewMetrica through Easy Access IP [5.1]. Further development of the tools and knowledge transfer has been facilitated through NewMetrica with applications in the UK and internationally. Prof. Scott has continued to work with the company

as a scientific advisor, developing the methodology for constructing pain and welfare scales based on the creation of single, composite indicators from distinct observable components. NewMetrica has grown to become a recognised leader in the field of pain and HRQL research [5.1] through commercialisation of the tools in two major markets: (A) NewMetrica's commercial licence arrangements with veterinary pharmaceutical companies have focused on service provision [5.2] to the veterinary community, capacity-building through continuous professional development (CPD) training, fundamental research and development in clinical trials and driving pharmaceutical sales; (B) NewMetrica issues online licences for non-commercial use of both their dog and cat acute pain tools [5.3], supporting clinical and academic research.

Change in professional practice within veterinary profession
International and national impact is evidenced in the change in professional practice as a result of first paper-based, then web-based and now app-based, pain and quality of life assessment tools. The acute tools are widely used in veterinary practices [5.2, 5.3] and veterinary hospitals around the world. The acute dog tool has been translated into Italian, German, Spanish, Norwegian, French and Swedish, addressing the absence of validated pain assessment tools in these languages. Each translation required cross-cultural validation (e.g. Italian in 2018 [5.4]) to define behavioural expressions. These are available via NewMetrica. The English-language version has been reproduced in the WSAVA Guidelines for the Recognition, Assessment and Treatment of Pain, published in May 2014 and endorsed by veterinary associations in 67 countries [5.5]. The full text of the WSAVA pain guidelines have been accessed 38,595 times (with 13,842 PDF downloads) since publication. Our paper [3.3], presenting the introduction of facial aspects to clinical pain assessment acute pain in cats, was recognised for its outstanding contributions in the field of small animal veterinary practice at the BSAVA awards in 2016; Prof. Reid and UofG were recognised for their "Outstanding Contribution to Animal Welfare" at the Ceva Animal Welfare Awards in 2019" [5.6].

The chronic pain/health related quality of life assessment tool for dogs, having undergone significant practical improvement from its original paper-based version, is now available as a web-based app [5.7] and on the Zoetis PetDialog platform [5.8b]. Additional statistical modelling has delivered an alert system to inform owners at stages when veterinary advice should be sought [3.6]. Additionally, a new online tool for cats has been developed, with a new design, in modular form, with a generic Quality of Life (QoL) module, and bolt-on additions for disease-specific characteristics [3.7].

Capacity-building: CPD delivered to drug companies and their partner veterinary practices has been a key impact pathway for the uptake of the tools into clinical practice. For the cat acute tool (CMPS-Feline), CPD meetings supported by Boehringer and in partnership with NewMetrica, have been conducted in 630 different practices and to 3,779 veterinary professionals (vets and vet nurses) in the period January to December 2016. The Glasgow Feline CMPS was very well received, with the majority of attendees adopting it for use in their practices [5.8a]. Boehringer Ingelheim offer an online version of this tool as part of its Metacam® (meloxicam) drug support (www.metacam-painscale.co.uk), and the accompanying five education webinars, which have been collectively viewed 2,800 times as part of their Boehringer Academy [5.8a]. Similarly, AnimalCare Ltd. offer their own branded versions of the Glasgow CMPS tools for cats and dogs within 'The PAC'—their 'Practice Assistance Centre' available to their network of veterinary practices. Other licensees of cat and dog tools include CEVA Animal Health (2016–2018) and Dechra (2017) [5.2]. Zoetis have also incorporated both HRQL tools in their online platform, PetDialog) [5.8bi] to allow owners to build a profile of their pet and to track their wellbeing.

UofG HRQL domains are included in a Zoetis Petcare Osteoarthritis checklist for owners [5.8bii] used in clinical veterinary practice. The development of the first psychometrically validated acute pain and chronic pain assessment tools for cats and dogs has stimulated and reframed the debate around how pain assessment should be conducted. The acute pain tools are widely used in clinical practice [5.2, 5.3, 5.4]. Online licenses issued between January 2016 and December 2020 for the CMPS-SF tool (dogs) number 2,455 in 76 countries, with the greatest volume in the UK, USA, Spain, Australia and Canada; 90% were specifically for vet practice usage. Over the same period,

licenses for the CMPS-Feline tool number 2,206 in 67 countries, primarily USA, UK, Spain and Canada; 93% were specifically for veterinary clinic use [5.2]. These numbers reflect changing practice in veterinary clinics, such as in the use of analgesics.

Vetmetrica is the brand name for NewMetrica's portfolio of structured questionnaire instruments to measure HRQL in animals. Since launch in January 2014, Vetmetrica.com has registered 169 veterinary practices and 2,179 owners (N.B. pharmaceutical companies also count as a single owner). The tools allow vets to involve owners with clinical follow-up, or to monitor an otherwise healthy pet and alert to a change in health status. To date, 12,194 owner assessments and 2,428 vet assessments have been completed [5.6], showing active engagement with the tool. The chronic pain tools have raised awareness in owners of subtle changes in pet behaviours, thus extending the reach beyond clinical practice to the wider community of pet owners, raising their awareness of pain and welfare issues. ***"[Vetmetrica's] real time monitoring allows for early identification of problems leading to quicker intervention and the results can be used to help guide owners' decisions and monitor responses to treatment."*** [5.9a]
The Zoetis Petcare Osteoarthritis Checklist now forms part of a North American Vet Tech course (NAVTA Course) [5.8biii, 5.9c]

Regulatory changes: FDA and medicines approval
Since its incorporation Newmetrica has worked closely with the US FDA Center for Veterinary Medicines (CVM) to ensure compliance with the US government's 21 CFR 11 standard for electronic data capture. This also ensures that the data resulting from the web-based apps and the subsequent statistical modelling meets the stringent quality assurance needed by the FDA CVM [5.10], opening the market for wider use in US clinical trials. These tools have provided the pharmaceutical industry with valid, reliable and responsive outcome measures to assess the efficacy of analgesic compounds in clinical trials. The tools have a role in supporting regulatory approval and are also used in the official documentation that accompanies veterinary products.

Recognising the benefits of HRQL assessment, a number of pharmaceutical companies have also used the UofG/NewMetrica-developed HRQL tools in clinical trials to bring new products to market.

Clinical trials
1. During 2017–18, Royal Canin (Gard, France) used VetMetrica-Canine in clinical trials of their SATIETY weight management product. Canine overweight and obesity affects nearly 60% of dogs in the UK, reducing quality of life. Use of the tool showed a significant improvement in HRQL as a result of weight loss in dogs on the diet product, which was launched in November 2019 [5.11a].
2. In 2016 and 2017 Elanco Animal Health Inc (Indiana, USA) used CMPS-SF to gain regulatory approval from the FDA for three different preparations of the non-steroidal anti-inflammatory robenacoxib for dogs (both oral and injectable) and cats (oral), demonstrating their effectiveness in the relief of postoperative pain [5.10b]. The same studies were also described in a post-authorisation approval (tablet and injection) from the European Medicines Agency (EMA) for a new indication of postoperative pain and inflammation in dogs (2019) [5.11b].
3. Aratana Therapeutics similarly used CMPS-SF to demonstrate product effectiveness to gain regulatory approval from the FDA for their novel local anaesthetic, bupivacaine liposome injectable suspension (NOCITA) for cranial cruciate ligament surgery. The slow-release formula addresses an unmet need for postoperative pain control post-surgery in the home environment. The Massachusetts Society for the Care & Protection of Animals stated, "*The introduction of NOCITA into the veterinary market has allowed us to greatly improve how we provide post-operative analgesia to our patients*". Between 2016–2018, Aratana earned USD10.8 million specifically for the NOCITA product with year-on-year growth. [5.11c]
4. Kindred Biosciences, Inc have used the HRQL-Feline tools to demonstrate improvement in QoL in anaemic cats treated with epoCat, (KIND-510a), a long-acting feline recombinant erythropoietin in a 6-week pilot field trial. Cats rapidly increased mean haematocrit and demonstrated statistically significant improvements across all three health-related QoL domains. These results are critical to ongoing clinical trial discussions with the FDA [5.11d].

Conceptual and cultural impact- assessment of pet health and wellbeing: The development of the validated HRQL assessment tools for cats and dogs have stimulated and reframed the debate around how pain assessment and its impact should be conducted. Since the HRQL tools are used by owners in their own home, this has raised awareness in owners of subtle changes in pet behaviour [5.8b, 5.11b] and when combined with the alerting system, these tools enable owners to seek veterinary support in a timely manner.

5. Sources to corroborate the impact

5.1. Letter from the CEO Newmetrica.

5.2. Details of online licences for non-commercial use of both their dog and cat acute pain tools are available (recording user location, practice and intended use)

5.3. Details of commercial licenses available on request, which will include information on licenses and outcomes of trials where tools have been used.

5.4. Italian version of Dog Acute Tool has been developed and published (The Italian Society of Veterinary Regional Anaesthesia and Pain Medicine, ISVRA) doi:10.12834/VetIt.699.3421.3.

5.5. a) WSAVA endorsement letter;
b) WSAVA Guidelines for Recognition, Assessment and Treatment of Pain (published on WSAVA website, and in Journal of Small Animal Practice, in May 2014). doi:10.1111/jsap.12200;
c) List of Countries endorsing WSAVA guidelines by Global Pain Council;
d) Guidelines of the American Animal Hospitals Association Pain Management Guidelines for Dogs and Cats (2015); e) Download metrics of the WSAVA pain guideline since its publication in May 2014 https://veterinaryrecord.bmj.com/content/172/5/114.3.altmetrics

5.6. a) Animal Welfare Lifetime achievement − CEVA 2019;
b) Simon Award (acute pain scales) − BSAVA 2016

5.7. Download metrics of the online alert tool

5.8. Capacity-building through industrial partners
a) Boehringer usage of tools: i) CPD training metrics; ii) App of Glasgow CMPS-Feline tool; iii) Promotional material for Glasgow CMPS-Feline tool Boehringer Ingelheim;
b) Zoetis Osteoarthritis Tool: i) PetDialogue app for HRQL; ii) Zoetis Dog osteoarthritis tool checklist; (iii) Press release on NAVTA course using Zoetis Tools.

5.9. Sample of articles aimed at veterinary practitioners to promote uptake or acute tools: including testimony from veterinary practitioners
a) Corletto, F. (2017) Using acute pain scales for cats. Veterinary Record 180, 444−446. Editorial by Federico Corletto (Head of Anaesthesia and Analgesia, Dick White Referrals, London; President, European College of Veterinary Anaesthesia and Analgesia) http://dx.doi.org/10.1136/vr.j2065
b) Reid, J., M. Scott, and A. Nolan, Pain assessment in companion animals: an update. In Practice, 2017. 39(10): p. 446−451. http://dx.doi.org/10.1136/inp.j4513
c) Course notes from Advanced Nursing and Critical Care (pdf available from HEI)
d) Testimony from Greenside Veterinary Practice.

5.10. FDA testimonial

5.11. Clinical trials and regulatory approval
a) Testimony from Royal Canine to assess health related quality of life in dogs on a weight loss program with a Royal Canin diet
b) Elanco Animal Health: i) tablet-form robenacoxib (Elanco study doi:10.1186/s12917-017-1100-x; FDA approval summary (NADA141−463), May 2016, see Section B – Substantial evidence, p.6); ii) injectable robenacoxib (Elanco study doi:10.1111/jvim.14698; FDA approval summary (NADA 141−443), November 2016, see Section B – Substantial evidence, p.7); iii) EMA assessment report.
c) Aratana Therapeutics: i) Aratana study doi: 10.1186/s12917-016-0798-1; published, Aug 2016—a subsequent unpublished pivotal trial, also using CMSP-SF, is described in the FDA approval; ii) FDA approval summary (NADA141-461), Aug 2016, see Section A, p.4 and Section B, p. 6; iii) MSPCA comment on Aratana's NOCITA.; iv) Practice User Testimony
d) Press release from Kindred Biosciences