

Outcome Measures for Companion Animal Clinical Trials - Choosing the Best of What's Available

Your choice of outcome measures determines the success of your trial and how much it will encroach on your budget. An ideal outcome measure is valid, reliable, responsive to clinical change and cost-effective. Osteoarthritis is a common target disease for the development of therapeutic interventions and is used here as an example.

According to orthopaedics specialists involved in the Canine Outcome Measures Program (COMP), it is vital to choose the instrument(s) that will best test the study hypothesis based on *function, pain and quality of life*, as well as *accessibility, ease of use, and cost effectiveness*. They recommend including at least one functional outcome and at least one validated observer-reported quality of life outcome instrument.¹

Currently there are various instruments available, and those described below are all easy to use and accessible, either in paper form or online. Their cost-effectiveness is related very much to the number of subjects required to produce a satisfactory outcome in terms of treatment effect. Whereas previously overall mean or median differences in scores between groups were used for this purpose, the current goal is to assess whether the treatment has a measurable effect for individual animals. The criteria for successful treatment of an individual animal are predefined, so that success or failure of the treatment in each animal can be determined. The number of treatment successes and failures in each group (generally treated vs placebo) can then be compared. This method has the advantage of reflecting how likely a treatment is to be effective in an individual animal, rather than in a group of animals and has been a requirement in regulatory (FDA) pivotal clinical studies evaluating NSAIDs for the treatment of pain in dogs.² Clearly the placebo effect (number of false positives occurring in the placebo group) is a very significant factor as the following hypothetical examples show (Minitab 17). For illustrative purposes we have chosen a 60% success rate for the treatment group.

Example	Treatment group % successes	Placebo group % successes	Number of dogs required to demonstrate a statistically significant difference between the groups	Power
1	60	20	23	80
2	60	30	42	80
3	60	40	97	80
4	60	50	388	80

The number of animals required to demonstrate a treatment effect has a significant bearing on the cost of a trial, and so choosing an outcome measure which is likely to have a low placebo effect can make a major difference to the overall cost.

Available Outcome Measures

Functional Outcome Measures

These fall into two categories – objective measures (peak

vertical force [PVF] via a force platform, activity collars) and subjective client-reported measures (clinical metrology instruments). The force platform provides reliable and objective data, but the need for specialised equipment, at a time when many clinical studies are conducted on client-owned dogs in veterinary practice, limits its practical usefulness. With the exception of the cat, where these have shown promise,³ activity collars have not gained popularity in clinical studies. This could be for a variety of reasons, including difficulty in establishing what is a clinically significant improvement and determination of success vs failure in individual cases; the need for regulatory compliance (21 CFR 11) and last, but not least, the cost of supplying monitors for all cases in a study.

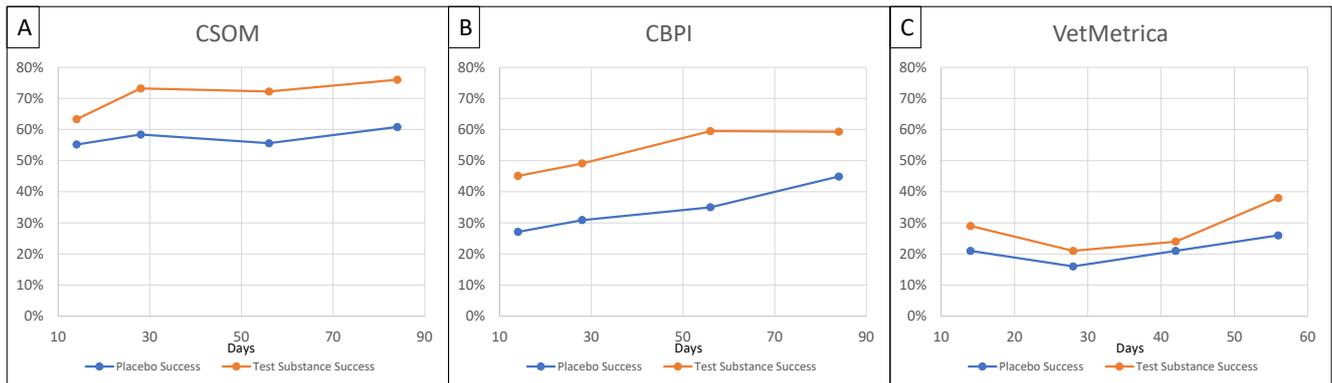
In contrast, owner-reported functional outcomes are widely used, despite their limitations which include a placebo effect (Figures 1A & B).

Between 2007 and 2009, three clinical metrology instruments were published for the dog, the Canine Brief Pain Inventory (CBPI) for osteoarthritis (OA)⁴ and osteosarcoma,⁵ the Helsinki Chronic Pain Index (HCPI) for OA⁶ and the Liverpool LOAD for elbow arthritis.⁷ More recently the Canine Orthopaedic Index (COI) was published.⁸ All have been validated to a greater or lesser extent, but a description of this is outwith the scope of this article and the reader is advised to consult the relevant literature before deciding which is more appropriate for a particular study. Use of these is limited to the investigation of OA, and osteosarcoma in the case of the CBPI, so they are very much disease-specific. Of these instruments, the CBPI is the most commonly used in regulatory trials. To the author's knowledge only one clinical metrology instrument exists for use in the cat, the Feline Musculoskeletal Pain Index (FMPI).⁹

Although it is not a clinical metrology instrument, the Client Specific Outcome Measure, derived from the Cincinnati Orthopedic Disability Index (CODI), first published in 2003, is a commonly used owner-reported functional outcome measure.¹⁰ This instrument asks the owner to score three specific functions of concern that they identify in their dog and, in doing so, 'tailors' the outcome to the individual. While this is an attractive concept, the instrument is not validated and results are subject to a significant placebo effect (Figure 1A).

Quality of Life (QoL) Outcomes

QoL is a general term used in a variety of disciplines in which it is accepted that QoL is, like pain, a multi-dimensional construct that is subjectively experienced by, and is uniquely personal to, the individual. Health-related quality of life (HRQL) is concerned with those aspects of QoL that change as a result of ill health and medical interventions and, because of its subjective nature, self-report is the gold standard for its



A & B show the success rates (%) of placebo and test groups in a trial investigating the efficacy of a monoclonal antibody in dogs with OA, using a client specific outcome measure (CSOM) and the Canine Brief Pain Inventory (CBPI)

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C shows the success rates (%) of placebo and test groups in a trial investigating the efficacy of a nutraceutical in dogs with a variety of chronic disease conditions, using VetMetrica.

measurement in human medicine. However our veterinary patients require a proxy who knows the animal best; its owner. It is clear then that measurement of HRQL is also an owner-reported outcome, but in accordance with the FDA Guidelines for Industry, asking an owner to rate their dog's HRQL on a 0 – 10 scale cannot be regarded as a valid measure, but a questionnaire instrument that draws such a conclusion from owner-reported observations of behaviour can be. This is borne out by the fact that in functional scales where developers have included global HRQL questions such as, 'Overall, how do you rate your dog's quality of life over the last 7 days?', for example the COI, the HRQL domain has proved non-responsive to clinical change.⁸

Currently the choice of HRQL instrument for OA studies is very limited. Other than VetMetrica (www.newmetrica.com) only two generic HRQL instruments to measure HRQL in dogs have been published,^{11,12} but these have been shown not to distinguish healthy from sick dogs,¹³ or their use is restricted to healthy dogs.¹²

VetMetrica is a generic, web-based HRQL questionnaire instrument which presents the owner with a series of questions regarding their dog's behaviour and uses these responses to generate a HRQL profile which encompasses four domains of QoL.¹⁴ Its focus is on using behavioural cues to measure how the dog 'feels' about its circumstances and in that regard it is unique. For diseases other than OA, disease-specific HRQL instruments have been described, but these tend to be based on limitations imposed by the disease rather than capturing the holistic experience of the animal by evaluating how it feels.

A refined version of the original 46-item VetMetrica questionnaire contains 22 items and the profile contains scores in *Energy, Happiness, Comfort and Calmness* (In Press). It will measure chronic pain through its impact on HRQL and

also the impact of any chronic disease that affects the QoL, so its applications are broad and not restricted to a single disease. To date, it has been shown to be responsive to clinical change in OA and lymphoma (unpublished) and obesity.¹⁵ Additional advantages in relation to its delivery via electronic data capture (EDC) include no missing data, minimal respondent bias, 21 CFR 11 compliance and the convenience of full integration with existing EDC systems. Early indications suggest that the placebo effect is significantly lower than that of other owner-reported instruments (Figure 1C).

Measuring Pain

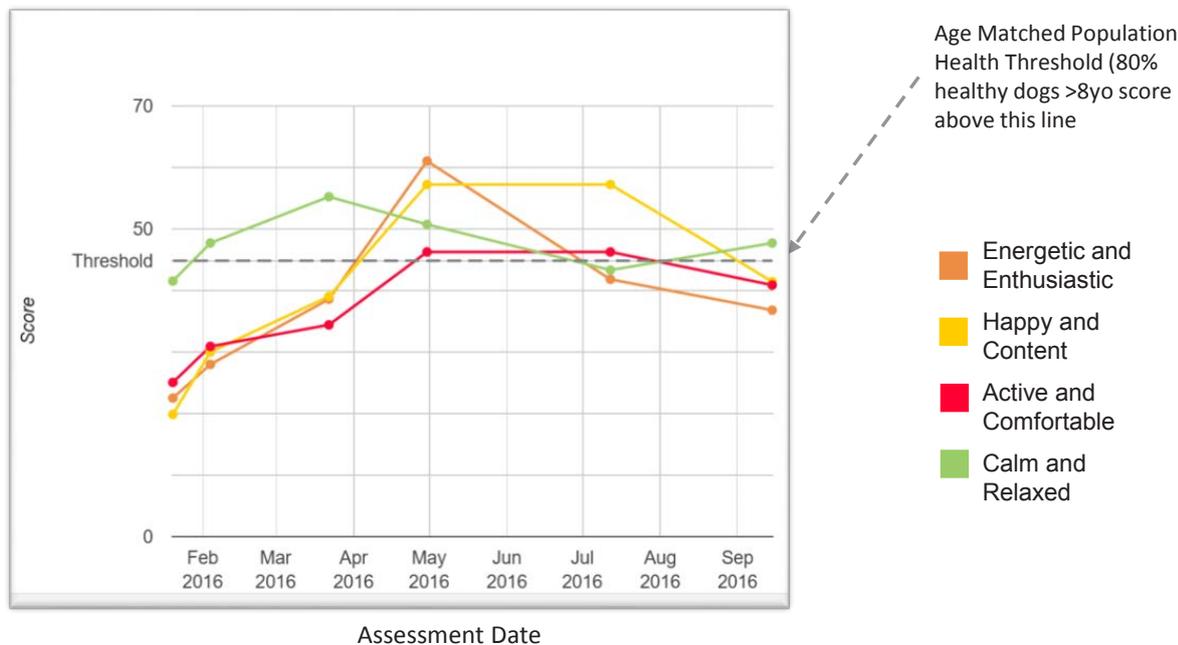
All of the instruments described will measure the chronic pain associated with OA with varying degrees of sensitivity, but while the functional measures (HCPI, CBPI, COI, LOAD, CSOM) do so by quantifying the physical limitation imposed by the disease, the HRQL measure (VetMetrica) focuses on measuring the impact of the pain on HRQL. Many of the instruments now used to measure human chronic pain are concerned primarily with measuring pain in this way because chronic pain interacts in a complex way with a patient's social, psychological and physical wellbeing. Work done in dogs has supported this approach in companion animals.^{16,17} Additionally VetMetrica measures HRQL (and the impact of chronic pain) on a continuum from worst to best, and so minimises floor and ceiling effects.

Scoring and Interpretation of Data

Appropriate interpretation of data is fundamental to the success of a trial. Outcome measures can be single-index scores which will only tell you the animal is better or worse, or they can be represented by a multi-dimensional profile which provides more information regarding the nature of change. Published information relating to the instruments described would suggest that the HCPI, LOAD and CSOM are associated with single-index scores, the CBPI has scores in two domains (pain severity and interference with function), the COI has

Case Example

Below is a case example of a dog with osteoarthritis, treated with NSAID alone. The first assessment is the baseline, before treatment. Treatment shows improvement in each of the four HRQL domains. The healthy dog average is at 50.



scores in four domains (stiffness, gait, function, QoL) with an aggregated total score and VetMetrica has scores in four domains (energy, happiness, comfort and calmness) which make up an HRQL profile. In addition to the numerical scores, VetMetrica has a graphical output (Figure 2) which relates the scores to the healthy dog population, which can be used for interpretation and case-screening purposes. In terms of interpretation of whether a case is deemed to be a success or failure, the CBPI, CSOM and VetMetrica all have an associated *a priori responder definition* which is determined empirically (CSOM) or by using statistical methods (CBPI18 and VetMetrica).

Conclusion

Owner-reported outcome measures are the mainstay of any trial designed to measure the efficacy of a therapeutic intervention, for whatever disease, painful or not. In general, these should include a measure of function and also HRQL. It is a foregone conclusion that they should have the key properties of validity, reliability and responsiveness, but judicious choice of what is available will ensure that your pocket is also well looked after!

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company set up to build on and continue research carried out by the University of Glasgow Pain and Welfare Group over two decades, to measure pain and health-related quality of life (HRQL) in non-verbal species. NewMetrica currently supplies scientifically robust questionnaire instruments to measure acute pain in dogs and cats and HRQL in dogs, the latter being web-based and suitable for EDC in clinical trials. A similarly web-based generic instrument to measure cat HRQL with a 'bolt-on' osteoarthritis disease-specific module is under construction and should be available early 2017. Please contact Jacky for further information by email Jacky.reid@newmetrica.com or phone +44 7876 683262