

<b>Institution: Royal Veterinary College (RVC)</b>		
<b>Unit of Assessment: A 6 Agriculture, Veterinary and Food Science</b>		
<b>Title of case study: Canine epilepsy: Improving the full spectrum of clinical outcomes and quality of life through medium chain triglyceride dietary supplementation</b>		
<b>Period when the underpinning research was undertaken: 2007 – 2020</b>		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Holger Volk	Lecturer in Neurology -> Professor of Neurology and Neurosurgery	03/09/2007 – 01/01/2019
Rowena Packer	Clinical Investigation Postdoctoral Researcher -> Independent Research Fellow -> Lecturer in Companion Animal Behaviour and Welfare Science	03/01/2014 – present
<b>Period when the claimed impact occurred: 01/08/13 – 31/07/20</b>		
<b>Is this case study continued from a case study submitted in 2014? N</b>		
<b>1. Summary of the impact</b> (indicative maximum 100 words)		
<p>Fewer than 1 in 6 epileptic dogs are seizure-free on standard medication. The RVC research team, focusing particularly on drug-resistant cases, has characterised co-morbidities and risk factors, together with relative risk for adverse drug effects and altered the profession's understanding of the epilepsy syndrome. Their work has demonstrated the value of dietary supplementation with medium-chain triglycerides (MCTs) as an adjunctive management option: enhancing seizure control, reducing drug side effects and behavioural abnormalities, and improving overall quality of life for pet and owner. An MCT-rich diet is now marketed by Purina for this application. Professional communications and novel owner-directed tools are driving the progression of more effective, holistic disease management.</p>		
<b>2. Underpinning research</b> (indicative maximum 500 words)		
<p>A research programme utilising the dedicated epilepsy clinic, established at RVC in 2004, was developed by Professor Holger Volk from 2007. With canine behaviourist and animal welfare scientist, Dr Rowena Packer, the risk factors for drug-resistant epilepsy were documented as being male and having previously experienced cluster seizures [1]. More in-depth study of drug-resistant canine epileptics showed that these dogs have a broader spectrum of brain dysfunction and demonstrate co-morbidities of anxiety [2], attention deficit/hyperactivity disorder [3] and cognitive dysfunction [4], sharing remarkable similarities with human epilepsy.</p> <p>The researchers, in collaboration with colleagues in practice and at Glasgow University, also demonstrated the relatively poor quality of life of canine epileptic patients and the negative effect recurrent seizures and the side effects of the standard antiseizure drugs (ASDs) had on the owners [5]. Based on these observed similarities and the promising effects of ketogenic diets in human patients with epilepsy, Volk proposed to Purina, the multinational pet nutrition company, trialling a diet high in MCTs, to assess possible reduction in seizure frequency. (Purina was already investigating ketogenic diets for age-related canine cognitive decline and Volk's then unpublished data demonstrated cognitive dysfunction was part of the epileptic syndrome.) A 6-month randomised controlled clinical trial involving drug resistant idiopathic canine epileptic dogs, comparing an MCT supplemented diet to a placebo diet in a cross-over design, demonstrated a positive effect of the test diet on seizure frequency and number of days per month when seizures occurred [6]. Of the 21 dogs, 15 (71%) had reduced numbers of seizures whilst on the diet and 14% achieved seizure freedom. Overall, dogs had 30% fewer seizures whilst eating the diet when compared to placebo (171 vs. 119 seizures). Considering these dogs</p>		

were already on drug treatment with their response to the pharmaceutical intervention not considered to be satisfactory, these results are remarkable and similar to drug trials in drug resistant canines. Furthermore, the behaviours associated with attention deficit/hyperactivity disorder displayed by epileptic dogs involved in this study (chasing and stranger directed fear) reduced when they were eating the MCT-enriched diet [3]. Volk and Packer went on to examine the effects of a dietary supplement of MCT added to the base diet of drug-resistant dogs in an independent multicentre study funded by the American Kennel Club. They corroborated the earlier diet trial results, showing similar reductions in seizure frequency together with reduction in drug-therapy related sedation and ataxia [7], and improvements in cognitive functioning [8] so contributing to improved quality of life of the dogs [7].

### 3. References to the research (indicative maximum of six references)

1. **Packer RM, Shihab NK**, Torres BB, **Volk HA**. (2014) Clinical risk factors associated with anti-epileptic drug responsiveness in canine epilepsy. *PLoS One*, 9(8), e106026. <https://doi.org/10.1371/journal.pone.0106026>
2. **Shihab N**, Bowen J, **Volk HA** (2011) Behavioral changes in dogs associated with the development of idiopathic epilepsy. *Epilepsy & Behavior* 21(2), 160–167. <https://doi.org/10.1016/j.yebeh.2011.03.018>
3. **Packer RM, Law TH, Davies E**, Zanghi B, Pan Y, **Volk HA**. (2016) Effects of a ketogenic diet on ADHD-like behavior in dogs with idiopathic epilepsy. *Epilepsy & Behavior* 55, 62–68. <https://doi.org/10.1016/j.yebeh.2015.11.014>
4. **Packer RMA**, McGreevy PD, Salvin HE, Valenzuela MJ, Chaplin CM, **Volk HA**. (2018) Cognitive dysfunction in naturally occurring canine idiopathic epilepsy. *PLoS One* 13(2), e0192182. <https://doi.org/10.1371/journal.pone.0192182>
5. Wessmann A, **Volk HA, Packer RM**, Ortega M, Anderson TJ. (2016) Quality-of-life aspects in idiopathic epilepsy in dogs. *Veterinary Record* 179(9), 229. <https://doi.org/10.1136/vr.103355>
6. **Law TH, Davies ES**, Pan Y, Zanghi B, Want E, **Volk HA**. (2015) A randomised trial of a medium-chain TAG diet as treatment for dogs with idiopathic epilepsy. *The British Journal of Nutrition* 114(9), 1438–1447. <https://doi.org/10.1017/S000711451500313X>
7. **Berk AB, Law TH, Packer RMA**, Wessmann A, Bathen-Nothen A, Jokinen TS, Knebel A, Tipold A, **Pelligand L, Meads Z, Volk HA** (2020) A multicenter randomised controlled trial of a medium chain triglycerides dietary supplement to improve management of canine epilepsy. *Journal of Veterinary Internal Medicine* 34(3), 1248–1259. <https://doi.org/10.1111/jvim.15756>
8. **Berk BA, Packer RMA, Law TH**, Wessmann A, Bathen- Nöthen A, Jokinen TS, Knebel A, Tipold A, **Pelligand L, Volk HA** (2020) Medium-chain triglycerides dietary supplement improves cognitive abilities in canine epilepsy. *Epilepsy & Behavior*. 107608. Advance online publication. <https://doi.org/10.1016/j.yebeh.2020.107608>

#### Other Quality Indicators

Funding received for this work has amounted to GBP912,743 between 2012 and 2020, including contributions from Biotechnology and Biological Sciences Research Council (BBSRC) Industrial Case Studentship Competition, the American Kennel Club, and a BBSRC responsive mode grant. Packer was awarded a BBSRC Future Leader Fellowship in 2017, her publication track-record associated with this body of work contributing to her success in this competitive scheme.

In 2016, Volk received both the International Prize in Canine Health for Outstanding Contribution in the Field of Canine Health and Welfare and the British Small Animal Veterinary Association's Bourgelat Award presented as primary recognition of outstanding international contributions to the field of small animal practice. Volk has also been invited to contribute a chapter 'Nutrition for Neurologic Disease and Cognitive Disorders' to the 9th edition of Ettinger's Textbook of Veterinary Internal Medicine, due for publication by Elsevier in 2021, internationally recognised as the authoritative text for the field.

Papers 3 and 5 are in the top 5% for their field based on the field weighted citation indices and paper 4 is in the top 10%.

**4. Details of the impact** (indicative maximum 750 words)

Epilepsy affects around one in 111 dogs. This equates to approximately 88,000 pet dogs in the UK and 693,000 in the US. More than 80% continue to experience seizures on standard medication, along with frequent adverse drug effects including sedation and ataxia. In addition, the associated behavioural abnormalities, identified by RVC as characteristic of idiopathic epilepsy, mean that management is particularly challenging. As epilepsy generally develops after a pet is acquired and a bond with the animal formed, owners frequently adapt their lifestyle to care for their animals, even to the extent of altering their employment to accommodate the dog's needs, which can severely affect their own quality of life.

Volk's role was critical in proposing to Nestlé Purina PetCare that a diet formulated with MCTs should be trialled in drug-resistant epileptic dogs and that this diet could also be useful in managing syndromes associated with idiopathic canine epilepsy that affect quality of life, such as attention deficit hyperactivity disorder (ADHD) and cognitive dysfunction syndrome [a]. Volk hypothesised MCT supplemented diets could be useful to reduce the frequency of seizures in dogs with idiopathic epilepsy that were refractory to drug therapy and, in collaboration with Purina, designed a randomized, placebo-controlled, double-blinded, crossover study trial to test this.

Purina funded the study to be conducted at the RVC, and the results led to the development and commercialisation of the patented NC NeuroCare™ diet – the first product of its kind shown to have significant positive benefit in treatment of idiopathic epilepsy as an adjunct to drug therapy and in the management of related syndromes (ADHD) [a]. Previous work at Purina had demonstrated a positive effect of a lower concentration of MCT supplementation on normal ageing dogs with cognitive decline. The acceptability and efficacy of the higher level MCT supplemented diet used in the studies with the RVC provided impetus to assess the higher level of MCT supplementation in ageing dogs with cognitive dysfunction syndrome and positive effects were demonstrated, which led to the diet being additionally marketed for this indication [a, b].

The product is now on sale in South America (Brazil, 2016; Mexico 2018), North America (2017), Canada (2017) and in Europe (2018) [Text redacted for publication] [a]. Purina has used the published paper presenting the results of the clinical trial conducted at the RVC in marketing this product to vets in North and South America [a, b]. [Text redacted for publication] To address the issues that owners may be unwilling to alter a pet's diet (for example reasons of costs or to avoid digestive disturbance) and so make this adjunctive approach to the management of canine epilepsy more accessible to a larger number of dogs, the RVC group showed the addition of a palatable MCT supplement to standard canine diets produced a similar effect.

A peer-reviewed published survey of 297 owners of dogs with idiopathic epilepsy, recruited via Facebook in 2017, following publication of the diet trial study, showed that 67% of owners had changed their dog's diet following diagnosis, with 46% giving dietary supplements, the most common being coconut oil (high in MCTs) or derived MCT oil (71%) [c]. To investigate perceptions of epilepsy research priorities by key stakeholders, online surveys of 414 owners of dogs with epilepsy, general practice (GP) vets, and veterinary neurologists were carried out by the RVC in 2016 and 2020. Non-drug therapies (including MCTs) were ranked highly across the three groups in both surveys and significantly increased in their perceived importance across the two time points. Within non-drug therapies, MCTs were rated 3rd highest out of 10 emerging non-drug therapies for their potential to positively impact epilepsy management in 2020, with the highest ratings by owners; MCT supplementation was considered of 'major' or 'great' impact by 33.7% of respondents (n=467) [d].

RVC's research has played a leading role in showing that canine idiopathic epilepsy, particularly in those animals that continue to have seizures whilst on antiepileptic drugs, has more widespread effects on the brain leading to significant co-morbidities that affect canine behaviour.

This concept was new to veterinary clinical practice and is now accepted by specialist veterinary neurologists. Its inclusion in a general veterinary educational textbook is now disseminating the understanding across the profession [e]. The print book has sold in 29 countries worldwide, with top markets being the UK, US, Italy and India [e].

Volk has taken the lead in educating veterinarians and owners about the scientific evidence upon which recommendations for diagnosing and treating canine epilepsy are based. He set up and led the International Veterinary Epilepsy Task Force in publishing 7 consensus papers on epilepsy classification, diagnostic approaches, treatment and outcome measures [f]. He has also co-authored 2 pivotal systematic reviews in canine epilepsy [g], defining the evidence based for antiepileptic drug efficacy and their adverse effects enabling veterinarians to evaluate the strength of evidence for recommending drug treatments. Additionally, Volk was the only UK author and co-chair on the 2016 American College of Veterinary Internal Medicine (ACVIM) consensus statement on seizure management in dogs, a review commissioned by the ACVIM to set down the state-of-the-art recommendations, where >10% of original papers cited providing the evidence for these recommendations were co-authored by the RVC group [h]. This consensus statement has been downloaded >50,000 times since publication [h]. Since 2013, Volk has also spoken extensively and internationally on this topic, giving >80 lectures at veterinary conferences in 17 countries. This case study's research has had significant media coverage both online and offline. There is a strong RVC Canine Epilepsy dedicated social media channel with 7,315 followers and during this REF period this case has generated 44,555 unique visitors to the RVC website. Mass media combined coverage exceeds 15,000,000 across countries including UK, USA, Australia, Spain, Portugal. It has featured in veterinary professional media online and/or print including Vet Times (circulation 18,000; monthly users online 528,256), VetSurgeon.org (monthly users online 14,536) TodaysVeterinaryPractice.com (60,000 users), VetPracticeNews.com USA (57,000 users) AnimalsHealth.es (33,000 users), veterinaria-atual.pt (46,000 users) and mrcvs.co.uk (21,000 members), and featured in consumer press and online sites including Australian Dog Lover (93,000 users/month), Dog Magazine (109,000 readers) and features on the American Kennel Club websites (5,000 member organisations) [i].

The RVC group has undertaken web-based and qualitative studies of owner perception of their pet's condition and consequent quality of life issues for both. Their findings have informed the RVC Pet Epilepsy Tracker App, developed in collaboration with the Epilepsy Society (who had created an app for the human condition). This was the first app to facilitate owner monitoring and improvement of the lives of their epileptic pets and includes educational material and advice for emergency situations. The app has been downloaded >27,600 times since 2015, translated into 4 languages (English, Dutch, French and German), and is in use in 84 countries [j]. The app is also assisting in veterinary care, as owners can send their dog's up-to-date medical history to their surgery. Detailed information can be recorded by owners regarding epileptic episodes, including duration, severity and what happened surrounding the event, which helps the vet better understand the patient's condition. This collection of longitudinal data by owners, previously inaccessible to the profession, is providing the means to better understand disease progression in individual dogs and creating a resource for long-term studies of the condition.

##### **5. Sources to corroborate the impact** (indicative maximum of 10 references)

*All evidence has been uploaded with the submission, unless otherwise stated as held by RVC.*

- a. Letter from Nestlé Purina PetCare corroborating role of RVC research in development of NC NeuroCare™ diet [Text redacted for publication]
- b. Marketing information from Purina websites (images of websites have been uploaded with submission as the below require a veterinary log in):
  - <https://www.purinaproplanvets.com/products/nc-neurocare-canine-formula/#indications>
  - <https://www.purinaproplanvets.com/research/> (video references [6])
  - <https://www.purinaproplanvets.com/research/life-changing-therapeutic-nutrition/>
  - [https://www.purinaproplanvets.com/media/452960/volk-study\\_br-j-nutr-2015-law\\_2.pdf](https://www.purinaproplanvets.com/media/452960/volk-study_br-j-nutr-2015-law_2.pdf) [6]

- c. Berk BA, Packer RMA, Law TH, Volk HA. (2018) Investigating owner use of dietary supplements in dogs with idiopathic epilepsy. *Research in Veterinary Science* 119, 276-284. <https://doi.org/10.1016/j.rvsc.2018.07.004>
- d. Epilepsy Priorities 2016 - 2020: Focus on Dietary Therapies Report (unpublished surveys conducted by Dr Rowena Packer).
- e. Textbook citing underpinning references - *Canine and Feline Epilepsy, Diagnosis and Management* (2014) Eds. De Rasio L. & Platt SR, CABI. [Held by RVC], plus email from CABI corroborating sales data.
- f. International Veterinary Epilepsy Task Force recommendations 2015:
- Hülsmeier VI, Fischer A, Mandigers PJJ, DeRasio L, Berendt M, Rusbridge C, et al. (2015) International Veterinary Epilepsy Task Force's current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs. *BMC Veterinary Research*, 11(1), 46. <http://doi.org/10.1186/s12917-015-0463-0>
  - Matiasek K, Pumarola I, Batlle M, Rosati M, Fernández-Flores F, Fischer A, Wagner E. et al. (2015) International Veterinary Epilepsy Task Force recommendations for systematic sampling and processing of brains from epileptic dogs and cats. *BMC Veterinary Research*, 11(1), 877. <http://doi.org/10.1186/s12917-015-0467-9>
  - Rusbridge C, Long S, Jovanovik J, Milne M, Berendt M, Bhatti SFM, et al. (2015) International Veterinary Epilepsy Task Force recommendations for a veterinary epilepsy-specific MRI protocol. *BMC Veterinary Research*, 11(1), 338. <http://doi.org/10.1186/s12917-015-0466-x>
  - Berendt M, Farquhar RG, Mandigers PJJ, Pakozdy A, Bhatti SFM, De Rasio L. et al. (2015) International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. *BMC Veterinary Research*, 11(1), 464. <http://doi.org/10.1186/s12917-015-0461-2>
  - Potschka H, Fischer A, Löscher W, Patterson N, Bhatti S, Berendt M. et al. (2015) International Veterinary Epilepsy Task Force consensus proposal: outcome of therapeutic interventions in canine and feline epilepsy. *BMC Veterinary Research*, 11(1), 1069. <http://doi.org/10.1186/s12917-015-0465-y>
  - Bhatti SFM, De Rasio L, Muñana K, Penderis J, Stein VM, Tipold A. et al. (2015) International Veterinary Epilepsy Task Force consensus proposal: medical treatment of canine epilepsy in Europe. *BMC Veterinary Research*, 11(1), 955. <http://doi.org/10.1186/s12917-015-0464-z>
  - De Rasio L, Bhatti S, Muñana K, Penderis J, Stein V, Tipold A. et al. (2015) International Veterinary Epilepsy Task Force consensus proposal: diagnostic approach to epilepsy in dogs. *BMC Veterinary Research*, 11(1), 470. <http://doi.org/10.1186/s12917-015-0462-1>
- g. Review articles: Charalambous M, Shivapour SK, Brodbelt DC, Volk HA. (2016) Antiepileptic drugs' tolerability and safety – a systematic review and meta-analysis of adverse effects in dogs. *BMC Veterinary Research*. 12, 79. <https://doi.org/10.1186/s12917-016-0703-y> and Charalambous M, Brodbelt D, Volk HA. (2014) Treatment in canine epilepsy – a systematic review. *BMC Veterinary Research*. 10, 257. <https://doi.org/10.1186/s12917-014-0257-9>
- h. Podell M, Volk HA, Berendt M, Loscher W, Munana K, Patterson EE, Platt SR. (2016) 2015 ACVIM Small Animal Consensus Statement on Seizure Management in Dogs. *Journal of Veterinary Internal Medicine*. 30(2): 477-90. <https://onlinelibrary.wiley.com/doi/full/10.1111/jvim.13841> plus email from ACVIM corroborating consensus statement download figures.
- i. RVC web/media statistics from Google Analytics; Meltwater/Signal PR systems; RVC social channels [Held by RVC].
- j. Unit download figures of Google and Android RVC Pet Epilepsy Tracker Apps [Held by RVC].