Institution: Royal Veterinary College
Unit of Assessment: A 6 Agriculture, Veterinary and Food Science
Title of case study: Feline chronic kidney disease: changes in clinical practice for routine diagnosis and management

1. Summary of the impact (indicative maximum 100 words)

Clinical research at RVC commencing in 1994 has changed clinical practice in management of feline chronic kidney disease (CKD) by transforming international consensus on diagnostic and treatment guidelines on proteinuria, hypertension and hyperphosphataemia. The research has informed the development of new products to manage hyperphosphataemia and diagnostics for identification of low level proteinuria in cats, deemed unimportant prior to publication of the RVC's research. RVC academics have worked in partnership with industry and used research results to change clinical practice guidelines through participation in consensus expert groups and increasing acceptance of new guidelines by outreach activities to general practitioners in UK, Europe, Asia and the USA in the form of publication of textbook chapters, lectures at major conferences and e-learning platforms to explain the underpinning research-based evidence.

2. Underpinning research (indicative maximum 500 words)

To address chronic diseases of ageing which are common problems faced by veterinary practitioners, requires engagement with first opinion practice on a long term basis. Since 1994 Professor Jonathan Elliott's group has worked in partnership with the animal charity, PDSA, which runs primary care practices nationally. (Elliott was appointed Lecturer in 1990, progressing to Professor of Veterinary Clinical Pharmacology in 2003.) Recruitment of cats with CKD to longitudinal study with disciplined data capture and standardised diagnostic and treatment protocols has generated cohorts of animals for cross-sectional, longitudinal and interventional studies. This long term strategy has yielded landmark publications in three areas of hyperphosphataemia, proteinuria and hypertension, all proven to be important factors in management of CKD. The group demonstrated that hyperphosphataemia and hyperparathyroidism could be treated by use of clinical renal diets and effective treatment was associated with improved survival [1] which complemented experimental data in rats, dogs and cats demonstrating the damaging effects of phosphate retention in CKD models.

The recognition by this group that clinical outcome of the CKD patient was associated with the severity of proteinuria at diagnosis [2] was a seminal observation that has changed thinking about feline CKD and led to the understanding that monitoring of proteinuria is an essential component of the management of the feline CKD patient. Furthermore, the association of low level proteinuria with increased risk of development of azotaemic CKD within 12 months of screening has reinforced this concept [3]. This research in its preliminary form informed the ACVIM Consensus statement on proteinuria and feeds in to all current guidelines on the management of CKD whereas prior to these discoveries proteinuria of this level was largely thought to be insignificant in the cat with CKD. The group also defined the prevalence of systemic hypertension in CKD patients [4] identifying that hypokalaemia is a significant risk factor and showed hypertension increases the severity of proteinuria [2]. They further explored the relationship between blood pressure management and post-treatment proteinuria, indicating the latter rather than post-treatment systemic blood pressure was the most important determinant of survival in these cats [5].

Most recently the group have shown that both hyperphosphataemia and proteinuria are independent risk factors for progressive deterioration in cats with CKD [6].

Other Quality Indicators

Elliott received the Pfizer Academic Award in 1998, the BSAVA Amoroso Award in 2001, the Petplan Scientific Award in 2005 and the European Society for Veterinary Nephrology and Urology Award in 2007 for contributions to companion animal medicine. Four PhD students from the group have been awarded the International Renal Interest Society award for their research contributions

(Penney Barber (2000), Harriet Syme (2002), Rosanne Jepson (2011) and Natalie Finch (2013).) Reference [1] awarded "Petsavers Award" for best clinical paper in Journal of Small Animal Practice, in 2001.

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

1. Elliott, J, Rawlings, JM, Markwell, PJ, Barber, PJ. 2000 Survival of cats with naturally occurring renal failure: effect of conventional dietary management. Journal of Small Animal Practice; 41, 235-242 DOI:10.1111/j.1748-5827.2000.tb03932.x

2. Syme, HM, Markwell, PJ, Pfeiffer, DU, Elliott, J. 2006 Survival of cats with naturally occurring chronic renal failure is related to severity of proteinuria. Journal of Veterinary Internal Medicine; 20(2):245-9 DOI: 10.1111/j.1939-1676.2006.tb02892.x

3. Jepson, RE, Brodbelt, D, Vallance, C, Syme, HM, Elliott, J. 2009 Evaluation of predictors of the development of azotaemia in cats. Journal of Veterinary Internal Medicine; 23 (4): 806-13 DOI: 10.1111/j.1939-1676.2009.0339.x.

4. Syme, HM, Barber, PJ, Rawlings, JM, Markwell, PJ, Elliott J. 2002 Prevalence of hypertension in cats with naturally occurring chronic renal failure. Journal of the American Veterinary Medical Association; 220, 1799-1804 DOI: 10.2460/javma.2002.220.1799

5. Jepson, R, Elliott, J, Brodbelt, D, Syme, HM. 2007 Effect of control of systolic blood pressure on survival in cats with systemic hypertension. Journal of Veterinary Internal Medicine; 21(3):402-9 DOI: 10.1111/j.1939-1676.2007.tb02982.x

6. Chakrabarti, S, Syme, HM, Elliott, J. 2012 Clinicopathological variables predicting progression of azotaemia in cats with chronic kidney disease. Journal of Veterinary Internal Medicine; 26(2):275-81 DOI:10.1111/j.1939-1676.2011.00874.x

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

The research has attracted repeated investment from pet food manufacturers to work with the group to improve their diets for cats with CKD, as well as being used by veterinary pharmaceutical and diagnostics companies to inform product development. Waltham Centre for Pet Nutrition and Royal Canin jointly provided funding grants to support staff and diagnostic work to run clinics. In addition, the companies have provided in-kind contributions of clinical renal diets used within the charity clinic of the PDSA and the Beaumont Sainsbury Animal Hospital, to provide high quality treatment for owners who otherwise could not afford to treat their cats. Over the impact period more than 1,000 cats and their owners will have benefited from this provision of free diagnosis and treatment, and have taken part in ongoing research [a].

This research has informed the development, refinement and improvement of dietary therapy for cats with CKD. In 2009 Royal Canin launched a reformulated Renal Special Diet; [text removed for publication] [b]
The group's research has stimulated the launch of two feed additives for the restriction of phosphate in the diet in cats. Bayer marketed Renalzin (lanthanum carbonate) in Europe in 2008 [c]. Bayer commissioned consultancy from Professor Elliott to assist in dissemination of the findings and implications for treatment, leading to a three-page feature article in the Veterinary Times[d].

A chitosan-based product named Epakitin in the US and Ipakitine in Europe was launched by Vétoquinol prior to the REF impact period, its final formulation guided by Elliott's proposals; [text removed for publication [e]. Vétoquinol has published four booklets / guidance notes on CKD and phosphataemia, all of which reference Elliott's research [f].

The group's research has underpinned the development of new diagnostic products. The proteinuria findings stimulated Idexx Laboratories Ltd to develop a test kit for measuring urine protein to creatinine ratio for its VetTest® Chemistry Analyser, used by 30,000 veterinary

practitioners worldwide [g]. The test kit was launched in 2005 in the UK and US following the presentation of RVC group data at conferences in 2003, enabling the first in-practice fully quantitative measure of urinary protein loss, and providing results which are both more specific and sensitive than the standard dipstick dye test. Since 2008 test kits have also been available for Idexx's Catalyst Dx chemistry analyser. [text removed for publication] [h]. Additional quantitative testing is still undertaken on samples sent by practitioners to diagnostic laboratories.

RVC's research provided a rationale for anti-proteinuric therapies for feline CKD, contributing to the rise in UK sales of Fortekor (Benazepril), Novartis's ACE inhibitor, for renal use[text removed for publication]. In February 2013, Boehringer-Ingelheim received marketing authorisation for Europe, for use in cats of Semintra (Telmisartan), an angiotensin receptor blocker for the management of proteinuria in cats with CKD [j]. The application to EMA directly references the RVC group's work [text removed for publication] [k].

[text removed for publication]

Data from the group's studies have informed currently accepted recommendations for the management of proteinuria and hyperphosphataemia in CKD [l,m].The International Renal Interest Society, which works to educate practitioners worldwide, has used the group's research to inform its diagnostic algorithms and treatment recommendations which are regularly updated. These were published by Elliott with A.D.J. Watson on behalf of the group in 2009, in *Kirk's Current Veterinary Therapy XIV*; an update has been invited for the next edition [n]. This is the standard text for setting the standard of diagnosis and care for veterinary patients. [text removed for publication] [o].

This paradigm shift in clinical practice, based on the research, is underscored in the widely-translated *BSAVA Manual of Canine and Feline Nephrology and Urology* (2nd ed, 2007), edited by Elliott and Grauer (Kansas State University). 3,000 copies of the *BSAVA Manual* sold worldwide 2007 - 2011, [text removed for publication]. It has been translated into Polish and Japanese, with Portuguese (for Brazil) and Russian editions under contract [p]. Other standard textbooks on feline clinical nutrition and nephrology of small animals, such as the Encyclopaedia of Feline Clinical Nutrition, also cover this work [q]. Elliott's chapter from the Encyclopaedia was first published on-line by the International Veterinary Information Service (IVIS) in July 2009 and in the first 8 months was accessed in English 5562 times and in French, 497 [r].

Elliott has been recognized as a Key Opinion Leader in this field through British and European veterinary association awards, and has contributed to the dissemination of the new best practice through international CPD activities since 2008, including invited presentations to veterinary professional conferences in the UK, USA, Italy, Sweden, France, Belgium, Germany and Thailand.

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

a. Clinical records of cats receiving free diagnosis and treatment. Held by RVC.

b. [text removed for publication]

c. http://www.renalzin.com/en/veterinary-professional/renalzin/why-renalzin/index.php [accessed 8 Aug 2013]

d. Elliott, J. Hyperphosphataemia and CKD. *Veterinary Times,* 38 (35),12 -16, 15 September 2008. http://www.vetsonline.com/Recherche/Resultats/Page/63c7214d2057b6d3451679205c521dde/2 [accessed 8 Aug 2013] Registration required for access.

e. [text removed for publication]

f. *Chronic Kidney Disease: Addressing Quality of Life and Life Expectancy*; *Suggested Guidelines in CKD*; *Phosphate Management in CKD*; *Educational Flashcards for Renal Management.* Vétoquinol. Copies held by RVC.

g. http://www.idexx.com/view/xhtml/en_us/smallanimal/inhouse/vetlab/urine-pc-ratio.jsf?SSOTOKEN=0) [accessed 8 Aug 2013].

h. [text removed for publication]

i. [text removed for publication]

j. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/veterinary/medicines/002436/vet_med_000269.jsp&mid=WC0b01ac058008d7a8 [accessed 8 Aug 2013].

k. [text removed for publication]

l. Lees, GE, Brown, SA, Elliott, J, Grauer, GF, Vaden, SL. 2004 Assessment and Management of Proteinuria in Dogs and Cats; ACVIM Forum Consensus Statement (Small Animal). *Journal of Veterinary Internal Medicine* 19(3):377-85. 2005. DOI: 10.1111/j.1939-1676.2005.tb02713.x

m. 'Recommendations for serum phosphate management in chronic kidney disease', published in *Phosphataemia: management in the treatment of chronic kidney disease: a roundtable discussion,* p6 – 7. (Discussion moderated by Elliott.) Vétoquinol. 2006. (http://www.vetoquinol.ca/documents/Quoi%20de%20neuf/Articles/Round%20table%20discussion.pdf [accessed 8 Aug 2013]

n. Elliott, J, Watson, ADJ. 2009 Chronic Kidney Disease: staging and management. In: *Kirk's Current Veterinary Therapy XIV.* Bonagura, JD, and Twedt, DC (eds.) St Louis: Saunders Elsevier. Chapter 192 pp. 883-392. ISBN 978-0-7216-9497-9

o. [text removed for publication]

p. *BSAVA Manual of Canine and Feline Nephrology and Urology (2nd Edition.)* 2007 Elliott, J., and Grauer, G.F. (eds). BSAVA Publications, Gloucester. ISBN 978 0 905214 93 1. Plus information supplied from BSAVA, by email dated 14 September 2012. Held by RVC.

q. Elliott, J, Elliott, D. 2008 Dietary therapy for feline chronic kidney disease. In: *Encyclopaedia of feline clinical nutrition*. Pibot P, Biourge V, Elliott D (eds). Aniwa SAS Ltd. Chapter 7 pp. 249-283. ISBN 9782747600842.

r. Information supplied by International Veterinary Information Service, by email from Royal Canin dated 8 March 2010. Held by RVC.