Methods and feasibility of conducting pragmatic clinical trials in small animal first opinion practice.

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For Ma and Pa, who first taught me to believe in myself.

i. Abstract

Chronic kidney disease (CKD) is an important cause of morbidity and mortality in cats, for which many research uncertainties remain unanswered. As for much of veterinary healthcare, the evidence base for treatment decision-making is limited. For the small number of research questions where randomised controlled trials (RCTs) are published, sample sizes are small, and the external validity of results can be limited because the patients included are not representative of the wider population who may have comorbidities. In addition, existing published research evidence does not always address outcomes of importance to treatment decision makers.

Pragmatic trials are a very new concept in veterinary healthcare where a literature search found only one pragmatic trial had been designed and carried out in full. However, they are well established in human healthcare. They are a sensible solution to many of the problems with the veterinary healthcare evidence base for several reasons. They address questions which are important to stakeholders and address outcomes of important to decision makers. They are designed to take place where everyday care happens and have less strict eligibility criteria than traditional RCTs, resulting in the inclusion of more diverse patient populations who represent the patients for whom the research will be used. The results are designed to be useful in everyday clinical decision making, in everyday clinical practice. They test real- world treatments and use flexible protocols, being designed to represent normal practice as far as possible. Their results are more widely generalisable than traditional RCTs and they are less expensive to carry out.

The aims of this PhD work were to investigate the existing published measures of treatment success in trials for cats with CKD and from there to establish the most important and most appropriate outcomes to use. This list would be designed to provide recommendations for future pragmatic treatment effectiveness trials of which treatment outcomes to assess and prioritise. In addition, this work aimed to establish the feasibility of extracting and using electronic patient records (EPRs)

from first opinion veterinary practice, as a data source for clinical trials for these patients. This data source was chosen because EPR use in pragmatic trials is well established in human pragmatic trials, and because the EPR is the location where the presenting signs, diagnosis, treatment and management and outcomes of large numbers of ordinary cats with CKD is already recorded and held.

A systematic review of outcomes assessed in published CKD treatment trials was carried out. This found a broad spectrum of outcomes that were assessed in the published literature. No core set of outcomes (COS) recommended for assessment in CKD treatment trials was found and little consistency was identified in the outcomes that were assessed between publications. To address this problem, research was conducted generating a COS for feline CKD. The panel of stakeholders involved in this process included an international panel of cat owners, clinical representatives, regulatory agencies and journal editors. A proposed list of important outcomes for a future COS was brought together via a three round eDelphi and an in-person consensus meeting. The final list created contained 29 core outcomes, grouped into four key areas: the veterinary consultation, blood and urine testing, living with CKD and CKD progression. Further refinement of this COS before it is finalised for inclusion in clinical trials is recommended, to streamline the outcomes into domains, potentially reduce by consensus the size of the final COS and agree by consensus the instruments to assess each domain.

One key outcome identified by the COS generation process and known to be of importance to decision makers for cats with CKD was quality of life (QoL). A systematic review of the published literature was conducted to identify all tools used for assessing feline QoL, and the range and quality of tools available. Many of the studies found that discussed QoL either did not assess QoL at all, or assessed QoL with only unvalidated, oversimplified tools. Few publications were found that assessed quality of life in a structured way and few used validated tools to assess QoL, although a validated tool for assessing QoL for cats with CKD was found. Once the full COS for cats with CKD was established, work was conducted to examine whether some of the outcomes highlighted could be measured using data collected in practice management software systems in veterinary practices as part of routine

veterinary healthcare. Data transfer from the databases of veterinary practices to those of laboratories, insurers and microchip registration companies is already well established, using XML schema. XML schemas describe the structure and content of the required data extract and present the data in a format which can be easily read by humans or computers. An XML schema was already published for the transfer of data pertaining to clinical research, 'Clinical Evidence Schema v1.0.5'. To accommodate data from multiple PMS and multiple veterinary practices this schema was adapted, restructured and some new data fields were added. A six-month data batch in XML format was extracted by a PMS, in accordance with the data specifications of the new schema, from 282 veterinary practices. Additional data was also provided by the PMS as Excel files. The whole data batch was deidentified using bespoke script in Microsoft Visual Basic. It was then cleaned and uploaded into a bespoke database written in MySQL. This destination database was then examined and explored using scripts written in data manipulation language and run on the dataset via the SQL Command Prompt.

The usefulness of the extracted patient data for possible treatment trials for cats with CKD was then established. Cats with CKD were identified using MySQL scripts, generating a disease prevalence of 2.8%. Validation showed this method to have 83.3% sensitivity, 99.5% specificity and a 40% false positive rate. A couple of relevant outcomes from the COS were extracted for feline CKD patients including blood pressure, bodyweight and survival time. CKD treatment interventions e.g. intravenous fluid therapy, or named therapeutics could be successfully identified within patient records and the longevity of these patients followed over time.

In conclusion, EPRs are used within human healthcare for pragmatic trials, however, very few pragmatic trials exist for veterinary healthcare. This PhD thesis has demonstrated that veterinary EPRs are a valuable and feasible data source for research. Pragmatic style trials are likely to address many of the evidence gaps which currently exist in veterinary medicine. Future veterinary research should look to EPRs as a proven, feasible data source, employing the use of COSs to direct the most important outcomes to extract. The next steps in this work should explore the potential for, and practicalities of, running treatment trials within a first opinion

veterinary practice environment. This will enable the profession to make real progress into filling the many evidence gaps in existence.

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Abbreviations

Researchers Initials:

HD	Hannah Doit (PhD student)
MB	Dr Marnie L Brennan (supervisor)
MD	Dr Marco Duz (supervisor)
NF	Dr Natalie Finch
RD	Dr Rachel S Dean (supervisor/ collaborator)

Terms abbreviations:

AKI	Acute Kidney Injury
ARF	Acute Renal Failure
BARK	Banfield Applied Research and Knowledge
BSAVA	British Small Animal Veterinary Association
CAM	Combined Approach Matrix
CATCH	Cats' Assessment Tool for Cardiac Health
CEVM	Centre for Evidence-based Veterinary Medicine
CHEW	Cat Health and Wellbeing
CHNRI	Child Health Research and Nutrition Initiative
CKD	Chronic Kidney Disease
CKF	Chronic Renal Failure
CKF	Chronic Kidney Failure
COMET	Core Outcome Measures in Effectiveness Trials
COMIS	Core Outcome Measurement Instrument Selection

CONSORT	Consolidated Standards of Reporting Trials
COS	Core Outcome Set
COSCAD	Core Outcome Set for Canine Atopic Dermatitis
CPRD	Clinical Practice Research Datalink
DDL	Data Definition Language
DML	Data Manipulation Language
EBVM	Evidence-based Veterinary Medicine
EHR	Electronic Health Record
ELISA	Enzyme linked immunosorbent assay
EPR	Electronic Patient Record
HCP	Health Care Professional
IRIS	International Renal Interest Society
JLA	James Lind Alliance
MRCVS	Member of the Royal College of Veterinary Surgeons
PCTU	Pragmatic Clinical Trials Unit
PCV	Packed Cell Volume
PMS	Practice Management Software
PPIs	Potential Personal Identifiers
PSP	Priority Setting Partnerships
QoL	Quality of Life
RCT	Randomised Controlled Trial
RCVS	Royal College of Veterinary Surgeons
RSP	Research Priority Setting

SAVSNET	Small Animal Veterinary Surveillance Network
SDMA	symmetric dimethylarginine
SQL	Structured Query Language
VCTN	Veterinary Clinical Trials Network
VMD	Veterinary Medicines Directorate
XML	eXtensible Markup Language

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1. Chapter 1: Introduction and review of the literature

1.1 Evidence for clinical decision-making

1.1.1 Evidence-based Veterinary Medicine

Veterinary surgeons, and owners of veterinary patients, and other decision-makers frequently have to make important decisions when choosing the most appropriate treatments or management strategies for the patients in their care. These decisions should ideally be guided by evidence-based veterinary medicine (EBVM). This can be defined as "the use of the best relevant evidence in conjunction with clinical expertise to make the best possible decision about a veterinary patient. The circumstances of each patient and the circumstances and values of the owner/ carer, must also be considered when making an evidence based decision" (Dean, 2013). The EBVM process of asking a pertinent question, synthesising evidence and making decisions is said to be conscientious and explicit, so that the 'how' and 'why' of decision making is carried out in a methodical way which can be explained and understood (Cockroft & Holmes, 2008).

The circumstances of the patient may relate to their amenability to particular treatments and handling, allergies or intolerances and the context and environment they live in. The circumstances and values of the owner or carer may relate to financial constraints, beliefs about quality of life and hoped for treatment outcomes, or how intensively animals should or should not be treated, and ability to medicate and handle the patient.

1.1.2 Evidence for treatment decision-making

The most relevant evidence is that in which the patients that are represented within the evidence reflect as closely as possible the patient for whom the decisions are being made, in both disease or condition and in breed, age, circumstances and comorbidities. In the context of veterinary healthcare, the type of evidence available that will address the question will vary (Dean, 2013). Multiple sources may

be available, or none may be available, again depending on the particular clinical question (Turner & Royle, 2015; Veterinary Record News and Reports 2014).

For treatment decision making, the most appropriate evidence is in the form of randomised controlled trials (RCTs) or systematic reviews or meta-analyses where multiple randomised controlled trials are compared and combined. A systematic review attempts to identify, appraise and synthesize all the evidence meeting pre-specified eligibility criteria to answer a specific research question (Jahan et al., 2016). In a meta-analysis the results of individual studies are combined to produce and overall statistic, and these are used in human healthcare in Cochrane Reviews to measure benefits and harms, providing a more precise estimate of an intervention's effects and reducing uncertainty (www.cochranelibrary.com/about/about-cochrane-reviews). Randomised controlled trials have been described as the 'gold standard' of evidence as to whether a treatment will do more harm than good (Sackett and Richardson 1997). In an RCT, confounders can be controlled and bias minimised (Akobeng, 2005; Attia, 2005). Confounding occurs when the effects of the exposure in the study on an outcome are mixed with the effects of additional factors, causing the true relationship between the two to be distorted (Rothman, 2004). A real association may become masked, or a false association may appear to be demonstrated and the clear causal links between treatments and outcomes become hard to establish (Skelly et al., 2012). Bias is defined as a process which produces results or conclusions which differ systematically from the truth (Sackett, 1979). Patient allocation between placebo (an inactive substance that looks like the drug or treatment being tested (www.nia.nih.gov/health/placebos-clinical-trials)) and intervention (the process or action that is the focus of a clinical study (https://clinicaltrials.gov/ct2/about-studies/glossary) or between two or more intervention groups is randomised, so that any differences in outcomes seen between groups is most likely attributable to the intervention that group has received. The sample size of patients within the study should be determined using a power calculation. An adequately powered study should avoid the study incorrectly concluding that there is no difference in outcomes between the two groups (a Type

II error), when in reality there was a difference, but the study did not detect it (Jones et al., 2003). Adequately powered studies can result in more confidence when read, because the results are reflective of reality and not an artificial creation due to the number of participants studied (Jones et al., 2003).

When there is no appropriate evidence available to support treatment decision making from randomised controlled trials or controlled trials, other forms of evidence are considered, alongside their strengths and limitations. Some evidence for treatment efficacy may come from observational cohort studies (Dean, 2013) or case-control studies. Cohort studies can provide evidence for risk factors for disease and prevalence, as can case control studies (Dean, 2013). In a cohort study, defined groups or cohort are followed over time to examine associations between exposures received and subsequent outcomes. The cohorts are identical except for in their exposure status (https://s4be.cochrane.org/blog/2017/12/06/case-control-and-cohort-studies-overview/). However, in a case control study the case and control groups are identical except for their outcome status. These studies look retrospectively to assess for statistically significant differences in the rates of exposure to defined risk factors in both groups to see if associations can be drawn between risk factor and outcome (https://s4be.cochrane.org/blog/2017/12/06/case-control-and-cohort-studies-overview/). Observational studies can assist in answering questions when it has not been possible to conduct an RCT, for example for treatments already authorised for use for which further funding for RCTs may be hard to obtain. Large observational studies may be less prone to selection bias and more representative of the normal population, increasing the external validity (the applicability of interventions in settings beyond the original study, (Fortin & Smith, 2013))of the results and may allow rarer treatment indications to be studied (Sharma et al., 2019). Where no primary evidence is available, case series or case studies, or anecdote and personal experience may all be used as veterinary evidence. All forms of evidence are valid, providing the strengths and weaknesses of each evidence form are carefully considered within the decision-making context (Dean, 2013).

When multiple evidence sources addressing the same clinical question are available they can be methodically combined, synthesised and evaluated in secondary evidence sources. For example, these could be complex systematic reviews or meta-analyses or the more rapid, narrower focused critically appraised topics (Brennan et al., 2020). A dedicated database of veterinary systematic reviews (VetSRev, https://vetsrev.nottingham.ac.uk/) is available for decision-makers seeking these synthesised forms of evidence. Critically appraised topics include clinical scenario best evidence reviews, e.g. BestBETs for Vets (https://bestbetsforvets.org/) or RCVS Knowledge summaries (https://knowledge.rcvs.org.uk/evidence-based-veterinary-medicine/veterinary-evidence/#knowledgesummaries). Combining multiple RCTs together where possible is important because if possible the studies should not be considered in isolation (Gopalakrishnan & Ganeshkumar, 2013). The more available well-designed studies are, the more confident the decision maker can be in the recommendations from the evidence (Khan et al., 2003).

1.1.3 Addressing Evidence gaps

Compared to human healthcare, the number and size of veterinary RCTs is small, likely due to limited resources and infrastructure. This reduces the replicability of the evidence base and reduces the opportunity to combine studies together to strengthen the evidence base (di Girolamo & Reynders, 2016; Oyama et al., 2017). Even when RCT evidence is available, a rigorous critical appraisal may find problems with trial design, the study population, outcomes chosen for assessment, follow up times and even the research questions asked.

As well as patient sample sizes often being small, the patients included in veterinary RCTs may have narrow inclusion criteria, reducing study participants to those with few comorbidities or those within a referral population only. The patients studied in RCTs are often not the patients seen in everyday practice (Rosner, 2012). The external validity of RCT trial results can be limited even in human healthcare

(Rothwell, 2005). In RCTs, patients with comorbidities are often excluded to obtain a homogenous sample (Fortin et al., 2006) so the applicability of the evidence they produce for real world, complex, multi-morbid patients is limited. The outcomes measured in veterinary trials are usually not chosen with input from patient owners or carers and treating veterinary surgeons, again limiting the usefulness of results (Rosner, 2012). Funding and structural limitations also mean that patient follow-up within the trial may be short. For example, some published evidence for feline CKD describes outcomes up to 60 days post treatment. Owners of cats with CKD may be interested in prognoses which span more time than that- multiple months or years. Research by Dean (2014) showed that all decision makers for feline CKD prioritised research into which treatments would improve survival as well as quality of life for these patients. It is likely that evidence for 60-day survival would not address this priority. All these concerns limit how applicable the evidence is, how appropriate it is to use, and how much it can assist decision-making.

More research is required to fill evidence gaps where none exists and to bridge the gap between some of the research evidence which does exist and the wider populations of patients that decision-makers are trying to apply it to. Pragmatic trials are one potential solution to many of the issues described.

1.1.4 Research uncertainties

1.1.4.1 Background

Prioritising the most useful and important research questions to address trials ensures that research meets stakeholder needs, avoids duplication and makes the best use of resources (Morton et al., 2022). Research is expensive to carry out and time and resource consuming (Fogel, 2018). The time input required from decision makers and owners in clinical trials, as well as the involvement and potential risk to the health of veterinary patients, means that trials should be designed to answer questions which are important, and for which there are true unknowns. Of the research unknowns for which there is true equipoise, it remains important to

prioritise research questions within those lists, so that the limited resources available are appropriately used. Equipoise is required to justify new trials from a research perspective. It can be understood as either when there is a balance of expert opinion as to the effectiveness of two interventions, or if there is a degree of uncertainty regarding the efficacy of an intervention (Freedman, 1987).

Many methods exist in human healthcare for prioritising research unknowns. These include the James Lind Alliance (JLA) Priority Setting Partnership (PSP) process, Research Priority Setting (RSP) collective activities used by The Cochrane Collaboration (https://methods.cochrane.org/prioritysetting/blog/james-lind-alliance-priority-setting-partnerships), The Child Health Research and Nutrition Initiative (CHNRI) method (Rudan et al., 2008) The Delphi method (McElroy et al., 2022), the Combined Approach Matrix (CAM) method (Ghaffar et al., 2004) and the Essential National Health Research method (Owlia et al., 2011).

1.1.4.2 Methods used to identify research uncertainties in veterinary healthcare

The JLA PSP process has now been used successfully for two areas of veterinary healthcare. JLA PSP uses a stepwise process to identify uncertainties, refine questions, review the literature and survey stakeholders to shortlist uncertainties. A stakeholder panel is assembled, and a Delphi process used to achieve group consensus on the top ten prioritised research questions (JLA Guidebook, 2021 www.jla.nihr.ac.uk/jla-guidebook/).

JLA PSP process in veterinary healthcare so far has focused on two areas. The top ten research priorities regarding the impact of canine surgical sterilisation on free roaming dog population management were published in 2021 (Collinson et al., 2021). In this study an online survey was used to collect unanswered research questions from international stakeholders. The responses underwent thematic analysis, and a collated indicative list of research questions was created. Literature reviews identified the true research uncertainties among these and the top ten uncertainties were prioritised from this list via a short survey and a Delphi

consensus process. Prior to this work, JLA PSP process was used for the first time in veterinary healthcare to identify the top ten research uncertainties in the treatment and management of feline CKD (Dean, 2014). Further detail on the approach used by Dean (2014) will be discussed later in this chapter.

1.1.5 Selecting the most appropriate trial outcomes

A key part of pragmatic trial design is selecting the outcomes to be assessed (Loudon et al., 2015). An outcome in a clinical trial is a parameter which can be measured to assess the effectiveness of what is being trialled (Williamson et al., 2017). An outcome should be objectively measured and clinically meaningful to the study participants (Williamson et al., 2017). For example, to determine the most appropriate diet for a particular veterinary patient might involve assessing several outcomes including: appetite, amount of food eaten, quality of life, coat condition and bodyweight. Some outcomes can be assessed objectively using specially designed data collection tools or instruments (Prinsen et al., 2014) or clinical equipment, for example, weight or volume of food eaten. However, appetite and coat condition are more objective outcome measures.

1.1.6 Core outcome sets for trials

In human healthcare, a core outcome set (COS) is an agreed minimum set of outcomes that should be measured and reported in all clinical trials for a specific disease from trial populations. The Core Outcome Measures in Effectiveness Trials (COMET) initiative bring people together who are interested in COS development, raise awareness of problems with outcomes in clinical trials, encourage the development and use of COS, promote involvement of patients in developing COS, and provide resources and encourage evidence-based methods in COS development (https://comet-initiative.org/About/WhatWeDo). They collate existing and in development COS in an online searchable database. The Core Outcome Measurement Instrument Selection (COMIS) project develop guidelines on the selection of instruments to measure the outcomes within a COS (Prinsen et

al., 2014). With the exception of one published COS for canine dermatology (Olivry et al., 2018), no additional COS has been established for veterinary healthcare. This leads to large numbers of outcomes being measured and reported in clinical research for many conditions. For example, a systematic review of outcome measures for canine osteoarthritis research (Belshaw et al., 2016) found many outcomes used with no consensus on the most useful or how to assess them. They reported a pressing need for consensus on outcomes reporting.

It is vital to involve all decision makers and carers in determining COS. The patient owners, carers and veterinary professionals examining and caring for patients should be represented by the populations of those same stakeholder groups in clinical trials. Only by doing this can the results of trials truly respond to the research needs, priorities and questions of these key stakeholders, with assessments which are meaningful and matter to them, and produce trial results from clinically relevant outcomes (Webbe et al., 2018). Improving trial outputs in this way will reduce research waste and allow results of research to be more easily compared and combined in systematic reviews and meta-analyses (Hughes et al., 2019).

1.2 Introduction to pragmatic trials

1.2.1 Background

Pragmatic trials were first defined (Schwartz & Lellouch, 1967) as a trial type designed to help chose between care options. This definition was later expanded upon (Roland & Torgerson, 1998) explaining that pragmatic trials evaluate effectiveness, which is treatment effects in routine clinical practice. Pragmatic trials can be considered at one side of a continuum or spectrum (Patsopoulos, 2011) where on the opposite side are explanatory trials, which are used to test causal research hypothesis (Schwartz & Lellouch, 1967) or evaluate efficacy, which is the effect of a treatment under ideal conditions (Roland & Torgerson 1998).

Explanatory style trials are designed for optimum determination of efficacy. They may have smaller sample sizes and risk overestimating benefits and underestimating harms (Ford & Norrie, 2016). Pragmatic style trials permit larger sample sizes of broader groups of patients, ideally including a relevant population for the intervention with a control group who are usually given 'standard care', and assess meaningful outcomes analysed at a high standard to show real world treatment effects (Ford & Norrie, 2016).

When designing a trial, the PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2) tool (www.precis-2.org/) can be used to assess and consider how pragmatic or explanatory a trial is in design. The tool assesses trials on a scale from 1-5 for nine criteria: eligibility, recruitment, setting, organisation, flexibility in delivery of intervention, flexibility in adherence to the intervention, follow-up, primary outcome relevance to participants and primary analysis of data.

Pragmatic trials design and reporting is recommended to be carried out according to the Consolidated Standards of Reporting Trials (CONSORT) (L. Turner et al., 2012). A number of initiatives have been developed to help with problems resulting from poor reporting, including the 25 item CONSORT Statement checklist (Zwarenstein et al., 2008). This is a minimum set of recommendations for reporting and is a standard evidence-based way to report transparent reporting of trial findings.

In human healthcare in the UK, the Pragmatic Clinical Trials Unit (PCTU) (www.qmul.ac.uk/pctu/) at the University of London lead and collaborate on many clinical trials and have their own methodological research programme. Their main focus is pragmatic trials but consider other trial types and work in many clinical areas, with strengths in colorectal surgery, mental health, primary care, women's health and critical care.

1.2.2 Routinely collected consultation data for pragmatic trials: human healthcare data

One way in which pragmatic trials are carried out in human healthcare is through the use of electronic health record (EHR) data. This data has the potential to provide evidence on clinical effectiveness, if the interventional studies and the patients and clinicians involved are representative of usual care (McCord et al., 2018).

EHR data which is routinely collected in human healthcare, also known as routinely collected health data is increasingly used for randomised controlled trials in human healthcare (Mc Cord et al., 2018). Using routinely collected EHR data for trials research is thought to reduce time, costs and resources required for the research, compared to traditional RCTs. It can expand the research agenda to questions not amenable to more traditional trials and offer new ways of collecting data, for example by embedding data collection and trial design within routine care (Mc Cord et al., 2018). Using EHR allows pragmatic trials to be performed, increasing the external validity of results (Mc Cord et al., 2018). Using EHR data also minimises the interference of pragmatic trials with routine care as much as possible (Meinecke et al., 2017). Trials using EHR data can require considerable infrastructure for data handling to be developed which can be expensive, and there may be problems with data quality and consistency, as well as for ethical approval processes (Mc Cord et al., 2018). To improve data quality, existing pragmatic trials often use a hybrid approach, combining EHR data with dedicated data collection forms. They may also optimise data quality by using automated query generation and pop-ups embedded in the health record system (Meinecke et al., 2017).

EHR data can also be used for actively or prospectively screening for eligible trial participants (Aung et al., 2016) and can be used for applying point of care randomisation (McCord & Hemkens, 2019). Longer follow up periods are available using EHR; one trial showed patient follow up times up to 55 years (Fitzpatrick et al., 2018). However, there may be some delays in collecting adverse event information when EHR are used for trials compared to traditional RCT trial

protocols (Mc Cord et al., 2018), but often when undertaking pragmatic trials, the EHR itself is or contains the intervention (Mc Cord et al., 2018).

In addition to potential for delays, there are other limitations to using EHR data. When working with this data, the representativeness of the EHR population for the specific research question needs to be established. Not all data within the EHR is usable, data may be incomplete or missing and due to differences in laboratory reporting, there may be measurement error or misclassification of data. Structured data fields may not always be used or may be incomplete (Gianfrancesco & Goldstein 2021). Data may be inaccurate or inconsistent (Botsis et al., 2010). Clinical notes (unstructured data) may not fully represent the patient and care must be taken to ensure that if information is not included, it does not mean a given problem does not exist (Gianfrancesco & Goldstein 2021).

Patients might enter an EHR database at any time point in their disease progression, making it difficult to establish whether a disease diagnosis is new or existing, which may become a source of confounding within a study if mistakes are made in classification, and whether a treatment therapy is established or just starting. This can lead to bias in results interpretation if therapeutic effects or risks vary over time (Farmer et al., 2017).

There are differences in the recording of treatment outcomes in the EHR compared to within traditional trial data collection methods. Some treatment outcomes require specialised equipment to measure them, which may mean they are not routinely recorded in the EHR as they are not being assessed, which may affect the scope of the EHR for identifying and extracting data on these outcomes (Bots et al., 2022). Databases of routinely collected data from the EHR include outcomes which matter to clinicians and patients, however they may typically lack outcomes of relevance for explanatory trials to explain treatment effects (Zwarenstein & Treweek. 2009). Data collection within the EHR may be less uniform than in traditional trials, and therefore the quality of outcome recording may be lower. The data collected may not capture sufficiently specific endpoints or adverse events

(McCord et al., 2021). A study by McCord et al. (2021) suggested that ascertaining trial outcomes using routinely collected EHR data may lead to those trials showing smaller treatment benefits than traditional trials not using routinely collected data. This could have implications for the applications of the evidence these trials produce.

1.2.3 Routinely collected consulation data for pragmatic trials: veterinary healthcare data

Veterinary research using EHR is already established with a number of research groups. The Small Animal Veterinary Surveillance Network (SAVSNET) at the University of Liverpool gather real time patient data from veterinary consultations and results of additional embedded short questions which assist in the classification of the disease process or body systems involved in the subject of the consultation (Radford et al., 2010). Their data is used for disease surveillance, understanding disease risk factors, describing antimicrobial use and resistance and reporting disease outbreaks (Brant et al., 2021; A. D. Radford et al., 2021; Singleton et al., 2021). The Veterinary Companion Animal Surveillance System (VetCompass) at the Royal Veterinary College in London also collect veterinary EHR from within the practice management software systems where this information is held. They use this data for epidemiological research and collect from over 1,800 veterinary practices in the UK (www.rvc.ac.uk/vetcompass/papers-and-data/original-publications). The data is also available to participating practices for their own audit and research. The research interests of VetCompass include antimicrobial stewardship, disease predispositions and risk factors and heat stroke among others (Buckland et al., 2016; E. J. Hall et al., 2022; O'Neill et al., 2019). In addition, they have begun an eClinical Trials project, which aims to analyse EHRs with novel statistical methods to evaluate the effectiveness of clinical interventions (www.rvc.ac.uk/vetcompass/research-projects-and-opportunities/projects/projects/vetcompass-eclinical-trials). The Veterinary Clinical Trials Network at the University of Nottingham is a group of veterinary practices

who are interested in participating in veterinary trials by using clinical practice data, and who participate in questionnaires, surveys and other forms of practice-based research with the Centre for Evidence-based Veterinary Medicine (CEVM). These three groups all work with patient data which is generated for veterinary practice, for billing, stock control and patient medical record keeping purposes, and not primarily for veterinary research. However, in the USA the Banfield Applied Research and Knowledge (BARK) initiative developed by the Banfield Pet Hospital is a bespoke data recording system which specifies, captures and records data fields of relevance to clinical research, for example blood test parameter measurements (www.banfield.com/en/pet-health/State-of-pet-health, (cat & banfieldcom, 2014)). Within the UK and USA, private veterinary practices and veterinary corporate groups will use their own EHR for clinical audit and quality improvement purposes (e.g. (Leicester et al., 2023).

Pragmatic trials by their design should involve little deviation from normal practice with respect to patient examination, testing, record keeping and follow up (Thorpe et al., 2009). This has not yet been established in veterinary healthcare. If the information from the veterinary consultation as recorded in the EHR could be collected from multiple PMSs and then the format standardised so that data from multiple EHR sources could be combined, this presents the potential for UK wide multicentre data collection. This EHR is a potentially highly valuable source of information for veterinary pragmatic trials - if the right information is there and can be extracted. Combining data from multiple practice management systems and multiple veterinary practices would increase the external validity and usefulness of the results generated. This PhD thesis will explore the feasibility and methods required for the extraction, combining and mining of veterinary EHR for use in pragmatic clinical trials research.

1.3 Pragmatic Trials in veterinary healthcare

1.3.1 Literature search

A literature search for veterinary pragmatic trials found very few published examples. Two databases were searched using the OVID interface: Medline (R) In-Process and Other Non-Indexed Citations (1946 to present) and CAB Abstracts (1910 to present). The search was carried out in September 2021. A selection of terms relating to veterinary medicine, and a selection of terms relating to pragmatic clinical trials, randomised controlled trials, and observational studies were searched for. The terms which returned results from each database are shown in Table 1.1.

Table 1.1 Search terms returning results on a search of the published literature for veterinary pragmatic trials

Database	**Keywords**	**Subject Headings**
CAB Abstracts	• veterinary • pragmatic trials • pragmatic • pragmatic clinical trial	• Veterinary medicine
Medline	• veterinary • pragmatic • pragmatic trial$	• Randomized Controlled Trial, Veterinary • Veterinary Medicine • Clinical Trials, Veterinary (as Topic) • Veterinary Drugs • Observational Studies, Veterinary (as Topic) • Clinical Trial, Veterinary • Observational Study, Veterinary • Pragmatic Clinical Trials (as Topic) • Pragmatic Clinical Trial

The search results from both databases combined returned only three manuscripts where veterinary pragmatic trials were mentioned or discussed (Jeffery et al., 2020; Kalnins et al., 2021; Porzsolt et al., 2011). It is possible that more pragmatic trials exist in veterinary medicine, which do not refer to themselves as pragmatic trials, or which have not been indexed as pragmatic trials.

The first manuscript identified (Porzsolt et al., 2011) was not in itself a pragmatic trial. Instead, it explained a suggested 'pragmatic' procedure for selecting appropriate study designs for interventional studies for dogs and cats with behavioural problems. The procedure was based on a ten-step procedure used in human healthcare research for selecting appropriate study designs for behavioural interventions.

In the second manuscript (Jeffery et al., 2020)the concept of pragmatic trials was explained and illustrated by description of a pragmatic trial design for using durotomy to treat acute intervertebral disc herniation in dogs. This aimed to address relatively poor outcomes (sometimes permanent loss of function) seen associated with severe thoracolumbar spinal cord injury following herniation. This manuscript discussed the differences between pragmatic and explanatory trials and explored the barriers to pragmatic trial interventions for these patients. For example, many patients may recover without intervention, this can lead to the 'signal' from the intervention being lost within the 'noise' of spontaneous recovery. Unless large sample sizes are included, the trial arms risk becoming unbalanced and different sizes of dogs may show different recoveries. They proposed that a pragmatic trial would include all cases of thoracolumbar spinal cord injury and for outcome measures, the owner's judgement of the patient's level of function and quality of life would be used. However, they also discussed that loose inclusion criteria and broad outcome assessments may become problematic if a treatment in a pragmatic trial fails, as it could be difficult to determine exactly why the failure has occurred. They also detailed the importance of clear definitions for standard care and outcomes, where standard care forms the comparator arm of a pragmatic trial to allow proper comparison with the intervention.

The final manuscript (Kalnins et al., 2021) reported a pragmatic trial which had been carried out. It described a single centre, parallel group pragmatic trial for antibiotic treatment of moderate grade dog bite wounds in dogs. Wounds were graded 1-5 and grades 3 (full thickness with dermis penetration but no systemic illness) and 4 (full thickness puncture or laceration with avulsion of underlying tissue and dead-space, underlying muscle trauma, possible joint penetration or abscess or systemic illness) were randomised to either receive amoxicillin-clavulanic acid or amoxicillin-clavulanic acid and enrofloxacin. Fifty patients were included and the complication rate due to infection at 10 days was examined as the primary outcome. A 4.2% difference in complication rate was seen, and amoxicillin-clavulanic acid without enrofloxacin was deemed non inferior to amoxicillin-clavulanic acid with enrofloxacin. Overall, the search of the veterinary literature revealed only three manuscripts. One manuscript reported a pragmatic trial which had taken place (Kalnins et al., 2021). One described a pragmatic trial protocol (Jeffery et al., 2020), however the trial itself had not taken place, and the final paper (Porzsolt et al., 2011) discussed pragmatic procedures for study design selection. The pragmatic trial which was reported to have been carried out (Kalnins et al., 2021)was published very recently. It seems that the concept of pragmatic trials is an emerging one within the veterinary field, and one where more research is needed.

There are other trials which have been conducted in veterinary medicine which appear pragmatic in some aspects of their design, without referring to pragmatic trial terminology. While reviewing the literature, one manuscript which was identified was the evaluation of pimobendan use in dogs with cardiomegaly study (EPIC; Boswood et al., 2016). Few RCTs in animals are as large as the EPIC study, which reported a sample size of 360 client owned dogs with myxomatous mitral valve disease (MMVD), in a prospective, multicentre, blinded, randomized, placebo-controlled trial. However, the inclusion criteria for the study may be considered too narrowly defined for a pragmatic trial. For example, they were highly specific in the sizes of: left atrial to aortic ratio, left ventricular internal diameter (in diastole) and vertebral heart sum. However, in a design consistent with pragmatic trials, some

comorbid patients were included, for example: dogs with stable hypothyroid disease. Patient outcomes were analysed according to 'intention to treat' which is commonly used in pragmatic trial design when ascertaining treatment effectiveness (Sedgwick, 2015). The primary outcome variables were broad and more consistent with the type of outcomes which might be found in a pragmatic trial design: time to composite of the onset of congestive heart failure, cardiac related death or euthanasia. However, additional outcomes were measured in this study which may have exceeded those likely to be assessed by all clinicians in normal practice, for example the detailed measurements made on echocardiography. In a truly pragmatic trial design, the outcomes assessed would reflect standard practice, as the results will be used to inform normal practice.

1.4 The case for studying feline chronic kidney disease

1.4.1 Background

Chronic kidney disease (CKD) of cats is a common condition seen in small animal veterinary practice. It can affect cats of any age, with a recent study reporting an overall prevalence of 1.2% in primary care practice. In the same study the prevalence increased with age, with 36% of cats aged 9 years and older affected (Conroy et al., 2019). Even higher prevalence has previously been reported in earlier studies where up to 80% of cats over 15 years were affected (Marino et al., 2014). Diagnosis is based on evidence of greater than three months duration of evidence of structural or functional kidney damage (Sparkes et al., 2016) and the disease is often quoted to become clinically apparent once over 75% of renal function has been lost (S. A. Brown et al., 1997) although this is not a recently published source. CKD causes clinical signs including polydipsia, polyuria, weight loss, inappetence, hypertension, weakness, lethargy, vomiting and anaemia (Sparkes et al., 2016). Bijsmans et al. (2016) report that the anorexia, weight loss and depression all impact on the cat's quality of life. Treatment strategies vary according to the stage of CKD once diagnosed, and in most cases by the time CKD is

diagnosed the damage to the kidneys is irreversible (Cannon, 2016). Therefore, in these cases, treatment primarily aims to reduce clinical signs and improve quality of life and life expectancy. The International Renal Interest Society (IRIS) publish guidance for staging CKD in dogs and cats once the diagnosis has been made, and appropriate treatment recommendations (http://www.iris-kidney.com/guidelines). Staging is carried out according to the outcomes on the blood creatinine, SDMA, urine protein: creatinine ratio and blood pressure. Staging is based on fasting blood creatinine assessed twice in the stable patient, and then substaging is carried out based on proteinuria and systolic blood pressure measurements. More recently, blood symmetric dimethylarginine (SDMA) measurements have been included in the staging guidelines as an additional evaluation of renal excretion. The staging guidelines were most recently updated in 2023.

CKD is a chronic condition, and once diagnosed, cats will live with CKD for the rest of their lives. Median survival times have been reported (Boyd et al., 2008) ranging from one month to three years, depending on stage of disease at diagnosis, with the shorter survival times seen with more advanced disease. It is likely that a wealth of information about these patients relating to their disease stage, clinical signs, treatment successes and failures and length of life after diagnosis, resides within the clinical notes. This is because while living with CKD, cats are likely to have multiple veterinary consultations to assess their clinical signs, CKD stage and allocate or adjust appropriate treatments and management strategies as required. Some patients are only diagnosed with CKD when the condition is at an advanced stage, and euthanasia is then carried out within days or weeks of diagnosis (authors own experience in clinical practice, also Boyd et al. (2008) discuss shorter survival times for cats with higher stage renal disease at 'baseline'- i.e. cats with higher stage of disease despite fluid correction for dehydration). However, information about these patients will still be recorded within their clinical notes.

1.4.2 Uncertainties in treatment and management of feline CKD

Treatment and management of feline CKD has been identified as a research area where many important questions remain unanswered. The sample sizes included in the existing trials on feline CKD are often relatively small, case inclusion requires satisfaction of specific criteria and may not include patients with comorbidities. This makes the results in these trials less pragmatic in nature and less generalisable to the population of cats diagnosed with CKD. Using the JLA PSP prioritisation process, Dean (2014) identified 28 unique, unanswered research questions important to veterinary surgeons and cat owners about feline CKD treatment, and identified and ranked the top ten treatment uncertainties in order of importance. A treatment uncertainty is said to occur when the questions about treatment cannot be answered by up to date information based on reliable systematic reviews of research evidence, so remain unanswered (https://www.jla.nihr.ac.uk/jla-guidebook/chapter-2/what-are-evidence-uncertainties.htm)

From Dean (2014), the top ten treatment uncertainties identified were:

1. What is the single best treatment for cats with CKD belonging to clients with a limited budget?
2. Do the veterinary kidney diets improve the life of cats with CKD?
3. What is the best alternative diet for cats with CKD if they won't eat the veterinary kidney diets?
4. Do ACE inhibitors (e.g. Fortekor) or angiotensin receptor blockers (e.g. Semintra) improve the life of cats with CKD?
5. Do subcutaneous fluids (fluids under the skin) improve the life of cats with CKD?
6. Do oral phosphate binders (e.g. Renalzin, Epakitin) improve the life of cats with CKD?

7. Are Non-steroidal Anti-inflammatory Drugs (NSAIDs e.g. Metacam) safe to use in cats with CKD?
8. Does vitamin B12 and Anabolic steroids (e.g. Laurabolin) improve the life of cats with CKD?
9. What is the best way of stopping vomiting in cats with CKD?
10. Would stem cell therapy help cats with CKD?

This prioritised list of unanswered research questions for CKD, the chronic nature of the disease and its importance as a cause of morbidity and mortality in cats all make more research urgently required, as well as a suitable candidate for exploring pragmatic trials further within veterinary medicine. The majority of questions included within the top ten list, excluding only question 10 regarding stem cell therapy, are all largely pragmatic in style. They reference treatments given by first opinion veterinary surgeons to treat and manage the condition under normal conditions in veterinary practice, and the outcomes in question are broad, and reflective of treatment effectiveness, rather than efficacy (Dean, 2014). To provide research evidence to answer the top ten questions, the patients included in trials would need to reflect the wider population to whom the research results will be applied, and patient and owner behaviour would also reflect normality with respect to compliance and potential difficulties in giving medication or treatments.

1.4.3 What does success look like for feline chronic kidney disease trials?

The outcomes of interest in some of the 'top ten' questions relate to 'improving the life of' cats, and reference specifically quality of life and length of life. However, for others it is not already known which outcomes would be the best to assess to fully answer the question. For example, questions around the 'single best treatment', 'safety' or 'best way of stopping vomiting'. What is meant by 'best', how can we measure 'best' and would veterinary nurses and veterinary researchers both

measure it in the same way? What makes a treatment 'safe' in the eyes of the veterinary surgeon or the owner? Does safety mean the same thing to different people? How can we be sure that the results of research will reliably answer the questions they aim to, in a way that all research users understand and are in agreement with? No consensus exists on the most important outcomes to assess for feline CKD. It appears that a wide range of outcomes are already examined and recorded in published treatment trials, with little agreement between trials on which to assess. This problem is not unique to feline CKD, or the feline species, and is likely to be reflected across the majority of other species and conditions treated within veterinary medicine. This was well illustrated (Belshaw et al., 2016) when 618 reported outcome measures were found when measuring canine osteoarthritis, of which only 10 were validated, with no consensus on which were the most appropriate or important. As part of exploring the feasibility of pragmatic trials for feline CKD, the current range and breadth of outcomes assessed in published treatment trials should be established, and a COS developed. If this could be done, then including outcomes from the core set in the pragmatic trial design would mean that the results of the trial would be relevant and useful for all research users and all who make decisions for feline CKD. People who make treatment decisions for these patients (e.g. veterinary surgeons and veterinary nurses), administer treatments, and care for these patients in veterinary clinics and at home (e.g. cat owners) are the most likely to have true treatment effectiveness goals in mind when developing a core set of outcomes for research.

1.4.4 Potential data source for addressing CKD research uncertainties

It is possible that the data on patients and treatment outcomes to answer questions like those that are unanswered for CKD are already being recorded in the electronic patient record, from within veterinary consultations for cats with CKD. If the data

exists and can be extracted, then there is the potential to use first opinion veterinary clinic patient records as a source of data for pragmatic clinical trials. If outcomes of interest are not already routinely recorded as part of treatment monitoring for these patients, additional data recorded may be required. However, this has the potential to reduce compliance and engagement with treatment trials in the veterinary clinic, as changing data recording radically from normal practice could require additional time and training for those inputting the data. Pragmatic trials using routinely collected data in human healthcare prefer to use data which is already routinely recorded (Mc Cord et al., 2018). If the data recorded for cats with CKD within their electronic patient records is both accessible and contains the information of interest, then the electronic patient record could become a valuable data collection tool for pragmatic trials in clinical practice on these patients. Little or no additional work or data recording by the clinicians may be required.

1.5 Outline for the PhD thesis

Working within the field of feline CKD treatment research, the overall aims of the research for this PhD programme were:

- To investigate and establish the most important and appropriate outcomes to use to assess feline CKD treatment success in trials
- To discover whether there is a published validated method for assessing quality of life in cats with CKD
- To investigate the feasibility of extracting patient data for cats with CKD from using veterinary practice clinical records
- To investigate the usefulness of veterinary practice clinical records as a data source for feline CKD pragmatic trials research, by assessing whether important treatment outcomes are recorded in the clinical record and whether they can be extracted for use

To meet these aims, the objectives of this research were:

- Carry out a systematic review of outcomes already published for feline CKD treatment trials
- Create a core set of outcomes for feline CKD treatment research, using consensus methods including eDelphi and a consensus meeting to include an international panel representing all treatment decision makers responsible for the care of these patients, for creation of their treatments and for the regulation and publishing of treatment research
- Carry out a systematic review of quality of life assessment tools for cats in the published literature
- Agree with veterinary practices and PMSs transfer of an extract of patient data from first opinion veterinary practice, with identifying information removed.
- Build a database to store the data extract in a format prepared for searching for important outcomes from the core set
- Develop structured query language scripts to identify cats with CKD and to find and extract important outcomes from their patient records

Figure 1.1 provides an overview of the thesis, and a short description of each chapter can be found below.

1.5.1 Chapter 2

In chapter 2 a systematic review of the outcomes already assessed in published CKD treatment trials was carried out to determine the number of outcomes assessed, the amount of agreement between studies, and also variation in outcomes assessed in published trials, and the outcomes evidence which is available to decision makers treating these patients.

1.5.2 Chapter 3

In chapter 3 the lack of a core outcome set (COS) for feline CKD was addressed. This study employed consensus methods including an eDelphi and a consensus meeting, to establish the most important treatment outcomes to all treatment decision makers. The outcomes were selected from the list of published outcomes found in chapter 2, and additional outcomes were suggested by panellists. A final list for a future core set was established and agreed for future CKD treatment trials.

1.5.3 Chapter 4

In Chapter 4, the core outcome 'quality of life' (QoL) from the COS was focussed upon. This outcome was also known to be of importance to treatment decision makers from work done by Dean et al. (2014). This chapter explored how best to assess of QoL. A systematic review of the published literature was carried out to discover the range and quality of assessment tools already published for feline patients and used in published literature. A published, validated tool designed for assessing QoL in cats with CKD was found.

1.5.4 Chapter 5

In chapter 5, the potential of accessing electronic patient records (EPRs) from veterinary practice to use as a data source for clinical trials was investigated. The data fields required were chosen, and an XML schema was used to describe and design the data structure. In agreement with a large group of veterinary practices using the same bespoke Practice Management Software System (PMS), a six month long retrospective data batch of all patient consultations was extracted, personally identifiable information was removed, and the data was cleaned and uploaded into a secure bespoke database. Both the database and the XML schema were designed to facilitate data from multiple PMSs, multiple veterinary practices and multiple patients to be extracted and combined into a single, searchable database.

1.5.5 Chapter 6

In chapter 6, the data extract and database described in chapter 5 was tested as a resource for clinical trials research for cats with CKD. The data was searched using

queries written in MySQL. Cats with CKD were successfully identified within the dataset and the method designed for this purpose was validated. Outcomes from the COS described in chapter 3 were successfully identified within the patient records of these cats, and then extracted for analysis. Specifically, bodyweight, blood pressure, endpoint for renal survival, and survival time. Demographic data for cats with CKD was extracted and described. In addition, preliminary work to identify treatment interventions for CKD within the patient clinical records was begun although further work to refine this process is needed. This study demonstrated that EPRs can be used to identify cats with CKD, begin to identify the treatments they have been given and then successfully find treatment outcomes of importance to decision makers. All of these stages are required for the use of veterinary EPRs as a data source for future pragmatic trials, without requiring additional work or time from the veterinary practices recording the data.

1.5.6 Chapter 7

In chapter 7, all chapters from this PhD thesis were gathered together to discuss the key findings from all studies in this work, what these findings mean for all stakeholders including: cat owners, veterinary surgeons and veterinary nurses, PMS providers, researchers, educators and industry (veterinary pharmaceutical companies, nutraceutical companies and manufacturers of veterinary prescription diets), and the next steps for each stakeholder group in the light of these research findings. Future work was discussed including dissemination of research findings, knowledge exchange, International Renal Interest Society collaboration, the future of core outcome sets in veterinary healthcare and methods for further harnessing the potential of EPR extracts from PMSs to help carry out clinical trials.

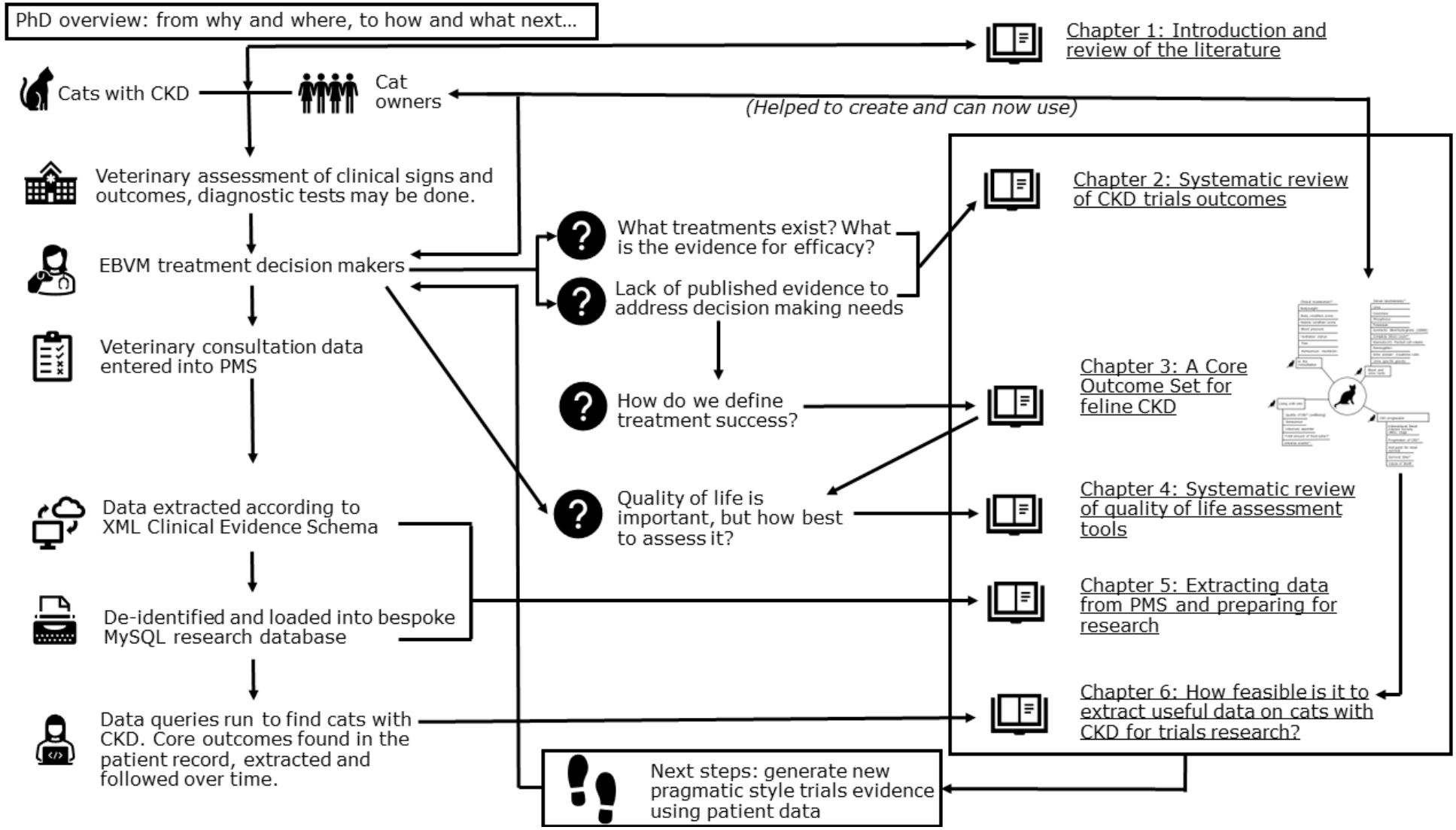


Figure 1.1 Overview of the PhD workflow

2. Chapter 2: A systematic review of outcomes recorded in feline chronic kidney disease treatment efficacy trials

2.1 Context

This review of the outcomes in treatment efficacy trials was carried out as part of a wider project which was being carried out by Dr Rachel Dean (RD) at the University of Nottingham and Dr Natalie Finch (NF) at the University of Bristol; an overarching systematic review of treatment efficacy trials for feline chronic kidney disease. The treatment efficacy review had not been published at the time of submitting this PhD manuscript. The original searches of the databases and the inclusion and exclusion of all manuscripts found was carried out by RD and NF. The final list of all included manuscripts was checked by RD, NF and HD to confirm all met the inclusion criteria and none should be excluded. HD then carried out the extraction of the outcomes recorded in the methods and results sections of the manuscripts as described in this chapter, alongside collation of a brief overview of each of the manuscripts including journal of publication, study type and intervention being assessed in the study.

2.2 Introduction

When choosing between treatment options for their patients, veterinary professionals aim to apply the principles of evidence-based veterinary medicine. This covers many different aspects of practice, but commonly involves establishing a diagnosis, agreeing the desired outcomes of any treatments proposed with the owner and involves reviewing the relevant published scientific evidence to discover the available evidence for treatment efficacy as it relates to the outcomes of interest.

Chronic kidney disease (CKD) of cats is a common condition seen in small animal veterinary practice. It can affect cats of any age, with a recent study reporting an overall prevalence of 1.2% in primary care practice. In the same study the prevalence increased with age, with 36% of cats aged 9 years and older affected (Conroy et al., 2019). Even higher prevalence has previously been reported in earlier studies where up to 80% of cats over 15 years were

affected (Marino et al., 2014). Diagnosis is based on evidence of greater than three months duration of structural or functional kidney damage, with it often quoted (although not from a recently published source) that once over 75% of the renal function is lost, CKD becomes clinically apparent (S. A. Brown et al., 1997). CKD impacts the cat's quality of life by causing anorexia, weight loss and depression (Bijsmans et al., 2016). Treatment strategies vary, and in most cases by the time CKD is diagnosed the damage to the kidneys is irreversible (Cannon, 2016). Therefore, in these cases, treatment primarily aims to reduce clinical signs and improve quality of life and life expectancy.

The primary cause of CKD is not always identifiable. Once CKD is identified treatments are targeted towards limiting the progression of the disease (Cannon, 2016). The IRIS staging process provides support and guidance to clinicians when managing CKD. The process helps understand the severity of disease, how quickly CKD is progressing and the most appropriate treatments for the patient at each stage of disease. How widely this staging process is used in published clinical trials for feline CKD is not yet known.

In clinical trials a treatment outcome is a measurement or observation used to capture and assess the effect of treatments, such as effectiveness or side effects (Williamson et al., 2017). It might be objective, e.g. blood pressure, or subjective e.g. demeanour. The efficacy of the treatment is assessed in accordance to the outcomes (Williamson et al., 2017). For example, for cats with kidney disease, does new medication "X" compared to no treatment, decrease blood pressure? If multiple research studies assess the same outcomes, their results can be more easily compared and combined. This helps build the evidence base for treatment decision making. If the evidence-base covers a wide and disparate selection of outcomes, it makes it difficult for clinicians to find the evidence they need to understand whether the available treatments can help them reach the treatment outcomes they wish to achieve for their patients. If the treatment outcomes of interest are not researched and the results published, the clinician may be left with no evidence base to inform their decision making.

2.3 Aim

The aim of this study was to conduct a systematic search of the published literature to identify the number and range of outcomes which had been measured and reported in published CKD treatment research, to discover what evidence is available to clinicians for treatment decision making in these patients.

Objectives:

1. Develop list of keywords and subject headings to identify manuscripts containing CKD treatment research
2. Develop inclusion and exclusion criteria for manuscripts
3. Run searches on appropriate database
4. Extract outcomes from included manuscripts

2.4 Materials and methods:

Systematic reviews are structured reviews which search for and identify manuscripts which have been published and are relevant to a specified research question. Inclusion and exclusion criteria are pre-defined and used to filter the search results in a structured manner (Jahan et al., 2016) so that the output is as specific as possible to the question of interest.

The search for the systematic review of feline CKD treatment efficacy was carried out in April 2018 by RD and NF. Searching was carried out through the University of Nottingham and University of Bristol libraries. The databases searched were PubMed (1970 onwards), CAB Abstracts (1910 onwards) and the first 2000 results from a Google search. Medline is available through PubMed and has 82.6% coverage of active veterinary journals, CAB Abstracts has been shown to have 97.5% coverage of active veterinary journals (Grindlay et al., 2012). Keywords and subject headings were used in searching both databases (Table 2.1). The limit of the first 2000 results from the Google search was chosen as an appropriate size limit for reasons of feasibility, and because from experience, search results become repetitive after this point with no new results found. The database search results were

collated in a common folder in EndNote (endnote.com) and then the manuscripts were downloaded. Full manuscripts were obtained from either the University of Nottingham or University of Bristol libraries, or via inter-library loans (British Library).

Table 2.1 Keywords and subject headings searched in the systematic review for outcomes recorded in chronic kidney disease treatment trials (2018)

Words searched for in systematic review	**PubMed (Medline)**	**CAB Abstracts**
Keywords	cat, cats, feline, felines, felis, renal failure, renal disease, renal insufficiency, kidney failure, kidney disease, kidney insufficiency	cat, cats, feline, felines, felis, renal failure, renal disease, renal insufficiency, kidney failure, kidney disease, kidney insufficiency
Subject headings	cats, felis, renal failure, kidney diseases	cats, felis, renal failure, kidney diseases

The inclusion criteria (Table 2.2) for the methods described in the manuscripts, were that the patient group should be client owned domestic cats with naturally occurring CKD. The study types included were randomised controlled trials, controlled trials without randomisation, and retrospective and prospective cohort studies. Manuscripts written in any language were included, any manuscripts not written in English would be translated. All treatments and interventions for CKD were included. Additionally, specific managements for hypertension, vomiting and inappetence were included and all management options including diet, supplements, transplant, dialysis and stems cells were included. Licensed and off-license treatments were included, and prescription only medicines, over the counter medicines, and supportive treatments were all included. Studies were included where the full study was reported, where studies were published or available through grey literature, and if only abstracts were found initially, the full methods and results needed to be available upon request. Studies were excluded from the systematic review results if the patients were cats with experimentally induced CKD, cats with acute kidney injury, or if the study

was in vitro. Study types excluded from this review were: case control studies, cross sectional studies, case series, pharmacokinetics and pharmacodynamics studies and narrative reviews. No languages were excluded from the results. The excluded interventions were: treatment for co-morbidities in CKD patients, for example, antibiotics for urinary tract infections, non-steroidal anti-inflammatories for osteoarthritis, methimazole for hyperthyroidism. If only the abstract of the study was available and the full manuscript was not available on request, the study was excluded.

Manuscripts were checked independently for inclusion and exclusion criteria by RD and NF. The final list of included manuscripts was agreed by RD and NF. HD then received a list of the included manuscript references, and rechecked that all had been correctly included according to the inclusion and exclusion criteria. All three reviewers had no competing interests.

Table 2.2 Inclusion and exclusion criteria for the feline chronic kidney disease treatment efficacy systematic review

Criteria	**Inclusion criteria**	**Exclusion criteria**
Patient Group	Client-owned domestic cats with naturally occurring CKD (defined by manuscript author)	Cats with experimentally induced CKD, cats with Acute Kidney Injury, In Vitro studies.
Study type	Randomised controlled trials Controlled trials without randomisation Cohort studies (retrospective and prospective)	Case control studies Cross sectional studies Case series/studies Pharmacokinetics/ pharmacodynamics studies Narrative reviews

Language	None (relevant manuscripts will be translated)	None
Intervention	Any intervention for CKD Specific management for hypertension Specific management for vomiting Specific management for inappetence Include management options such as diet, supplements, transplant, dialysis, stem cells Includes licensed and off license drugs, Prescription Only Medicines and Over The Counter, supportive treatment	Treatment for co-morbidities in CKD patients e.g. antibiotics for urinary tract infections, NSAIDs for osteoarthritis, methimazole for hyperthyroidism
Publication type	Full study reported Published literature Grey literature Abstracts (full methods and results available on request)	Abstracts (methods and results not available on request)
Availability	Able to obtain through University of Nottingham or University of Bristol library	Unable obtain whole manuscript

	or inter-library loan or by request	

2.4.1.1 Extraction of outcomes from included manuscripts

Once the list of included studies was finalised, copies of all included manuscripts were downloaded. The materials and methods and results sections of all manuscripts were then examined by HD. All outcomes described in the methods or results section of the manuscripts were extracted. Outcomes were extracted regardless of whether they appeared in the methods section or results section or both sections. Parameters were identified from all three stages of the treatment process (before, during and after) and the methods and results sections for completeness, to capture all things which had been assessed, not just those which were reported in the final results, in case of selective outcome reporting (Gluud, 2006; Higgins et al., 2011) bias. It was also hoped that extracting parameters measured before intervention could be used for a baseline assessment, to show outcome change during the study.

A Microsoft Excel spreadsheet (Microsoft 365) was created listing each manuscript's author and year of publication, and all outcomes for each manuscript were then listed, one per cell. All extracted parameters and outcomes were then combined as a single list, sorted alphabetically, and duplicates were removed. Outcomes which were deemed to be the same in meaning but with different descriptions could be combined to consolidate the final list of unique outcomes. For example, smell of breath and halitosis could be combined into the composite outcome halitosis. The resulting final list of unique outcomes extracted from all studies was then reorganised into core theme groups of different overarching approaches for ease of understanding. Following this, a new table was created listing all unique outcomes and all included manuscripts. This was then repopulated with a number 1 in each cell, to show which unique and composite outcomes had been extracted from which manuscript.

This systematic review was not registered and the protocol was not published, prior to carrying out the review. The data collection forms are not publicly available and extracted data is available only as presented within this thesis.

2.5 Results

The search returned 2967 manuscripts from CAB Abstracts and 2198 manuscripts from Medline. A total of 4557 duplicates were removed, leaving 1088 unique manuscripts remaining. Out of the unique manuscripts remaining, 20 met the inclusion criteria for the systematic review. Nineteen manuscripts were available in English, one manuscript had to be translated from Japanese (Sawashima et al., 2002).

2.5.1.1 Identifying unique outcomes

The 20 manuscripts were examined for outcomes which could be identified and understood. Some outcomes were discarded at this stage; ten papers referred to examination of a urine sample, however the tests carried out on the sample were not clearly explained. Where no tests were described under the urine test heading, it was discarded as non-specific. In addition, the outcomes "deviation" and "neurohormones" were discarded as their meaning was unclear. The outcome "serum phosphorus to calcium ratio" was discarded as both serum phosphorus and serum calcium were already included from other papers.

A total of 341 identifiable outcomes were extracted from the included manuscripts. Forty-one of these outcomes (39% of all outcomes extracted) were unique, appearing in only one manuscript. Three hundred outcomes appeared in two or more of the included manuscripts. Two hundred and thirty-eight of the duplicate outcomes were removed, either because they were exact duplicates, or because their meanings were similar enough to be combined to make composite outcomes. For example, diarrhoea, frequency of diarrhoea and digestive system diarrhoea were all combined to make one outcome, diarrhoea. The remaining 103 unique outcomes were made up of 62 unique and composite outcomes and 41 unique original outcomes (Figure 2.1). Table 2.5 shows all outcomes extracted from each paper and how frequently each outcome was extracted in this review, the top ten most frequently extracted outcomes are summarised in Table 2.4: urea, creatinine, clinical signs/full clinical examination, bodyweight, blood biochemistry, complete blood count, total calcium, urine specific gravity, potassium and phosphate. The most frequently extracted outcomes were

urea and creatinine, both extracted from 16 papers each. Forty-one outcomes occurred only once each. On average, each outcome appeared in 3 papers.

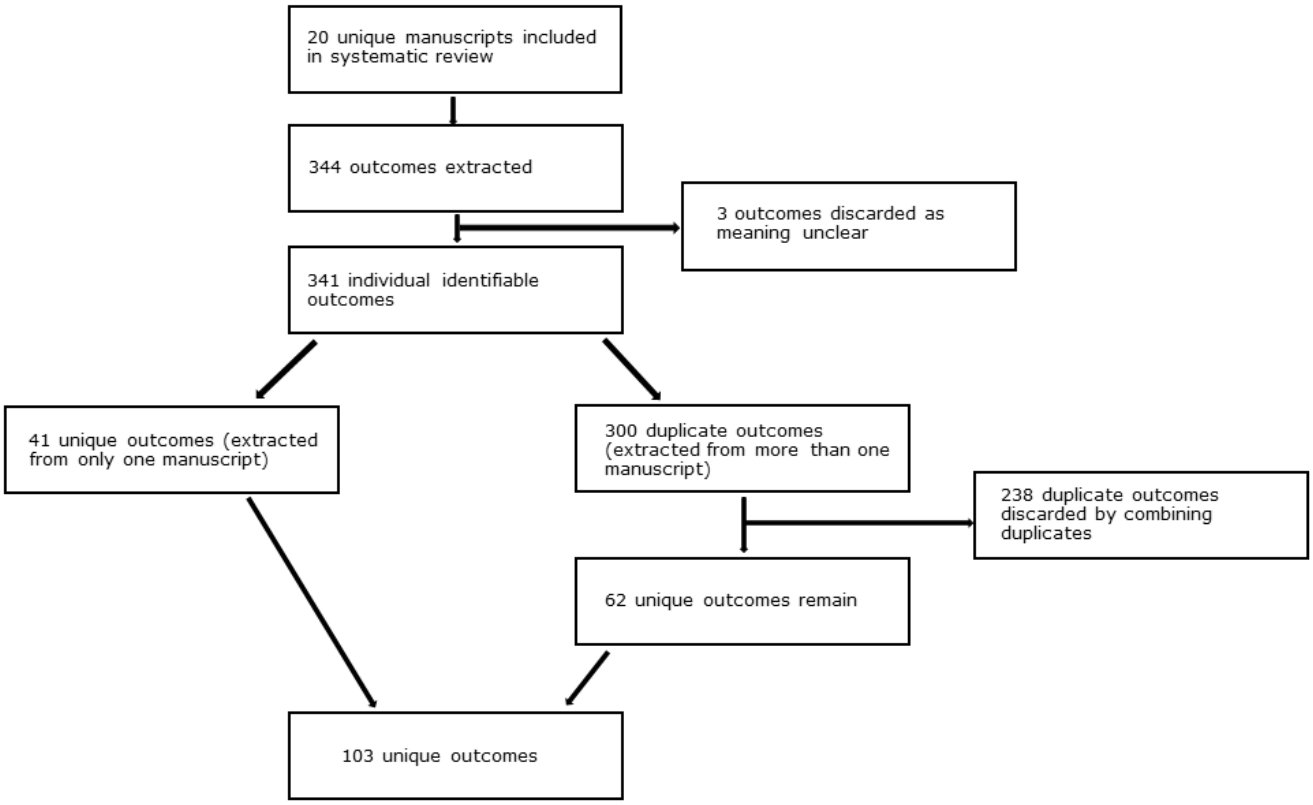


Figure 2.1 Number of outcomes extracted from 20 unique manuscripts from a systematic review, showing how many were discarded as duplicates and the total number of unique outcomes identified.

2.5.1.2 Number of outcomes extracted, per manuscript

The greatest number of outcomes extracted from one paper was 34 (Mizutani et al., 2006) and the smallest number of outcomes extracted from one paper was three (Plantinga et al., 2005; Rishniw & Wynn, 2011). The average number of outcomes extracted per paper was 17. Fourteen papers assessed 10 or more unique outcomes each Figure 2.2 shows a comparison of the number of outcomes extracted from each manuscript.

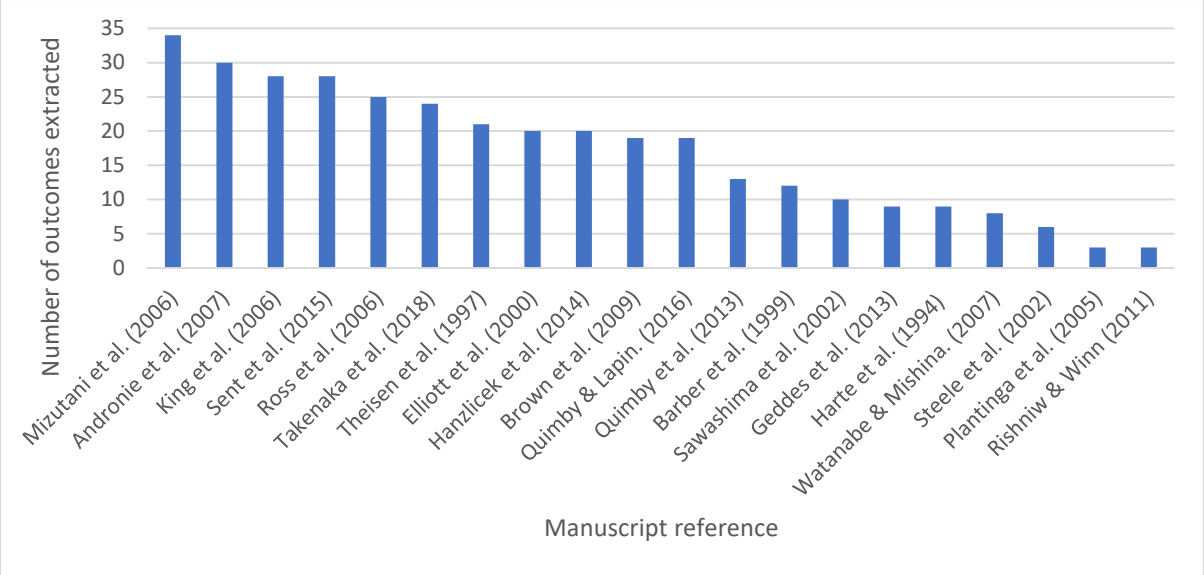


Figure 2.2 Total number of outcomes extracted from each manuscript included in the systematic review (descending order)

2.5.1.3 Origin of manuscripts and study types

The manuscripts included in this review, were published in a range of journals. The only journal which published more than one manuscript was the Journal of Veterinary Internal Medicine which published seven of the manuscripts (Table 2.3). All manuscripts were published since 1994, with three being published before the year 2000, ten published between 2000 and 2009, and seven published from 2010 onwards. A brief overview of study type all the trials to be controlled trials or randomised controlled trials except for one (Plantinga et al., 2005) which was an observational type cohort study. All manuscripts were journal articles, except Andronie et al., (2007) which was a bulletin.

Table 2.3 Brief overview of study information and where manuscript published for all 20 manuscripts included in the systematic review

Author and year of publication	**Article title**	**Intervention given**	**Total no. outcomes extracted**	**Article type**	**Journal name**
Andronie et al. (2007)	Use of hypoproteic diets in feeding cats diagnosed with chronic renal failure	Hypoproteic diet	30	Bulletin	Bulletin of University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca. Veterinary Medicine
Barber et al. (1999)	Effect of dietary phosphate restriction on renal secondary	Dietary phosphate restriction	12	Journal Article	Journal of Small Animal Practice

	hyperparathyroidism in the cat				
Brown et al. (2009)	Gene therapy by electroporation for the treatment of chronic renal failure in companion animals	Gene therapy	19	Journal Article	BMC Biotechnology
Elliott et al. (2000)	Survival of cats with naturally occurring chronic renal failure: effect of dietary management	Low protein and low phosphate diet	20	Journal Article	Journal of Small Animal Practice
Geddes et al. (2013)	The effect of feeding a renal diet on plasma fibroblast growth factor 23 concentrations in cats with stable azotemic	Veterinary renal diet	9	Journal Article	Journal of Veterinary Internal Medicine

	chronic kidney disease				
Hanzlicek et al. (2014)	The effect of Chinese rhubarb, Rheum officinale, with and without benazepril on the progression of naturally occurring chronic kidney disease in cats	Chinese rhubard (Rheum officinale) with and without benazepril	20	Journal Article	Journal of Veterinary Internal Medicine
Harte et al. (1994)	Dietary management of naturally occurring chronic renal failure in cats	Restricted protein and phosphorus diet	9	Journal Article	The Journal of Nutrition

King et al. (2006)	Tolerability and efficacy of benazepril in cats with chronic kidney disease	Benazepril	28	Journal Article	Journal of Veterinary Internal Medicine
Mizutani et al. (2006)	Evaluation of the clinical efficacy of benazepril in the treatment of chronic renal insufficiency in cats	Benazepril	34	Journal Article	Journal of Veterinary Internal Medicine
Plantinga et al. (2005)	Retrospective study of the survival of cats with acquired chronic renal insufficiency offered different commercial diets	Diet	3	Journal article	The Veterinary Record

Quimby & Lapin. (2016)	Evaluating Sucralfate as a Phosphate Binder in Normal Cats and Cats with Chronic Kidney Disease	Sucralfate	19	Journal Article	Journal of the American Animal Hospital Association
Quimby et al. (2013)	Mirtazapine as an appetite stimulant and anti-emetic in cats with chronic kidney disease: a masked placebo-controlled crossover clinical trial	Mirtazapine	13	Journal Article	The Veterinary Journal
Rishniw & Winn (2011)	Azodyl, a synbiotic, fails to alter azotemia in cats with chronic kidney disease when sprinkled onto food	Azodyl	3	Journal Article	Journal of Feline Medicine and Surgery

Ross et al. (2006)	Clinical evaluation of dietary modification for treatment of spontaneous chronic kidney disease in cats	Diet with reduced protein, phosphorus and sodium, and supplemented polyunsaturated fatty acids	25		Journal of the American Veterinary Medical Association
Sawashima et al. (2002)	Inhibition of naturally occurring feline chronic renal failure by dietary-protein restriction	Low protein diet	10	Journal Article	??
Sent et al. (2015)	Comparison of Efficacy of Long-term Oral Treatment with Telmisartan and Benazepril in Cats	Telmisartan and benazepril	28	Journal Article	Journal of Veterinary Internal Medicine

	with Chronic Kidney Disease				
Steele et al. (2002)	Effects of angiotensin-converting enzyme inhibition on plasma aldosterone concentration, plasma renin activity, and blood pressure in spontaneously hypertensive cats with chronic renal disease	Angiotensin-converting enzyme	6	Journal Article	Veterinary Therapeutics

Takenaka et al. (2018)	A double-blind, placebo-controlled, multicenter, prospective, randomized study of beraprost sodium treatment for cats with chronic kidney disease	Beraprost sodium	24	Journal Article	Journal of Veterinary Internal Medicine
Theisen et al. (1997)	Muscle potassium content and potassium gluconate supplementation in normokalemic cats with naturally occurring chronic renal failure	Potassium gluconate supplementation	21	Journal Article	Journal of Veterinary Internal Medicine

Watanabe & Mishina. (2007)	Effects of benazepril hydrochloride in cats with experimentally induced or spontaneously occurring chronic renal failure	Benazepril	8	Journal Article	Journal of Veterinary Medical Science

Table 2.4 The top 10 most frequently extracted outcomes for feline chronic kidney disease treatment found in 20 manuscripts identified via a systematic review.

Outcome	**Number of times extracted**
Urea	16
Creatinine	16
Clinical signs/ full clinical examination	14
Bodyweight	13
Blood biochemistry	12
Complete blood count	10
Total calcium	10
Urine specific gravity	10
Potassium	9
Phosphate	8

Table 2.5. Total number of outcomes extracted and the total number of times each outcome was extracted from 20 manuscripts identified as part of a systematic review on treatments for CKD in cats.

Outcome group	Outcomes	Andronie et al. (2007)	Barber et al. (1999)	Brown et al. (2009)	Elliott et al. (2000)	Geddes et al. (2013)	Hanzlicek et al. (2014)	Harte et al. (1994)	King et al. (2006)	Mizutani et al. (2006)	Plantinga et al. (2005)	Quimby et al. (2013)	Quimby & Lapin. (2016)	Rishniw & Winn (2011)	Ross et al. (2006)	Sawashima et al. (2002)	Sent et al. (2015)	Steele et al. (2002)	Takenaka et al. (2018)	Theisen et al. (1997)	Watanabe & Mishina. (2007)	Total times outcome extracted
Owner might notice at home	Overall history						1								1							2
	Appetite for food	1		1					1	1		1					1		1			7
	Overall amount of food eaten each day				1								1		1							3
	Thirst			1																		1

	Drinking behaviour	1								1							1					3
	Vomiting			1					1	1		1	1									5
	Number of bowel movements each day			1																		1
	Diarrhoea			1			1		1	1												4
	Constipation												1									1
	Urination	1		1						1							1					4
	Halitosis	1							1													2
	Condition of coat/ fur	1							1	1												3
	Exercise tolerance			1																		1
	Activity level			1								1							1			3
	Weakness								1													1

	Wellbeing		1		1																2
Examined in veterinary consultation	Change in demeanour compared to at start of study																1				1
	Clinical signs/ full clinical exam	1	1		1		1		1	1		1			1	1	1	1	1	1	14
	Body condition score											1			1						2
	Body weight	1	1	1	1		1	1	1	1		1				1	1		1	1	13
	Palpable size of kidneys																1				1
	Respiration									1											1

	Ocular funduscopic examination													1							1
	Presence of lacerations in the mouth/ gingivitis	1							1	1											3
	Mucous membrane colour	1																			1
	Neurological signs								1	1											2
	Mentation			1																	1
	Faecal phosphorus concentration												1								1

Urine tests	Urine protein to creatinine ratio						1		1	1					1		1		1			6
	Urine creatinine									1			1									2
	Urine specific gravity	1	1		1	1	1		1	1							1		1	1		10
	Urine glucose	1																	1			2
	Urine sediment	1			1																	2
	Level of blood in the urine	1														1						2
	Urine pH	1																		1		2

	Urine leukocytes	1																				1
	Urine bilirubin	1																	1			1
	Urine urobilinogen	1																				1
	Semiquantitative urine albumin ELISA						1															1
	Urine nitrites	1																				1
	Urine ketonic bodies	1																				1
	Urine culture				1		1								1							3
	Urine hormone			1																		1

	measurement																					
	Urine metabolism			1																		1
	Urine biochemistry			1	1															1		3
	Urine sodium											1							1			2
	Urine potassium											1							1			2
	Urine phosphorus											1										1
	Urine calcium											1										1
	Fractional excretion of phosphorus in urine											1										1

	Quality of life			1	1				1	1									1			5
CKD progression and lifespan	Progression of renal dysfunction														1	1						2
	IRIS stage/ stage of disease					1						1					1					3
	Survival time			1	1						1											3
	End point for renal survival								1	1			1		1		1					5
	Cause of death/ why the cat has died				1		1								1		1					4

	Renal histology at autopsy								1													1
	Overall assessment of efficacy									1												1
Involvement in a clinical trial	Occurrence of adverse events						1			1		1					1		1			5
	Difficulty administering/ giving treatments to the cat						1															1
	Owner not giving the treatments to the cat		1		1		1										1		1			5

	Time enrolled in study						1															1
	Biochemistry	1	1	1	1		1	1	1			1	1			1		1		1		12
Blood tests	Albumin	1						1		1				1			1		1			6
	Globulin																		1			1
	ALP								1	1							1		1			4
	ALT								1	1							1		1			4
	AST									1									1			2
	Chloride									1					1				1			3
	Creatinine	1			1	1		1	1	1	1	1	1	1	1	1	1		1	1	1	16
	Ionised calcium		1												1							2
	Phosphate		1		1	1		1	1	1							1				1	8
	Phosphorus											1	1		1					1		4

	Potassium				1				1	1		1	1		1		1		1	1		9
	Protein (protein in the urine comes from protein in the blood)								1	1						1					1	4
	Sodium								1	1			1							1	1		5
	Total calcium	1	1			1			1	1			1		1		1			1	1		10
	Urea	1	1		1			1	1	1	1	1	1	1	1	1	1			1	1	1	16
	Complete blood count	1		1			1	1	1				1		1				1	1	1		10
	Packed cell volume				1			1							1		1				1		5
	Erythrocyte count	1								1													2

	Haematocrit	1					1			1					1		1					5
	Haemoglobin	1															1					2
	White blood cell count	1								1							1					3
	Total plasma solids	1		1				1	1	1					1				1			7
	Carbon dioxide														1					1		2
	HC03-bicarbonate														1					1		2
	Aldosterone																	1				1
	Plasma renin activity																	1				1
	Levels of renin angiotensin																				1	1

	aldosterone components																				
	T4					1	1		1							1					4
	Plasma parathyroid hormone		1		1	1								1							4
	AAA1,25 dihyroxycholecalciferol		1																		1
More advanced testing	Insulin-like growth factor 1			1																	1
	Fibroblast growth-factor 23					1															1
	C-tetraethylammonium																		1		1

	bromide clearance																				
	Decrease in creatinine clearance														1					1	2
	H-inulin clearance to represent glomerular filtration rate																		1		1
	Blood pressure				1	1	1								1		1	1			1	7
	Abdominal radiography						1															1
	Abdominal ultrasound						1															1

	Renal biopsy to measure the α-SMA index															1						1
	Muscle potassium content from a triceps biopsy																			1		1
	Total number of outcomes per manuscript	30	12	19	20	9	20	9	28	34	3	13	19	3	25	10	28	6	24	21	8	

2.5.1.4 IRIS staging outcomes

The outcome “IRIS stage” or “stage of disease” occurred in three manuscripts. The individual outcomes which need to be assessed for IRIS staging are: blood creatinine (found in 16/20 manuscripts), SDMA (found in no manuscripts), urine protein: creatinine ratio (found in 6/20 manuscripts) and blood pressure (found in 7/20 manuscripts). The composite outcome IRIS stage was included in a minority of manuscripts (3/20).

2.5.1.5 Grouping outcomes into themes

The 103 unique outcomes were then grouped into nine themes: parameters the cats’ owner might notice at home (e.g. exercise tolerance); parameters examined in the veterinary consultation (e.g. body condition score); urine test parameters (e.g. urine specific gravity); parameters related to CKD progression and lifespan (e.g. survival time); parameters related to being in a trial (e.g. occurrence of adverse events); blood test parameters (e.g. Packed Cell Volume); more advanced testing (e.g. Plasma Renin Activity). Three rounds of discussion and grouping took place between RD, MB and HD, before the nine theme groups were finalised (Table 2.5).

2.6 Discussion:

2.6.1.1 Overall findings

To the author’s knowledge, this is the first systematic review of outcomes assessed in published research to be carried out for feline CKD. Systematic reviews of current published literature on treatment outcomes are a vital part of evaluating the research evidence available to decision makers, and an important step in beginning to establish standardisation on what is investigated and reported in trials, and where evidence gaps exist.

This systematic review found over 100 unique outcomes were recorded in feline treatment efficacy systematic reviews. A large proportion of the outcomes identified were only extracted from one manuscript each, increasing the variety of outcomes found overall which makes comparison between treatment trials almost impossible. Many of the outcomes extracted were specific to a particular aspect of CKD or specific treatments for CKD.

2.6.1.2 IRIS guidelines

The IRIS CKD guidelines (www.iris-kidney.com/guidelines) are used by clinicians treating cats with CKD in small animal veterinary practice to stage severity of disease and guide treatment and management strategies. They are the most formalised assessment system available to clinicians treating cats with CKD, and they provide some consensus and support for decision making with this important condition. The guidelines are created by veterinary surgeons and the SDMA section of the recommendations is based on published literature (www.iris-kidney.com/guidelines). However, other stakeholder and decision makers who care for cats with CKD are not included in developing the guidelines and the guidelines and staging system have not been validated. Therefore, the accuracy of IRIS staging in determining disease status is not fully known. This systematic review found that IRIS staging itself was not consistently assessed or reported, nor were the individual outcomes which together make up the IRIS staging process. One outcome (SDMA) did not appear in any manuscripts in this review. Blood pressure and urine protein: creatinine ratio both appeared in less than half of the manuscripts included. Blood creatinine however was included in the majority of manuscripts (16/20). The composite outcome IRIS stage was included in a minority of manuscripts (3/20). In some manuscripts, part of the outcomes required to perform IRIS staging were assessed, without a full IRIS stage assessment of their patients being completed. However, this may be explained in part by date of publication. The IRIS group first formed in 1998, with the current proposed CKD stages and their linking to treatment recommendations first being published in 2002, and most recently updated in 2019 (www.iris-kidney.com/about/iris_history.html). Therefore, some studies found in this review may have been published before IRIS recommendations were available, or before the IRIS staging system was developed to where it stands at present. Measuring all outcomes required and completing IRIS staging in future treatment trials may give more information on the efficacy of treatments being trialled and could be useful to the veterinary practitioner who is using these manuscripts for evidence-based treatment decision making.

2.6.1.3 Clinicians and owners using the published evidence base

The usefulness and usability of the existing published evidence base found by this review are impacted by; the large number of outcomes found, the wide variability in type of outcomes found, and the presence of some outcomes which were more unusual, or may not be fully understood by decision-makers. These tended to be specific to one specific research study, requiring specialised methodologies or techniques to assess them (e.g. C-TEA clearance as a measure of effective renal plasma flow). Treatment decision making, and progress assessment by clinicians are both likely to be affected by status of the existing evidence base. Clinicians wanting to compare their own patient outcomes to those in published research may find this difficult if specialist equipment or laboratories are needed to assess the outcomes of interest. Evidence may not be available on the outcomes of interest for specific treatments being considered. Where evidence is lacking, or there is no validated method for assessing the outcome it may be difficult for clinicians to compare their own patient's treatment results with the published literature and have confidence that assessments are being carried out correctly and are comparable with the results that have been published. Where there are evidence gaps in the published literature it could be difficult for clinicians to predict and monitor their patient's responses to treatments, or to know which treatments are the most appropriate to use. It will also make it harder for the effectiveness of treatment in each patient to be determined.

Many of the outcomes found in this systematic review could be assessed in the normal veterinary consultation using equipment which is likely to be available in most clinics (e.g. urine specific gravity), or could be observed by owners at home (e.g. overall amount of food eaten each day). The inclusion of these outcomes in future trials could therefore be valuable to treatment decision-makers. An additional gap in the evidence base for feline CKD is the lack of understanding of which outcomes are already routinely or rarely assessed by clinicians in the consultation and veterinary clinic, and also which outcomes cat owners monitor and assess at home. In addition, the time period over which outcomes are assessed in the literature may not fully reflect the expected lifespan of cats with CKD. Therefore, whether or not the outcomes currently assessed in the published literature are the most appropriate outcomes, reflective of treatment success throughout the life of cats with CKD, is at present not known.

A consensus is needed, including the expertise of all treatment decision makers, on the most important outcomes to include in future treatment trials. Consensus should also be reached on the best ways to assess the outcomes, to ensure results are valid, repeatable and reliable. The consensus should include the opinions of cat owners, veterinary clinicians and veterinary nurses who care for these patients, researcher, representatives of the companies producing treatments and all others who are stakeholders in the decision making and treating of these cats. Joined up thinking, producing consensus on the most important outcomes to assess, would mean the results of future treatment trials could be more helpful for treatment decision making and their results more easily applied to patients in the veterinary clinic. A consensus on outcomes would enable the results of trials to be more easily compared and combined (for example in systematic reviews or meta-analyses), increase the usefulness of feline CKD treatment trial research, and reduce research waste. Outcomes should also be validated for how well they assess feline CKD.

2.6.1.4 Study limitations

Although two key databases shown to have a wide coverage of the veterinary literature were used for this study, had additional databases been used then more studies meeting the inclusion criteria may have been found. The literature search for the treatment efficacy review, which this treatment outcomes review forms a part of, was last updated in 2018. It is possible that further studies meeting the inclusion criteria for this review may have been recently published, and a search update could be carried out to assess this. In addition, the meaning of a small number of study outcomes was unclear, and these were discarded from the review results. Further clarity on these outcomes could be gained by writing to the manuscript authors, and this could allow these additional outcomes to be included.

2.7 Conclusions

There is no evidence at this time as to which outcomes are the most important to clinicians or to the owners of cats with CKD, who are responsible for both the practical care and financial support of these patients. The wide variety of outcomes found by this review highlights the inconsistencies in the evidence base and the potential difficulties faced by

treatment decision makers, both clinicians and cat owners, when synthesising evidence and integrating the existing evidence base into their decisions.

Reporting guidelines:

The information presented in this chapter has been reported according to the PRISMA 2020 checklist (Page et al., 2021) and all items are present, except for those relation to a risk of bias assessment. This has not been carried out as it was not thought to be appropriate for the type of results extracted in this study.

3. Chapter 3 Pathway to creating a core set of outcomes for feline CKD: identifying outcomes which are important to stakeholders.

3.1 Context

Chapter 2 highlighted the lack of consensus on the most important outcomes to measure in feline chronic kidney disease (CKD), and the difficulties that creates when trying to integrate the published evidence into treatment decision making. This study begins to address this clear need by developing a core set of outcomes for future treatment trials, initially by identifying the outcomes all stakeholders think are important. All treatment decision makers were involved, including patient advocates (cat owners). The methodology used was adapted from human healthcare where the concept of core outcome sets is well established, as when this work began only one core outcome set was published for veterinary healthcare.

This study was published in July 2021 in a special edition of Preventive Veterinary Medicine. doi: 10.1016/j.prevetmed.2021.105348

The full manuscript can be seen in Appendix 1.

Within this study, 80% of the work was carried out by HD, and 20% by the co-authors of the manuscript, ML Brennan, RS Dean, M Duz and NC Finch.

3.2 Introduction

When cats are diagnosed with CKD, their owners and veterinary surgeons have important decisions to make about which treatments to administer. Further decision making is required as CKD progresses. Internationally recognised guidelines published by the International Renal Interest Society (www.iris-kidney.com) can help to support treatment decisions. However, no consensus has been reached to date on which parameters would give the most useful information to aid the decision-making process. Published clinical trials

often use several parameters to diagnose CKD and monitor its progression (chapter 2), but different parameters are used in different studies and information on all parameters is not available for all tested treatment options. This limits the evidence available to inform decision-making and highlights the need for consensus on best practice.

It is imperative that in determining the most effective treatment and management strategies for a particular disease, the most relevant outcomes that matter to patients, clinicians and clients need to be measured during veterinary clinical trials. A Core Outcome Set (COS) can be defined as an agreed set of outcomes or outcome measures that should be measured and reported as a minimum in any trial conducted relating to a particular disease (www.comet-initiative.org). This concept originated in human healthcare and has been used most notably in rheumatoid arthritis studies, with a COS originating from the Outcome Measures for Rheumatology Clinical Trials (OMERACT) initiative (Tugwell et al., 2007). Since this COS was created, the consistency of measurement of the core outcomes proposed has been shown to improve (Kirkham et al., 2013). It is well established in human healthcare that without COSs, the outcomes reported in trials may not be reflective of endpoints that are meaningful for health service users (Williamson et al., 2012). Additionally, the use of high quality COSs is increasingly mandated by research funders and journal editors (Webbe et al., 2018). The Core Outcome Measures in Effectiveness Trials (COMET) Initiative was created to foster methodological research, to bring researchers together, develop resources, improve user engagement and raise awareness of COSs. An internet-based resource has been created where all existing COSs and those under development can be registered (Williamson et al., 2012). The creation and use of COSs permits the robust comparison of results between studies, facilitating evidence-based clinical decision-making (Clarke & Williamson, 2016), and reducing unnecessary research waste (Hughes et al., 2019b).

The Delphi process is frequently used in the development of COSs (Kottner et al., 2018). The Delphi process is a recognised and structured methodology for gathering opinions from experts and stakeholders that facilitates convergence of opinion (agreement) on decision-making on a particular topic (Williamson et al., 2017). An eDelphi is an online electronic form of a Delphi process and is typically carried out using questionnaires or email (D. A. Hall et al., 2018). Information or questions are presented in a number of questionnaire rounds or

via email to an anonymous panel (Okoli & Pawlowski, 2004). Initially the panel gives their answers independently. In subsequent rounds they are presented with the anonymised answers from the rest of the group and are allowed to change their own answers in light of that information (Barrios et al., 2021; Williamson et al., 2017). This method helps to create a group consensus of opinion, without allowing any individuals to dominate or influence the decision-making process (Sinha et al., 2011) . It is recommended that a consensus meeting follows an eDelphi process, where the results are confirmed, clarified and streamlined, and any misunderstandings or disagreements in the group consensus are addressed in a chaired, structured way (Williamson et al., 2017).

Prior to this study, the only veterinary COS identified in the peer reviewed literature was COSCAD'18, published in 2018 and related to canine atopic dermatitis (Olivry et al., 2018).This COS contained three outcomes: veterinary assessment of skin lesions, owner assessment of pruritis and owner reported global assessment of treatment efficacy (Olivry et al., 2018) . Since publication it has been used either completely or in part, in trials for: immunoglobin reactivity to food antigens (Pucheu-Haston & Mougeot, 2020), hydrolysed protein diet (Weemhoff et al., 2021) and use of prednisolone therapy as an adjunct to reducing oclacitinib dose frequency (Olivry et al., 2022) . There is no evidence in the peer reviewed literature of any COSs being created for the feline species.

3.3 Aim

The original aim of this study was to create a core set of outcomes for feline CKD treatment efficacy. The scope of this COS aimed to cover domestic cats with naturally occurring CKD at any stage of disease progression, for all treatment and management interventions including therapeutics, nutraceuticals and special diets. The original aim of this work was to create a COS suitable for trials research, for measuring and reporting in all future feline CKD treatment efficacy trials.

The objectives of this study were to:

1. Use the results from the outcomes systematic review (chapter 2) to build an eDelphi to prioritise the most important outcomes. Decide upon percentage agreement required for consensus and inclusion in the final core outcome set.
2. Source and invite a balanced panel of stakeholders to complete the eDelphi.
3. Run an in-person consensus meeting for the stakeholders to finalise the core set and resolve any misunderstanding or disagreements in the scoring of the outcomes into or out of the final core set
4. Present the core outcome set

3.4 Materials and methods

3.4.1 Systematic literature review

In April 2018, a systematic literature review was conducted, focused on identifying all parameters that had been measured and reported in published randomised controlled trials relating to CKD treatments (chapter 2). There were 20 publications which met the inclusion and exclusion criteria for the review. From these, 103 individual parameters were extracted that had been assessed in treatment efficacy trials for CKD. A table of these outcomes is shown in Appendix 2. The parameters were then arranged into groups according to when and how each parameter might be measured. These groups were: parameters the cats' owner might notice at home (e.g. exercise tolerance), parameters examined in the veterinary consultation (e.g. body condition score), urine parameters (e.g. urine specific gravity), parameters related to CKD progression and lifespan (e.g. survival time), parameters related to being in a trial (e.g. occurrence of adverse events), blood test parameters (e.g. Packed Cell Volume) and more advanced testing (e.g. Plasma Renin Activity).

3.4.2 eDelphi process

The eDelphi was designed to build consensus on the most important parameters to measure when treating cats with CKD. The process used three iterative rounds of online questionnaires. The rounds were completed anonymously by an international panel of stakeholders, who represented a number of different types of decision maker involved in the treatment, management and care of cats with CKD (Table 1). All of the questionnaires in the first 2 rounds were carried out using Online Surveys (https://www.onlinesurveys.ac.uk, Jisc, Bristol, UK) and all data was password protected. Only HD and MB had access to the Online Surveys dashboard.

3.4.3 Questionnaire development

The first round contained two questionnaires, the second round contained one questionnaire (third questionnaire), and the third round (fourth questionnaire) consisted of individually created word documents (Figure 3.1). The four questionnaires used in the eDelphi were piloted by members of the Centre for Evidence-based Veterinary Medicine (CEVM) research group before they were used in the study.

The parameters extracted from the systematic review were divided between the first two questionnaires (round 1 of the eDelphi). These were presented to the panel, arranged in the groups as described. The definition of a COS was explained. Panellists were asked to consider each parameter individually and rate the importance of including the parameter in the COS using a Likert scale (1-9; 1 being not important, to 9 being very important to include). Alternatively, instead of giving a rating they could also choose “I do not understand what this parameter is” or “I do not understand the importance of this parameter”. Consensus for a parameter to be included in the COS was defined a priori as 80% of participants rating the parameter as 8 or 9. Consensus for exclusion from the COS was defined as 80% of panellists rating a parameter as 1, 2 or 3. It was defined in the study protocol that where greater than 10% of panellists or a whole stakeholder group answered “I do not understand what this is” for a parameter, additional definitions would be given, and the parameter re-presented to panellists for re-rating. In round 1 of the eDelphi, panellists were encouraged to suggest new parameters they felt had not already been

presented to them during the eDelphi process. Questionnaire 1, round 1 can be seen in Appendix 3.

In round 2 (questionnaire 3), the panellists were presented with two sets of parameters to rate. The first set were new parameters suggested by panellists in round 1. The second set were parameters which more than 10% of panellists in round 1 said they did not understand, with new definitions given to enhance understanding.

In round 3 (questionnaire 4) the panellists were given the anonymised results from the whole panel's ratings (median and range) from the previous two rounds, alongside the rating they had each given to the parameters. This information was presented in a table in a Microsoft Word (Microsoft 365) document and the final column of the table allowed them to either select a new rating for each parameter or choose to keep their rating the same (Appendix 4). Any parameters which had already reached the consensus threshold for inclusion or exclusion from the COS were not reconsidered at this stage. The tables were created individually for each panellist and returned by email directly to the first author's password protected email account.

All results from all three rounds (four questionnaires) of the eDelphi were processed using Microsoft Excel (Microsoft 365). After all rounds were completed, all parameters had been rated by all panellists twice and a shortlist of parameters proposed for the final COS created.

3.4.3.1 The eDelphi panel structure:

The panel was structured to represent an international group of experts, reflecting the important stakeholders in decision making for cats with CKD. The stakeholder groups included in the panel when it was designed were: clinical representatives (first opinion vets, researcher vets, referral vets, industry representatives, veterinary nurses and clinical pathologists), journal editors, regulatory agency representatives and cat owners with

experience of CKD. More detail on the selection criteria for panellists in each group is shown in Table 1.

Table 3.1 Selection criteria for each stakeholder group included in the eDelphi for creating a core outcome set for cats with chronic kidney disease

Stakeholder Group	Selection criteria
Cat owners	Either currently own a cat who has been diagnosed with CKD or have owned a cat within the past two years who had been diagnosed with CKD.
First opinion vets	Vets working in first opinion veterinary practice, either small animal/ mixed or cat only practice. Not seeing cases at a referral level. Must be seeing cats with CKD.
Researcher vets	Researching cats with CKD or seeing referral patient cats with CKD.
Industry	Must be working for a company making either special diets or pharmaceuticals or nutraceuticals for the treatment and management of CKD in cats and working directly with those products. One representative per company involved.
Veterinary nurses	Working as a veterinary nurse in either first opinion or referral practice and caring for cats with CKD.
Clinical pathologists	Work must involve pathology of CKD in cats in some form.
Regulatory agencies	Working for the VMD or RCVS.
Journal editors	Currently working in an editorial role for a journal which publishes research on feline medicine and feline research.

VMD = Veterinary Medicines Directorate; RCVS = Royal College of Veterinary Surgeons

3.4.3.2 Recruitment:

The study was advertised via posts on the Facebook and Twitter accounts of HD and the CEVM. It was also advertised on a dedicated research page on the CEVM website and within veterinary specific Facebook forums via HD. In addition, feed and pharmaceutical companies making treatments or diets for cats with CKD were emailed and invited directly, either via known contacts within the company or via the companies' general enquiries email address. Journal editors from journals publishing research on feline medicine, and the Veterinary Medicines Directorate (VMD, who assure the safety, quality and efficacy of veterinary medicines in the UK) and the Royal College of Veterinary Surgeons (RCVS, who regulate the educational, professional and ethical standards of veterinary surgeons) were invited in the same way (either known contacts or via general email addresses). Known contacts of the authors, who were working in the treatment or management of feline CKD were also invited by direct email. The study was also advertised during a PhD researchers' presentation day at the University of Nottingham. Prospective panellists registered an interest in taking part by completing a short questionnaire on Online Surveys (https://www.onlinesurveys.ac.uk, Jisc, Bristol, UK), designed to ascertain personal experience of owning cats with CKD, their qualifications, job role and which stakeholder group they belonged to.

eDelphi panel selection process:

For the stakeholder groups where the number registered as interested exceeded the number required, the panel was purposefully selected from all those registered by discussion among members of the research team. The aim was to ensure that the invited panellists would be as international as possible, with the widest possible variety in: country of origin, date and country of veterinary degree graduation, and role working with cats with CKD. The names of registered panellists were available to the whole research team at this stage only, to aid with selection of the most appropriate panellists for each group. Veterinary surgeons were selected to ensure included individuals graduated from a range of universities across a number of years. The balance of stakeholder group proportions was decided in advance to be as close as possible to that used in the HOME group methodology study (Schmitt et al., 2011). In the HOME study, 25% of the whole panel were patients, 60% were clinical representatives and 15% were a combination of journal editors and regulatory

agency representatives. In this study, the only way a parameter could reach consensus for inclusion without all stakeholder groups being in agreement, was if the majority of the owners and the clinical representatives rated it at 8 or 9 on the Likert scale. It was thought that if this happened, the parameter would be important enough for inclusion, without needing agreement from journal editors and regulatory agencies. Otherwise, agreement was needed from all stakeholder groups for the 80% threshold to be reached for each parameter.

3.4.3.3 Administering the questionnaires:

Personalised email links to each questionnaire were sent out using Online Surveys (https://www.onlinesurveys.ac.uk, Jisc, Bristol, UK). Each panellist was assigned a code number and letter, for example "O4" for owner number 4, so that their responses and stakeholder group could be tracked anonymously through the results. These codes were automatically captured by the online surveys site when a questionnaire was filled in. All questionnaires were otherwise filled in anonymously. Only HD had access to the list of names and codes, and this information was password protected. If panellists failed to complete a questionnaire they were not included in subsequent rounds of questionnaires as the results of the eDelphi were cumulative. Reminder emails were sent to all panellists at regular intervals for each questionnaire, and panellists were encouraged to ask for more time to complete the questionnaires if required.

3.4.4 Consensus meeting

After the eDelphi was completed, a one day in-person consensus meeting was held to finalise the COS. This had two purposes; to address borderline parameters and to streamline the final COS.

3.4.4.1 Borderline parameters

These were defined as parameters that had been the closest to reaching the 80% consensus threshold for inclusion in the eDelphi but had not passed the threshold. Stakeholder responses to the eDelphi for the borderline parameters were separated into cat owner responses and Healthcare Professional (HCP) responses. HCPs in the context of this study were defined as all panellists who were not in the cat owner group. This was to mirror methods from a human healthcare COSs, where patient responses were compared to HCP responses (Harman et al., 2015) and advised by discussions with an experienced COS consensus meeting facilitator. The purpose of the consensus meeting was then to clarify and reach agreement on the ratings for parameters over which there has been the greatest disagreement in ratings between stakeholder groups in the eDelphi rounds (Thorlacius et al., 2018). The meeting was designed to ensure that both patients and HCPs fully understood the definitions of each parameter and had the opportunity to understand and appreciate each other's perspectives. This meant the final whole group ratings on each parameter reflected a shared agreement, borne out of mutual understanding.

Identifying the borderline parameters for which there was the greatest disagreement between groups was carried out using two different approaches. Firstly, by extracting the parameters with the highest percentages of the whole panel rating them as 8 or 9 (excluding those which had already reached the inclusion threshold). The second approach examined the percentages of owners and HCPs who had rated each parameter 8 or 9, and the difference between the two groups. Those where it appeared there had been the greatest disparity between the two groups ratings were targeted for discussion. For example, parameters where over 80% of HCPs had rated it as 8 or 9, but only 50% of owners had rated it as 8 or 9.

Within the consensus meeting parameters were fully discussed, defined and re-rated so that the interests and priorities of both groups could be understood by the whole panel, with the final rating fully representing the true agreement of the whole panel. Borderline parameters were shown to all panellists one by one during the meeting and were discussed. They were then re-rated anonymously and individually by all panellists. Consensus for inclusion in the final COS after discussion and re-rating was pre-defined as over 80% of the whole group of panellists rating the parameter as 8 or 9 on a Likert scale (1-9; 1 being not important, to 9

being very important to include). Consensus for exclusion from the final COS was pre-defined as over 80% of panellists as a whole group rating the parameter as 1, 2 or 3 on the Likert scale.

3.4.4.2 Streamlining the COS

In the second phase of the consensus meeting, the original COS shortlist from the eDelphi, and any parameters voted in after the additional borderline parameters had been discussed, were presented to the panellists as a list. A session of chaired discussion and voting was planned to streamline the parameters into a more manageable list by grouping them into body systems or similar categorisations. This aimed to make the final COS as straightforward to use and understand as possible.

3.4.4.3 Recruitment and selection criteria

The aim for the consensus meeting was to include an international panel of stakeholders, representing the same stakeholder groups as in the eDelphi. The requirements for each stakeholder group (Table 1) remained the same. All stakeholders who took part in the eDelphi and all those who had initially registered an interest in participating in the study were invited to participate in the consensus meeting. Some potential dates were circulated to check availability. If a panellist was unable to attend, they were asked if they could recommend a colleague so that the research team could directly invite them to the meeting. Where additional panellists were needed, suitable contacts who met the selection criteria and were known to the authors were invited. The aim was to achieve an equal number of owners and HCPs for the consensus meeting panel, so that discussions and ratings resulting from the meeting would be as balanced as possible.

3.4.4.4 Pre-meeting preparation

Panellists were provided with a list of the borderline parameters from the eDelphi in advance prior to the discussion. This included the anonymous ratings of owners, Healthcare Professionals (HCPs) and the whole group. They were also provided with a definition of a

COS and an agenda for the day. All pre-meeting paperwork provided can be seen in Appendix 5 and 6). They were asked to think in advance about their opinion on the inclusion of each of the parameters in the COS, and whether there was anything about each parameter that they did not understand. They were also asked to consider how they might streamline the list of outcomes.

3.4.4.5 Meeting logistics

The meeting was held at a central location (a hotel by Birmingham International airport) with good transport links, in July 2019. Travel, food and accommodation costs (where required) were paid by the research team to facilitate attendance. The meeting was in-person without options to join remotely. Both phases of the consensus meeting were attended by the same group of panellists. The meeting was chaired by an impartial chair, experienced in chairing consensus meetings for human healthcare COSs. The cat owners were invited to a separate meeting on the same day at an earlier time, to introduce themselves to each other and the chair. They were given the opportunity to ask questions and the importance of their role was explained. This was done to mirror the pre-meetings seen for patients in development of humans COSs. These are thought to help the patients to bond as a group and empower them to contribute to discussions in the main meeting.

At the start of the main meeting, everyone (panellists, chair and the study team) introduced themselves to each other. They explained their experience of owning or working with cats with CKD, the eDelphi stakeholder group they had represented (if applicable, some panellists joined the process at the consensus meeting stage but had not taken part in the eDelphi), and the consensus meeting group they represented (owner or HCP). A short presentation outlining the aims of the study, the eDelphi results, and the aims of the consensus meeting was given. The panel were also shown a video from the Core Outcome Measures in Effectiveness Trials (COMET) Initiative explaining the purpose of COSs.

When rating was carried out it was done anonymously using the online interactive presentation software Mentimeter (www.mentimeter.com). Panellists anonymously rated the parameters online when directed to do so by the chair. They either used their own tablet or smartphone device, or used one provided to them by the research team on the day. The software identified each panellist's response as an owner or HCP. After each parameter had been voted on, the results of the vote were displayed graphically on a projector screen. Throughout the meeting, the research team assisted with the presentations, note taking, photographic documentation of the day, technical support and one team member assisted a partially sighted panel member to participate in the voting process. The partially sighted panel member was provided with all documentation in Braille on the day of the meeting (and electronically to read with a screen-reader in advance of the meeting) and was given assistance with the voting process.

Consent

Each panellist on the eDelphi specifically consented to participate during the first questionnaire. Each panellist in the consensus meeting gave their written consent to participate. All panellists were advised that their responses would be confidential and anonymous, and that participation was voluntary.

The protocol for this study was not published in advance of the study being conducted.

3.5 Results

Figure 3.1 demonstrates progression during the study from lists of outcomes generated during the systematic review, to the final COS. It shows the number of parameters included and excluded at each round of the eDelphi and consensus meeting process. The number of panellists completing the work at each stage is also given.

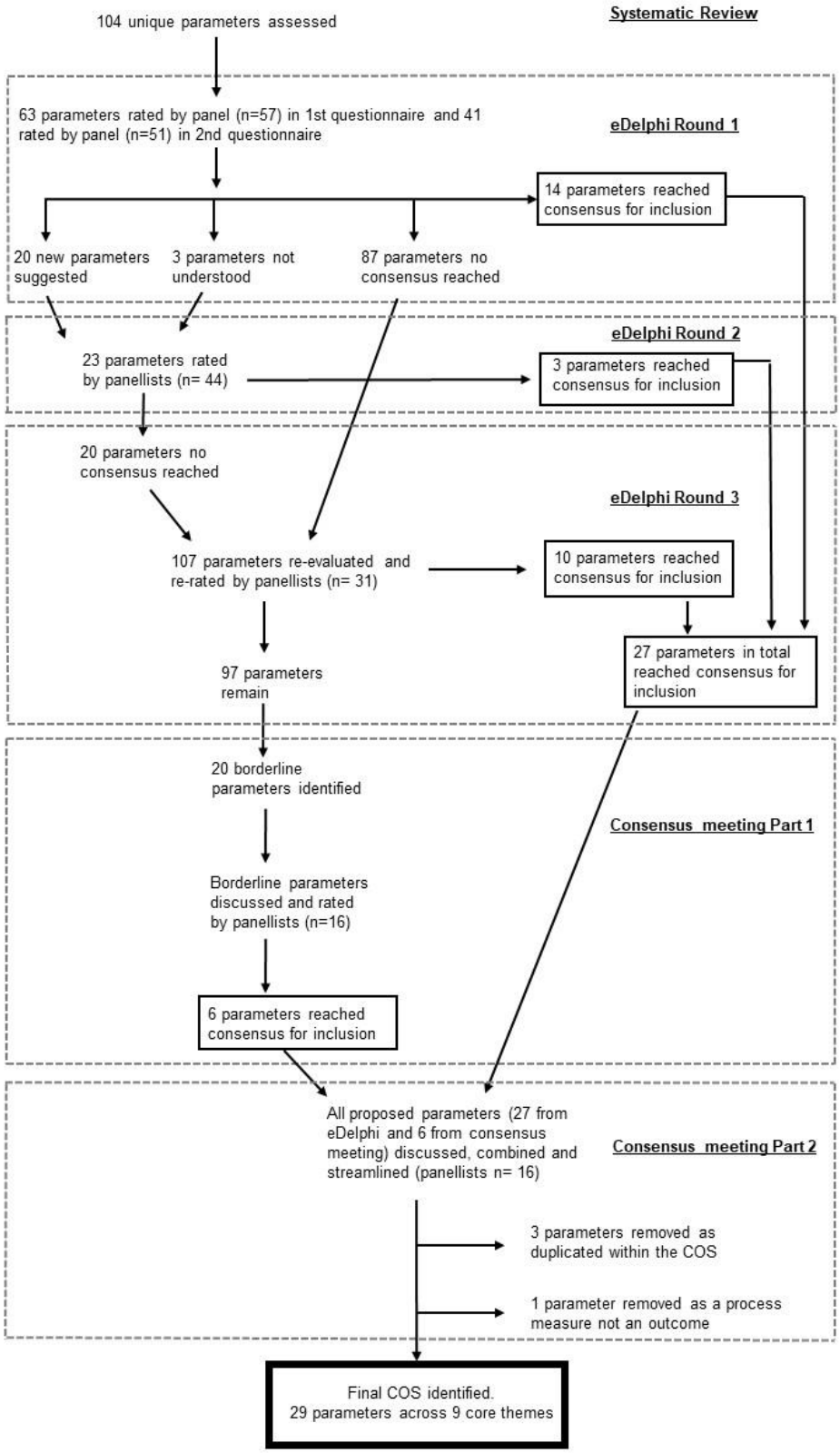


Figure 3.1 Developing a core outcome set: flowchart from parameters extracted in the systematic review of chronic kidney disease treatment efficacy to the final core outcome set, showing how many parameters removed at each stage of the process.

3.5.1 eDelphi

Two hundred and nine people registered an interest in joining the study panel via the short questionnaire. Of these, 147 were UK based, and 62 were from outside the UK, based in: Ireland, USA, Canada, Portugal, Netherlands, Spain, France, Denmark, Sweden, Switzerland, Japan, Australia and New Zealand. The smallest groups to register an interest in participating were the stakeholder groups "Regulatory Agencies" and "Journal Editors". For these groups combined, 11 people registered an interest in participating in the study. The planned size of these stakeholder groups jointly was 15% of the final panel size. The resulting final panel was 73 people (where 11 people = 15% of panel size). The breakdown of panel numbers can be seen in Table 2. The predefined characteristics for each group were also fulfilled (Table 1). However, full equality across all these categories was not possible due to the spectrum of applications received from prospective panellists.

Table 3.2 The eDelphi panel which was selected to participate in creating the core outcome set, showing the sizes of each stakeholder group and the selection criteria.

Stakeholder group (percentage of total panel size)	**Number of panellists in each group**	**Detail on selection criteria for stakeholders**
Cat owners (25%)	18	Either currently own a cat who has been diagnosed with CKD, or have owned a cat within the past two years who has been diagnosed with CKD.
Clinical representatives (60%)	14	Vets working in first opinion veterinary practice

	14	Researchers or vets with additional qualifications
	10	Pharmaceutical and food industry representatives
	4	Veterinary nurses
	2	Clinical pathologists
Regulatory Agencies (7%)	5	Working for the VMD or RCVS
Journal Editors (8%)	6	Currently working in an editorial role for a journal which publishes research on feline medicine and feline research

For the eDelphi panellists, their history of owning cats with CKD, and the year and country of their veterinary degree qualification can be seen in Table 3. In addition to the cat owners, some panellists from each stakeholder group had experience of cat ownership. However,many panellists had not owned cats with CKD. The geographical origin of the eDelphi panellists is further detailed in Table 4.

Table 3.3 The eDelphi panel for the core outcome set, showing their experience of owning cats with CKD and (for veterinary graduates) the year and location of their veterinary degree qualification.

Stakeholder group (number of panellists)	**Experience of owning a cat with CKD**				**Year of Graduation from Veterinary Degree**					**Veterinary Degree graduation location**			
	Currently own a cat with CKD	Within previous 2 years	Prior to the previous 2 years	Never	1970-1979	1980-1989	1990-1999	2000-2009	2010-2019	UK	Europe	International	Not a veterinary graduate
Owners (18)	12	6	0	0									
Vets working in first opinion practice (14)	2	1	3	8	0	1	5	3	5	7	4	3	
Industry (10)	1	1	2	6	0	2	0	6	2	6	2	2	
Researcher vets (14)	3	5	2	4	0	2	3	5	3	8	2	3	1
Vet nurses (all either Level 3	1	2	0	1									

Diploma or Uni degree) (4)													
Clinical pathologists (2)	0	0	1	1	0	0	1	0	1	0	1	1	
Regulatory agencies (5)	0	0	0	5	1	0	0	4	0	3	0	2	
Journal editors (6)	1	0	3	2	0	3	2	0	0	3	0	2	1

Table 3.4 Country of origin of all eDelphi panellists for creating the core outcome set, divided by stakeholder group.

Stakeholder group	UK	Isle of Man	Ireland	USA	Canada	Netherlands	France	Spain	Portugal	Switzerland	Australia	Russia
Owners	9	1	1	5	1	1						
Vets working in first opinion practice	10				2				1		1	
Industry	5			1			1	1		2		
Researcher vets	10			2					1			1
Veterinary nurses and Clinical pathologists	5										1	
Regulatory agencies	5											
Journal editors	4			1	1							

In the first two questionnaires (round 1), the 103 parameters identified from the systematic review were presented to the panellists for rating for the first time. The first questionnaire was completed by 57/73 panellists and the second questionnaire by 51/57 panellists (Table 5). After these two questionnaires were completed, 14 parameters had reached consensus for inclusion in the COS (Table 6), and no parameters had reached consensus for exclusion from the COS.

Table 3.5 Number of panellists in each stakeholder group who completed each round of the eDelphi.

eDelphi round number		**1**		**2**	**3**
Stakeholder group	Invited to join eDelphi panel	Questionnaire 1	Questionnaire 2	Questionnaire 3	Questionnaire 4
Cat owners	18	15	13	1	7
Vets in first opinion practice	14	11	8	7	1
Industry represent-tatives	10	9	8	7	6
Vets working in research	14	11	11	11	11
Qualified veterinary nurses	4	1	1	1	1
Clinical pathologists	2	2	2	2	0
Regulatory agencies	5	4	4	3	2
Journal editors	6	4	4	3	3
Total	73	57	51	44	31

Table 3.6 Following the first two questionnaires (round 1) of the eDelphi, these parameters had reached consensus for inclusion in the core outcome set. Questionnaire 1 completed by 57 panellists and questionnaire 2 completed by 51 panellists.

Parameter	**Percentage of panellists rating the parameter 8 or 9**
Urine protein: creatinine ratio	94.7
Creatinine	94.4
Phosphate	92.6
Urea	92.6
Quality of life	91.2
Urine specific gravity	89.5
End point for renal survival	86.0
Blood pressure	85.2
Biochemistry	85.1
Full clinical examination	84.2
Body condition score	84.2
IRIS stage/ stage of disease	82.5
Survival time	82.5
Packed Cell Volume (PCV)	81.5

In the third questionnaire, the 20 new parameters that had been proposed by panellists (Appendix 2) were presented for rating, alongside the parameters which greater than 10% of panellists nominated that they did not understand (n=3 parameters). Further definitions were provided alongside the three "not understood" parameters. These three parameters were: semi quantitative urine albumin ELISA, fractional excretion of phosphorus in the urine

and C-TEA clearance as a measure of effective renal plasma flow. None of these three parameters reached consensus for inclusion in the COS later in the study. This questionnaire was completed by 44/57 panellists (Table 5). After the third questionnaire, 3 additional parameters had reached consensus for inclusion in the COS; hydration status, pain and discomfort, symmetric dimethylarginine (SDMA).

The fourth questionnaire was sent to the 44 panellists who completed the third questionnaire. The fourth questionnaire was completed by 31/44 panellists (Table 5). After the fourth questionnaire was completed, 10 additional parameters had reached consensus for inclusion in the COS; occurrence of adverse events, overall assessment of efficacy, owner not giving the treatments to the cat, time enrolled in study, cause of death, haematocrit, progression of renal dysfunction, appetite for food, muscle condition score, and protein in urine.

Over all three rounds and four questionnaires in the eDelphi, proportionally more panellists were lost from the cat owner and first opinion vets groups than in the other stakeholder groups (Table 5). From the cat owner group, between two and three panellists failed to complete every questionnaire, so that the 4th questionnaire was completed by 7/18 panellists (39%). From the vets in first opinion practice group, between one and three panellists failed to complete every questionnaire, until the 3rd round (4th questionnaire) where six panellists did not complete the questionnaire. Out of the 14 vets in this stakeholder group, only 1 (7%) remained by the end of the eDelphi. The highest completion rates throughout the eDelphi were seen in researcher vets (79%, n=11/14) and industry (60%, n=6/10) (Table 5).

After the three rounds of eDelphi had been completed, 27 parameters were proposed for inclusion in the COS, 20 were considered borderline and none had been excluded.

3.5.2 Consensus Meeting

The consensus meeting was held in Birmingham, England in July 2019 and attended by an international group of 16 individuals, representing all eDelphi stakeholder groups except journal editors. From all invitations sent, 21 registered to attend the meeting. However, five were unable to attend on the day due to illness, travel issues or for personal reasons. The numbers of owners and HCPs who attended the meeting were well balanced (nine owners and twelve HCPs), with nearly all stakeholder groups represented.

Of the 16 meeting panellists in attendance; six were cat owners, of whom four currently owned a cat with CKD and two had owned a cat with CKD in the previous two years. Two of the owners had formed part of the eDelphi panel and four were new to the process at the consensus meeting stage. Three came from the UK, one from Ireland and two from the USA. The other 10 attendees were all HCPs, of which 9 came from the UK and 1 from Canada. Five had taken part in the eDelphi process (one from industry, three vet researchers and one from regulatory agencies) and five were new to the process at the consensus meeting stage (one first opinion veterinary surgeon, two from industry, one veterinary nurse and one from regulatory agencies). Of the nine with veterinary degrees, all graduation dates were within the last 10-30 years, predominantly from UK universities, however three were from international universities.

Of the five panellists unable to attend (all from the UK), three were cat owners, two of whom had been involved in the eDelphi. There was one industry representative who was new to the study process, and one first opinion veterinary surgeon who had already been involved in the eDelphi.

3.5.2.1 Borderline parameters

Twenty borderline parameters were identified for discussion prior to the meeting and can be seen in Table 7 alongside the meeting outcome for each parameter, following group discussion and rating. Once all 20 had been discussed and rated independently by the panel, a further six parameters had reached the definition of consensus for inclusion in the COS (complete blood count, bodyweight, change in demeanour, haemoglobin, potassium, overall

amount of food eaten) and five parameters had been excluded (thirst, overall history, palpable size of kidneys, drinking behaviour, erythrocyte count). Of the remaining 9/20 parameters, one (difficulty administering/ giving treatment to the cat) was discounted as it was decided by consensus to categorise it as a "process measure" rather than a true outcome. It was acknowledged that being unable to give a treatment may lead to a full or partial treatment failure. However, it was recognised that this was not a reflection on the efficacy of the treatment alone, and more about the process of administering the treatment. Two parameters were not voted on because after group discussion, it was decided that these duplicated parameters already included in the proposed COS (phosphorus, wellbeing). The final six parameters (constipation, H inulin clearance, ocular funduscopic examination, decrease in creatinine clearance, weakness, mentation) were discussed but not voted on as it was agreed they would not add to or improve the content of the final COS by being included as additional separate parameters. However, mentation was included in the final COS as an aspect of demeanour, and wellbeing was included as part of a quality of life assessment.

Table 3.7 Parameters defined as 'borderline' for inclusion after the eDelphi stage was completed, which were then discussed and rated in the consensus meeting stage of the core outcome set development process.

	Percentage of each stakeholder group who rated the parameter 8 or 9 on a Likert scale 1-9.			
Borderline parameter	**Whole eDelphi Panel (n=31)**	**Owners in eDelphi (n=7)**	**Healthcare Professionals (HCPs) in eDelphi (n=24)**	**Consensus Meeting Results: Overall % of panellists rating the parameter 8 or 9 on a Likert scale 1-9, (n = 16)**
Complete blood count	77.4	57.1	87.5	93.7
Bodyweight	77.4	71.4	83.3	100
Phosphorus	77.4	85.7	79.2	Not voted
Change in demeanour	77.4	85.7	79.2	87.5
Thirst	77.4	100	75	12.5
Wellbeing	74.2	85.7	75	Not voted
Haemoglobin	74.2	85.7	75	93.7
Overall history	74.2	85.7	70.8	12.5
Erythrocyte count	74.2	57.1	79.2	6.25
Difficulty administering/ giving treatments to cat	74.2	71.4	79.2	Not voted

Potassium	71	71.4	75	81.2
Overall amount of food eaten	71	71.4	75	87.5
Mentation	67.7	42.9	79.2	Not voted
Drinking behaviour	64.5	85.7	62.5	18.7
Ocular funduscopic examination	61.3	28.6	75	Not voted
Palpable size of kidneys	54.8	100	45.8	0
Weakness	38.7	71.4	33.3	Not voted
Constipation	32.3	71.4	16.7	Not voted
Decrease in creatinine clearance	32.3	71.4	25	Not voted
H inulin clearance	29	71.4	20.8	Not voted

Not voted = these parameters were discussed but not voted on by themselves as it was decided they would not add to the content of the final COS.

3.5.2.2 Streamlining the COS

The six parameters proposed for inclusion during the consensus meeting were discussed alongside the 27 parameters that reached inclusion as a result of the eDelphi process (33 in total). The use of flipcharts and lists created by the study team during the course of the meeting helped as a visual aid during the streamlining process. Phosphate from the eDelphi results list was replaced by phosphorus from the borderline parameters as it was felt that this was more biologically appropriate. Three parameters were then removed from the shortlist of 33 parameters as it was felt that what they represented was already addressed

by other parameters within the COS list. These were: progression of renal dysfunction, time enrolled in study, urine protein. One parameter (overall assessment of efficacy) was removed from the list as it was decided to be more of a measure of the process of the study, than a true outcome. This left a final agreed shortlist of 29 parameters, which were streamlined into main outcome areas. When this study was published, the final COS was presented as discussed in the consensus meeting, by streamlining into 9 main outcome areas, these are shown by * in Figure 2. However, here the parameters are regrouped by type to show when and where they might be assessed, and which parameters relate to similar areas. The groups “in the consultation” and “blood and urine tests” are likely to be assessed at the veterinary clinic during consultation and testing, the group “living with CKD” contains many parameters which will be observed by the cats owner, over periods of time at home. The group “CKD progression” contains more complex parameters, likely to be reached in discussion with owners and veterinary professionals, with some testing potentially required on some parameters.

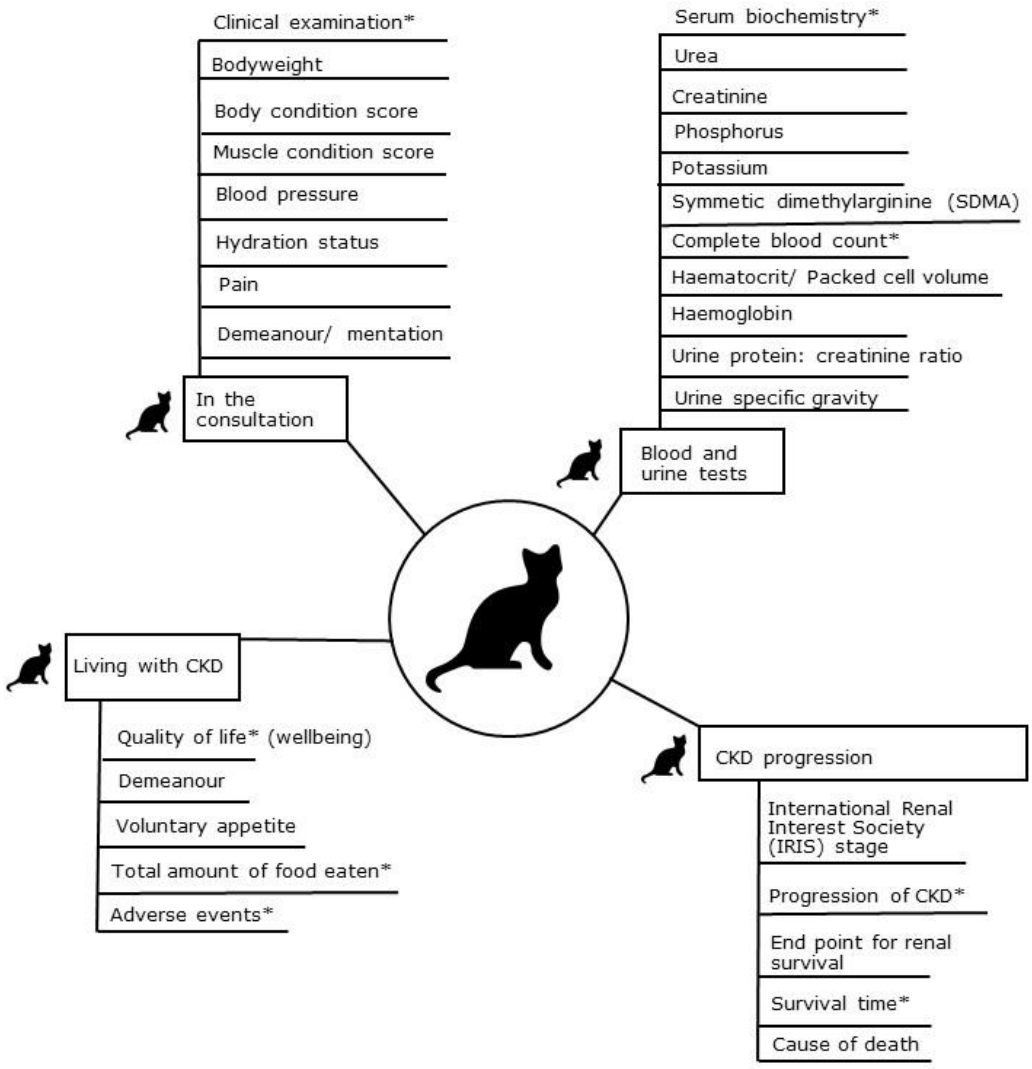


*Figure 3.2 Final proposed core outcome set for feline chronic kidney disease trials (*denotes which outcomes were considered core outcome groups by the consensus meeting, e.g. core outcome survival time, to include cause of death)*

Table 3.8 Final results for all parameters which were included in the final core set after reached the 80%, listed in descending order for percentage of panel rating it 8 or 9 on the Likert scale.

Parameter	**Stage at which parameter reached consensus for inclusion in the COS**	**Percentage of whole panel rating the parameter 8 or 9 on a Likert scale 1-9**
Bodyweight	Consensus meeting	100
Urine protein: creatinine ratio	eDelphi	94.7

Creatinine	eDelphi	94.4
Complete blood count	Consensus meeting	93.7
Haemoglobin	Consensus meeting	93.7
Adverse events	eDelphi	93.5
Urea	eDelphi	92.6
Phosphate	eDelphi	92.6
Quality of life (wellbeing)	eDelphi (eDelphi)	91.2 (74.2)
Urine specific gravity	eDelphi	89.5
Demeanour (mentation)	Consensus meeting (eDelphi)	87.5 (67)
Demeanour	Consensus meeting	87.5
Overall/ total amount of food eaten	Consensus meeting	87.5
Cause of death	eDelphi	87
Haematocrit (Packed cell volume)	eDelphi	87.0 (81.5)
End point for renal survival	eDelphi	86
Blood pressure	eDelphi	85.2
Serum biochemistry	eDelphi	85.1
Clinical examination	eDelphi	84.2
Body condition score	eDelphi	84.2
Hydration status	eDelphi	84

Progression of CKD	eDelphi	83.9
International Renal Interest Society (IRIS) stage	eDelphi	82.5
Survival time	eDelphi	82.5
Pain (and discomfort)	eDelphi	81.8
Symmetric dimethylarginine (SDMA)	eDelphi	81.8
Potassium	Consensus meeting	81.2
Muscle condition score	eDelphi	80.6
Voluntary appetite	eDelphi	80.6

Table 3.7 explores how closely each parameter reaching the final COS passed the 80% threshold for inclusion in the COS. The table shows at which stage of the study each parameter was included, and the percentage of the whole panel rating it 8 or 9 at that time. The highest percentage of panellists rating a parameter for inclusion was reached by bodyweight, where 100% of the panel rated it important enough to include in the COS. The remainder of the top five ratings were for urine protein: creatinine ratio, serum creatinine, complete blood count and haemoglobin.

3.6 Discussion

3.6.1 Future potential of the core set of outcomes proposed by this study

This study aimed to create a COS for all future treatment efficacy trials for feline CKD, for therapeutics, nutraceuticals and special diets. The hope was that the final COS would be suitable for inclusion in all treatment trials.

This is the first COS to be attempted for the feline species and the second within for veterinary healthcare. It represents the views of stakeholders involved in decision-making regarding cats with CKD including owners and veterinary surgeons, veterinary nurses, clinical pathologists, researchers, industry and regulatory agency representatives.

Once consolidated, the COS will be valuable in the design and interpretation of future treatment efficacy or effectiveness trials for cats with CKD. It will have implications for veterinary clinical decision making as to which the most important indicators for monitoring disease progression may be. As the future COS becomes integrated into treatment trials, using the COS for monitoring patients in the veterinary clinic will allow comparison of patient outcomes to those published in the clinical trials, to see whether the patient's condition is progressing as expected. In addition, the COS both as it currently stands and in the future, represents consensus of opinion from all stakeholders including cat owners. Therefore, following the COS in treatment decision making and treatment success monitoring should ensure that the outcomes most important to cat owners are included. The COS could also be used to highlight the most important parameters to discuss with cat owners, and which they most easily can monitor at home, increasing the agency of owners in caring for their cats. Having clearly defined outcomes to monitor may also help vets and owners to know when treatment is not progressing as hoped and may help to shape discussions around palliative care or euthanasia. Overall, using the COS could help direct discussions in the veterinary consultation and ensure that the treatment outcome priorities of cat owners are reflected in the decisions taken, and the follow-up monitoring to those

decisions. This may improve shared decision making between cat owner and veterinary surgeons, and ultimately, treatment compliance.

In addition to using the COS in veterinary consultations, the COS will also be valuable for veterinary undergraduate and postgraduate education, and veterinary nurse education. The priorities of both veterinary surgeons and veterinary nurses were included in the development of this COS and it is hoped the final result will reflect the CKD treatment outcomes most important to both groups. The COS could be used to frame learning around the presentation, progression and monitoring of feline CKD patients, educational case discussions and as a framework for developing treatment and monitoring plans for these cats, both as inpatients and outpatients.

3.6.2 The relative size of the final core outcome set

All 29 currently included parameters are likely to be individually of importance to participants. The threshold definition for consensus for parameter inclusion used in this study was much higher than those used in human COS studies previously. It is also higher than the 70% threshold used in the only other existing veterinary COS, COSCAD'18 (Olivry et al., 2018) . A systematic review of Delphi methodology found the most common definition of consensus used was percentage agreement, and the median threshold to define consensus was identified as 75% of participants scoring an item 1, 2, 3 or 7, 8, 9 (Diamond et al., 2014). Some examples from human COS development include a recent COS from urology, where a cut-off of 75% or more of participants rating an outcome as critically important on a 9-point Likert scale, was used in developing a COS for haemodialysis therapy (Evangelidis et al., 2017). Additionally, in developing a COS for prostate cancer, effectiveness trials used a cut off of 70% of patients scoring the top two scores on a 9-point Likert scale (MacLennan et al., 2017). The higher threshold used in our study could translate to increased certainty that all parameters included in our COS are very important to the stakeholder groups represented on the panel. These panellists represent decision makers at

all levels of feline CKD diagnosis, treatment, and management and means that the outcomes included are of importance to a wide spectrum of stakeholders.

However, despite this, the size of the final COS reached in this study is large and compared to some COSs in human medicine, this COS may seem too large to be integrated fully into future treatment trials in its current size and form. This is due to the practicalities of trial design to run statistical tests on 29 outcomes, and the fact that measuring 29 outcomes for the COS may be too many to carry out and leave trial designers little or no capacity to include extra outcomes of their own interest. Some larger COS in human medicine have been published, for example SCORE-IT for type II diabetes (Harman et al., 2019). HD was invited to observe the consensus meeting stage of this study when learning about COS development. SCORE-IT contains 18 outcomes across five domains. It was published after the eDelphi in this PhD work had been completed and as the consensus meeting was being planned and carried out.

Following feedback from experienced COS developers, further reflections on this PhD work, and research which has been published since the study in this PhD chapter was carried out, several likely methodological causes for the size and content of the existing COS as it stands have been identified.

1. **Content: the current COS incorporates a mixture of 'domains' (the 'what to measure') e.g. progression of CKD and 'instruments' (the 'how to measure) e.g. urine protein creatinine ratio. Possible explanation: study design.**

   This has resulted from the way the study was designed as a mixture of domains and outcomes were included in the original eDelphi, as they were identified from the systematic review of treatment outcomes carried out. Future COS developers for veterinary healthcare should consider distinguishing between domains and outcomes at an early stage, ideally before conducting the eDelphi. The first rounds of COS development are intended to decide the 'what' to measure (Williamson et al., 2012), and a steering group of stakeholders representing all treatment decision makers could be used to filter out the what (domains) from the how (instruments)

and ensure that all were understood by all stakeholder types. The domains could then be presented to stakeholders for the eDelphi and consensus meeting processes. This would follow more closely methodology used in creating COSs for eczema (Schmitt et al., 2011). Alternatively, Harman et al. (2019) catergorised the outcomes they were preparing for inclusion in the eDelphi by grouping and categorising them according to taxonomy created by Dodd et al. (2018). Their steering group reviewed all outcomes prior to the eDelphi and refined the list according to perceived clinical importance and how often the outcome had been used. Outcomes were then described in plain language and those definitions reviewed before the eDelphi commenced. In future veterinary COS development, including additional pre-eDelphi processing, grouping, defining and filtering of outcomes could give a smaller, better understood and more relevant starting point. This would reduce the workload required by eDelphi participants and may lead to the final set being more coherently grouped, better filtered into 'domains' and 'instruments', and potentially smaller too.

Following establishment of consensus on the domains or outcome groups to use in future veterinary COSs, the COSMIN standards could be used to develop the recommended 'how to measure' (instruments) (Williamson et al., 2011). The resulting COS would likely contain a small number of domains with recommended instruments to assess each of them, and would be more feasible for inclusion in future clinical trials.

2. **Size: the current COS size is large. Possible explanations: study design.**

There are two possible explanations for this, both resulting from the study design. The first is that the COS is a direct result of how the study was designed. A large number of outcomes were included at the start of the eDelphi and so the resulting final group being also large is possibly unsurprising. Using a steering group to refine the size of the eDelphi input list (as described in point (1) above could help to address this.

The second reason also results from the study design. In developing this COS participants were asked to individually rank each outcome to decide it's importance and ensure that everything of importance was included. Outcomes were considered in isolation as to each's own importance and panellists were not encouraged to consider choosing e.g. their top three outcomes, nor were outcomes ranked against each other. Had the consensus meeting stage been designed for panellists to use the eDelphi as a starting point and then choose their top most important outcomes from there, consider the responses of others and refine those choices, a smaller final COS could have been proposed. In the final eDelphi round of developing a COS for human eczema, participants were asked which domains they recommended including into the final core set (Schmitt et al., 2011). If this additional stage had been incorporated into the COS for feline CKD, the final set may have been much smaller.

When the consensus meeting for this PhD work was planned, the experienced chair who facilitated the meeting advised that in their experience the consensus meeting stage would not be used to remove from the COS parameters already voted into the COS during the eDelphi, as the consensus meeting group are likely to be smaller and should not be allowed to overrule what has already been decided. However, had the consensus meeting also included questions on each participant's 'most important' outcomes from the included list, and had this been used to further refine the COS, similar to methodology by Schmitt et al. (2011), then the final COS may have been smaller and more practicable for use in future clinical trials.

3. **Size: the current COS is large, and content (domains and instruments). Possible explanation: what is known about existing feline CKD research.**

As already discussed, the relative size of this COS is large and it includes a mixture of domains and instruments. This may have resulted from the outcomes available from the systematic review for study input, which are a result of existing published feline CKD treatment research. Many of these outcomes may be more likely to be considered as instruments than outcomes. Prior to this PhD research there was no

consensus on important domains to assess in CKD treatment, and many publications reported treatment efficacy on granular individual parameter measurements which are less complex, for example: blood pressure, bodyweight, appetite, urine protein, or similar. These may be more reflective of 'instrument' type outcomes. 'Domain' type outcomes in existing published research include: progression of renal dysfunction and occurrence of adverse events. The study participants voted on inclusion of outcomes, and may have been influenced to include those outcomes already familiar to them from existing research, some of which may be due to familiarity from what they encounter in the existing published literature (creating a self-perpetuating cycle) and some due to known clinical or at-home care experiences of looking after these patients.

The concepts of domains and instruments are not familiar within veterinary research at present and it is perhaps unsurprising therefore that the study results include a mixture of both. Partly as a reflection of familiarity with current research and as a function of the mixed domains and instruments they were presented with for consideration.

3.6.3 Possible limitations in panel size and diversity, perceived understanding of included outcomes, and loss to follow-up

Although the eDelphi and consensus meeting methodologies are well recognised for enabling the achievement of group agreement, a COS can only ever represent the views of those who have participated in its creation. It is possible that the outcomes proposed in this study may have been slightly different if the balance of stakeholder groups had been different or if the number of panellists had been larger. However, there is no agreed best sample size for the Delphi technique. It is recognised that more members will increase the reliability of group judgements (Murphy et al., 1998), and a minimum of 7 respondents per stakeholder group is suggested to be large enough for a consensus process (Linstone, 1978). The stakeholder groups included in COSCAD'18 (Olivry et al., 2018) were similar to those in

the current study. However, the methodology in COSCAD'18 was different as no consensus meeting was included.

During the consensus meeting in the current study, the reasoning behind the inclusion of each parameter was discussed. However, this detail was not formally captured for understanding as part of this study. It is interesting that two parameters assessed in IRIS staging of cats with CKD, urine protein creatinine ratio and serum creatinine were within the top five most highly agreed upon parameters.. Whether owners rated certain parameters as important because they have been informed by their vets that they are important, from their own experiences of caring for patients with CKD, or because they have done their own research is not known. It is hard to capture where the concept of which parameters are important comes from and how those initial opinions are formed by participants prior to taking part in the study. It is likely that many of the parameters reaching consensus will have been discussed within veterinary consultations where CKD is being assessed and managed, and perhaps this association causes these parameters to be perceived as more important. Conversely, owners are likely to be the better advocate for which parameters are most important for a cat at home, and veterinary professionals may be influenced by their discussions within consultations with these owners.

The eDelphi included for all outcomes an option that the participants "did not understand the meaning of a parameter" or "the importance of a parameter". In addition, consensus meeting participants were encouraged to consider in advance if there were any parameters they did not understand, and during the consensus meeting there were discussions between participants as to each's understanding of the meaning and use of parameters. Despite these precautions being taken, it is possible that not all parameters were fully understood by all participants, particularly those without veterinary training.

Within the study as it was designed, each participant's understanding of the meaning of parameters was not tested, so it is not clear whether everyone answering the eDelphi had the same understanding of the meaning and significance of all parameters. Especially as some parameters included were very highly specialised to research studies and not tests with which owners or many practicing veterinary professionals would be familiar. This means that the final results may have been impacted, as there is a risk that not all

parameters were fully understood, or not understood to have the same meaning by all people, which may have led to hidden biases in the final set of included parameters.

This problem could be remedied in future veterinary COS development by changes to the early methodology of the study, with a steering group developed and utilised for creating definitions where required, prior to the eDelphi commencing.

Despite some loss to follow up, it is hoped that panel size remaining through all stages of COS development was sufficient. Although some panellists were lost from each stakeholder group, every group was still represented at all stages of this COS development, with the exception of the consensus meeting. No journal editors attended the meeting, despite a number of invitations being distributed. Proportionally the greatest number of panellists were lost from the groups: "vets in first opinion practice", where the greatest loss of panellists occurred between eDelphi rounds 2 and 3, and "owners" where there was a gradual loss of panellists from all stages, resulting in 61% of owner panellists lost by the 3rd round of the eDelphi. However, the greatest number of parameters reached consensus for inclusion during the first two questionnaires and the greatest losses in panel members happened after these questionnaires were completed. Therefore, any impact from this on the overall results should be minimal. In addition, being prescriptive in relation to the number of participants included from each stakeholder group in the design of the study enabled opinions from a broad base to be gathered and ensured that no one stakeholder group could dominate. Feedback from panellists who took part in the consensus meeting was very positive, they found the experience rewarding and interesting. Comments included the following:

- *"Thank you for the invitation to attend this meeting, it was an interesting and thought-provoking discussion - I look forward to seeing what the core outcome set is narrowed down to."*
- *"Thank you so much again for today – it was so interesting and I really enjoyed the whole day. I thought that (the facilitator) did a superb job of facilitating discussions, summarising viewpoints and guiding us all through everything. It was a real joy to be*

involved in this project and I am so pleased that I could attend. I am really looking forward to hearing about the next steps of the project…"

- *"Thank you again for organising this super interesting meeting!"*
- *"I just wanted to say thank you to everyone for making yesterday a very rewarding and interesting day. A real team effort and I for one feel I have learnt a great deal and feel very privileged to have been asked to take part. As always so much more I could have added but its only later when you have had time to digest."*
- *"Thanks for inviting us to be a part of your important work. We appreciate what you're doing."*
- *"Thank you so much for the invitation to the event today. It was very enjoyable and stimulating."*

The panels for both the eDelphi and consensus meeting were international. However, due to the geographical range of panellists who registered for the study, the majority of panellists were from the United Kingdom and were all English speaking. It is possible that consensus on the final COS may have been different if the panels had been more geographically and linguistically diverse. Employing options for hybrid consensus meetings in the future, where some participants attend in person and some attend virtually, could help to improve the diversity of consensus meeting participants. Conversely, consensus methodologies are usually employed to be complementary to quantitative evidence (which they are not designed to replace) (Mukherjee et al., 2015), or when empirical evidence lacking or contradictory (Murphy et al., 1998), or when an area is contentious (Lemieux & Scott, 2011). They are not designed to be 'representative' but to assist decision-making by creating a structured approach to gathering expert opinion (Okoli & Pawlowski, 2004).

3.6.4 Assessing the outcomes in the core set

Many of the parameters proposed here are likely to be familiar to veterinary professionals examining and treating cats with CKD. Most are objective parameters with established methods for measurement and assessment (e.g. serum biochemistry, survival time), or

should be more straightforward to measure and record in standard clinical trial design (e.g. adverse events, cause of death). The more subjective parameters (e.g. quality of life – Chapter 4) may be more difficult to assess. However, the initial focus of the development of any COS is always to establish what to measure and then later in the process, decide how to measure it (Williamson et al., 2012). The next stage of this work should focus on establishing the most appropriate assessment tools for each parameter proposed in this COS.

3.6.5 Future developments for COSs

The methodologies used here appeared to translate well from human healthcare to the veterinary field and could be utilised with some further improvements, considering the methodological points discussed earlier, for determining COSs for other veterinary diseases of importance. Further work is required to determine whether the improved approach will work well for additional diseases and conditions in felines, and in a range of other veterinary species.

Specific recommendations for the feline CKD COSFollowing feedback from experienced COS developers, it is proposed to consider the set of outcomes proposed in this study as part of the process of developing a COS for feline CKD, but that the process has not yet been fully completed. It is proposed that the set of outcomes reached in this study now needs further refining and collating, to ensure it is more practical for trials and contains only the absolutely most important CKD outcomes. A further future chaired consensus meeting could filter out the domains ('what to measure') (Williamson et al, 2012) from the instruments ('how to measure') in the existing set, and propose the most important three to four domains. Next the COSMIN standards should be used to decide whether the instruments proposed already here are the best ones to assess the domains, which instrument for which domain, or whether other instruments would be preferable. This meeting should be international and include all relevant stakeholders. It is possible that a virtual online meeting would be the best way to facilitate inclusion of a wide range of stakeholders. If the structure of the feline CKD COS could be adapted to one of key domains of important with

subdomains and instruments to assess them, this additional structure could help ensure the final COS was more readily usable for trials and having stakeholder engagement in the shortlisting of potential domains and subdomains would ensure these were all useful, relevant and understandable to all.

Trials COSs are distinct from COSs for clinical practice (Leshem et al., 2020), and further work on the COS for feline CKD could also look to evaluate the current list of important feline CKD outcomes, edit if required and agree by consensus any alterations required to develop a clinical practice set for feline CKD. The scope of this additional work would need to be clearly defined from the outset to ensure that the final clinical practice COS is fit for purpose, as sets for clinical practice are different from trials COSs. Participants who developed the existing COS were informed it was for trials. A clinical practice set aims to assess health domains in clinical practice and provide a list of suitable instruments to do so. Clinical practice sets can be larger than trials sets because the disease monitoring requirements in practice can be different to trials. Clinicians can then choose their preferred instruments for measuring domains in clinical practice (Leshem et al., 2020).

3.7 Conclusions

This work aimed to create the first COS ever for cats, and the second ever in veterinary medicine. Good progress has been made towards that aim, and further work as described can finish the process, refining the COS to an agreed set of the most important domains, with associated measurement instruments. The consensus methodologies successfully brought stakeholders together to consider outcomes for the COS and propose an important set. Once finalised, including the COS in future CKD treatment trials will strengthen the evidence base available to decision makers, making it easier for trials to be compared and combined, and will reduce research waste.

Reporting guidelines:

The information presented in this chapter has been reported according to the COS-STAR statement (Kirkham et al., 2016) and all items are present or where absent, have been explained within the text.

3.8 Acknowledgements

Without the participants in the eDelphi and consensus meeting, this study would not have been possible. We are grateful for their insight and contributions. We would also like to thank Dr Sara Brookes for chairing the consensus meeting, and Dr Paula Williams for her advice with the study. In addition, thank you to the Centre for Evidence Based Dermatology at the University of Nottingham for their support and advice, and Boehringer Ingelheim for providing financial support for the consensus meeting.

4. Chapter 4: A systematic review of the published literature to find assessment tools for cats for the chronic kidney disease trials core outcome 'quality of life'.

4.1 Context

Quality of life (QoL) was identified as an important outcome to assess for cats with chronic kidney disease (CKD) in both the core outcome set for treatment trials (Chapter 3), and in work by Dean (2014) ascertaining the top treatment uncertainties for cats with CKD, where quality and quantity of life were both considered key in 'improving the life of' cats with CKD. In order to assess any outcome, appropriate measurement instruments must be selected. A systematic review of existing published instruments is identified by the Core Outcome Measurement Instrument Selection (COMIS) project (Prinsen et al., 2014) as an important early step in selecting the most appropriate instruments to assess each outcome in the core set. This systematic review of QoL tools for cats was carried out to fulfil this step, as there was no systematic review already published.

The results of this systematic review were published in The Veterinary Journal in March 2021. Doi: 10.1016/j.tvjl.2021.105658 the full manuscript can be seen in Appendix 7.

Within this systematic review, 90% of the work was carried out by HD, and 10% by the co-authors of the manuscript, ML Brennan, RS Dean and M Duz.

4.2 Introduction

Quality of life considerations are central to virtually every aspect of the welfare and humane care of animals, particularly health care (McMillan, 2000). Quality of life or the well-being of animals is a parameter regularly discussed and assessed in a range of environments (e.g. shelters, laboratory animal facilities, zoo and wildlife premises, veterinary practices, homes of owners etc.) by a number of different individuals (e.g. veterinary surgeons, pet owners,

and other caregivers in these environments) including researchers developing novel treatments (Arena et al., 2019; Duncan et al., 2002; Lambeth et al., 2013). There is currently debate over the most suitable definition for QoL in animals and no widely accepted definition for QoL in animals exists (Gaynor and Muir, 2014). The "lack of a suitable definition of QoL in animals makes objective measuring of quality of life challenging" (Belshaw et al., 2015). QoL can be operationally defined (Belshaw et al., 2015) as "an individual's satisfaction with its physical and psychological health, its physical and social environment and its ability to interact with that environment".

Regardless of a current lack of consensus relating to the definition of QoL, assessment of QoL is an important component of veterinary surgeon and owner decision-making for many conditions. Veterinary surgeons are likely guided in their formulation and monitoring of treatment regimens by the owner's perception of their cat's QoL (Reynolds et al., 2010). In fact, QoL assessment forms a part of the decisions made at many stages of veterinary treatment, including; whether to seek veterinary advice (Hoyumpa Vogt et al., 2010), how to compare efficacy of treatments, and euthanasia decisions (McMillan, 2000). Euthanasia is commonly elected when treatment fails to maintain adequate patient QoL. If medications incur negative effects; for example, difficulty in administering medication, then treatment itself can decrease perceived QoL (Reynolds et al., 2010). Veterinary surgeons treating dogs with osteoarthritis describe weighing up the balance between quantity and QoL when making decisions about treatments (Belshaw et al., 2016).

Work carried out by Dean (2014) looking at current treatment uncertainties for cats with chronic kidney disease (CKD) identified the top ten uncertainties for this condition. Over half of this top ten were concerned with whether treatments would "improve the life of" cats with CKD, where "improve" referred to both QoL and length of life (Dean, 2014). It is likely that these two outcomes are also important to those caring for cats with other diseases and conditions. In addition, the outcome QoL was identified in five out of 20 papers included in a systematic review of CKD treatment trial outcomes (Chapter 2). QoL was subsequently identified as a core outcome in the COS for CKD (Chapter 3). On a Likert scale 1-9 where 9 is

very important to include in the COS, 91% of panellists in the eDelphi stage of the COS development, rated QoL as 8 or 9. The next stage in COS development is to establish, by consensus, outcome measurement instruments for each outcome in the core set. The Core Outcome Measurement Instrument Selection (COMIS) project (Prinsen et al., 2014) developed guidelines for this process. They identify four steps. Step 1: conceptual considerations, Step 2: find existing outcome measurement instruments by means of a systematic review and/or literature search, Step 3: quality assessment of the outcome measurement instruments by means of evaluation of the measurement properties and feasibility aspects of outcome measurement instruments, Step 4: generic recommendations on the selection of outcome measurement instruments for outcomes included in a COS (Williamson et al., 2017b). Once all methods for assessing or measuring a particular outcome have been identified and their properties assessed, a further consensus process is undertaken to agree on which tool should be used to assess each outcome in the COS.

4.3 Aim

The aims of this study were to carry out a systematic review of the published literature where domestic cats and QoL are mentioned. Identify how QoL was assessed in cats with or without medical conditions in this literature. Extract and describe all assessment methods to determine the number and range of different assessment tools published.

Objectives

1. Develop a list of keywords and subject headings appropriate for finding manuscripts where QoL of cats is discussed and assessment of QoL is carried out.
2. Create inclusion and exclusion criteria to narrow down the search results.
3. Search appropriate databases to find manuscripts.

4. Read and search included manuscripts for where QoL is mentioned and extract information on whether QoL is assessed and how that assessment is carried out, whether the assessment method is named, validated and simple or complex.
5. Summarise findings

4.4 Materials and methods

For the purposes of this work, a QoL assessment tool was defined as 'any form of assessment or categorisation of a cat's QoL or well-being'. As no widely accepted definition for QoL in animals exists (Gaynor and Muir, 2014), each manuscript was not searched for a definition of quality of life. If a manuscript described that an assessment of QoL or wellbeing had been carried out, it was deemed eligible for analysis for the purposes of this review.

4.4.1 Search methods

The OVID interface was used to search two databases: Medline (R) In-Process and Other Non-Indexed Citations (1946 to present) and CAB Abstracts (1910 to present). The search was carried out in March 2018. Search terms were adapted for cats from the quality of live review conducted for dogs (Belshaw et al., 2015). The search terms were the same for both databases and were linked with Boolean terms and the abstract, title, original title, broad terms and heading terms within publications were searched. The keywords used were: cat, cats, feline, felines, felis, quality of life, QOL, well being, wellbeing, well-being and quality-of-life. The subject headings used were: cats and quality of life.

4.4.2 Inclusion and exclusion criteria

The output from both databases were then exported into EndNoteX6 software (Thomson Reuters) to remove duplicates and apply inclusion and exclusion criteria, as listed in Table 4.1. The criteria for inclusion were as follows: (1) Written in English; (2) Full study available and published in peer reviewed literature; (3) Able to obtain through University of Nottingham library or inter-library loan request to the British Library Document Supply

Centre; (4) About domestic cats either privately owned, or managed within other environments (e.g. shelters, teaching organisations) or used for research purposes; (5) Make reference to QoL or well-being within the title or abstract of the manuscript; (6) Make reference to QoL or well-being within the Materials and Methods section; (7) Study type is either randomised controlled trial, or controlled trial without randomisation, or cohort study, or case-control study, or cross sectional study or case series or case study; (8) QoL or well-being of cats is assessed within the manuscript; this may be done with a specified tool. For criteria 1-5, only the titles and abstracts of each manuscript were assessed, although whether the full manuscript was available was also checked at this stage.

Table 4.1 The criteria for inclusion and exclusion of manuscripts in this systematic review.

Criteria No.	**Criteria**	**Inclusion**	**Exclusion**
Title and abstract screening			
1	Language	English	Any language other than English
2	Publication type	Full study reported Published literature	Non-peer reviewed literature (defined as Journal not stated on Ulrichsweb: https://ulrichsweb.serialssolutions.com as "refereed/ peer reviewed"). Grey literature Abstracts only available (methods and results not available on request) Book/book section/generic

3	Availability	Able to obtain through University of Nottingham library or inter-library loan request to the British Library Document Supply Centre	Cannot obtain manuscript in full
4	Population of interest	About domestic cats either privately owned, or managed within other environments (e.g. shelters, teaching organisations) or used for research purposes	Wild or big cats In vitro studies Any other species
5	Subject	Make reference to QoL or well-being within the title or abstract of the manuscript.	No reference to QoL or well-being within title and abstract
Whole manuscript screening			
6	Subject	Make reference to QoL or well-being within the	Does not make reference to QoL or well-being within the materials and methods section

		materials and methods section	
7	Study type	Randomised Controlled trials Controlled trials without randomisation Cohort studies Case-control studies Cross sectional studies Case series Case study	Narrative reviews Conference proceedings
8	Assessment	Assessment of QoL or well-being of cats within the study was made, may use a specified tool to do so.	Discuss QoL without actually providing an assessment of QoL or using any tool. Manuscripts which mention QoL or well-being but do not assess it in any way.

QoL = quality of life

Language was assessed by examining the citation information within the EndNote software. Publication type was also assessed by examining the citation information, and by searching for the journal on Ulrichsweb (https://ulrichsweb.serialssolutions.com) to see if the title was listed as “refereed”. These criteria were also assessed at the whole manuscript level if it was

unclear from the above sources. The population of interest and subject criteria were assessed by reading the title and abstract. It was decided that only domestic cats would be included as it was thought that there may be variation in what constitutes good QoL between domestic and wild cats.

The criteria numbers six, seven and eight (Table 4.1) were then assessed at the full-text stage, including study type. The manuscripts were examined for the inclusion and exclusion criteria by assessment of the materials and methods section of the manuscripts. The terms "quality of life" or "well being" and an indication of some form of assessment had to be mentioned within this section for the manuscript to meet the inclusion criteria. Reporting of the method of assessment within the manuscript was also required. For those manuscripts where the tool or form of assessment was not reported within the materials and methods section but was mentioned elsewhere in the manuscript, the results section was also investigated.

All publications were assessed by HD for all inclusion and exclusion criteria. A random sample of 15% of the papers meeting the initial inclusion criteria (language, publication type, availability, population of interest and subject) were assessed independently by MB for the remaining inclusion and exclusion criteria (study type and assessment). The random sample was extracted by listing the papers in a Microsoft Excel worksheet, one per row. Each row was allocated a unique random number via the random number function. The list of papers was then reordered by this number in ascending order, and the top 15% of papers was extracted for the sample. The results of the two independent assessments were compared and any disagreements were discussed between HD and MB until agreement was reached. Both reviewers had no competing interests.

4.4.3 Information extracted

From each manuscript remaining after application of the inclusion and exclusion criteria at the full-text stage, the following information was extracted into a Microsoft Excel Spreadsheet: full reference details for the manuscript, the name of the QoL tool (if applicable), a brief description of the tool, whether the tool was unique and used for the first time or referenced elsewhere, and whether it had been validated within the study (i.e. an assessment was made as to whether the tool was truly measuring what it was designed to measure) (Belshaw et al., 2015). The tool could be applied by researchers, veterinary surgeons or cat owners or carers.

Tools were then classified by type as to the level of detail of their QoL assessment. Tools classed as "structured" were those in which more than one question or assessment was carried out and these tools attempted to go into detail regarding the cat's life or behaviour. The remaining tools either consisted of only "one word" (where QoL assessment was defined by description with one word, e.g. poor), or "single scale" (where QoL was defined by a number on a scale e.g. from 1-5), or "other" (where the QoL tool did not fit any of the previous descriptions). The validated tools were then examined in greater detail.

This systematic review was not registered, and the protocol was not published, prior to carrying out the review. The data collection forms are not publicly available and extracted data is available only as presented within this thesis.

4.5 Results

The search results returned 1138 unique manuscripts. Figure 4.1 gives a summary of the number of manuscripts which were included and excluded from this review, and the number of QoL assessment tools extracted from the included manuscripts.

Of the 1138 manuscripts, 96 met the inclusion criteria 1-5 when screened at the title and abstract level, and all 96 additionally met criterion 6 when screened at whole manuscript

level (Figure 4.1). Double assessment was carried out on 36 citations by MB and HD and resulted in initial disagreement about the inclusion of 1/36 manuscripts (97% agreement). After discussion, it was agreed that the manuscript should be excluded by both reviewers.

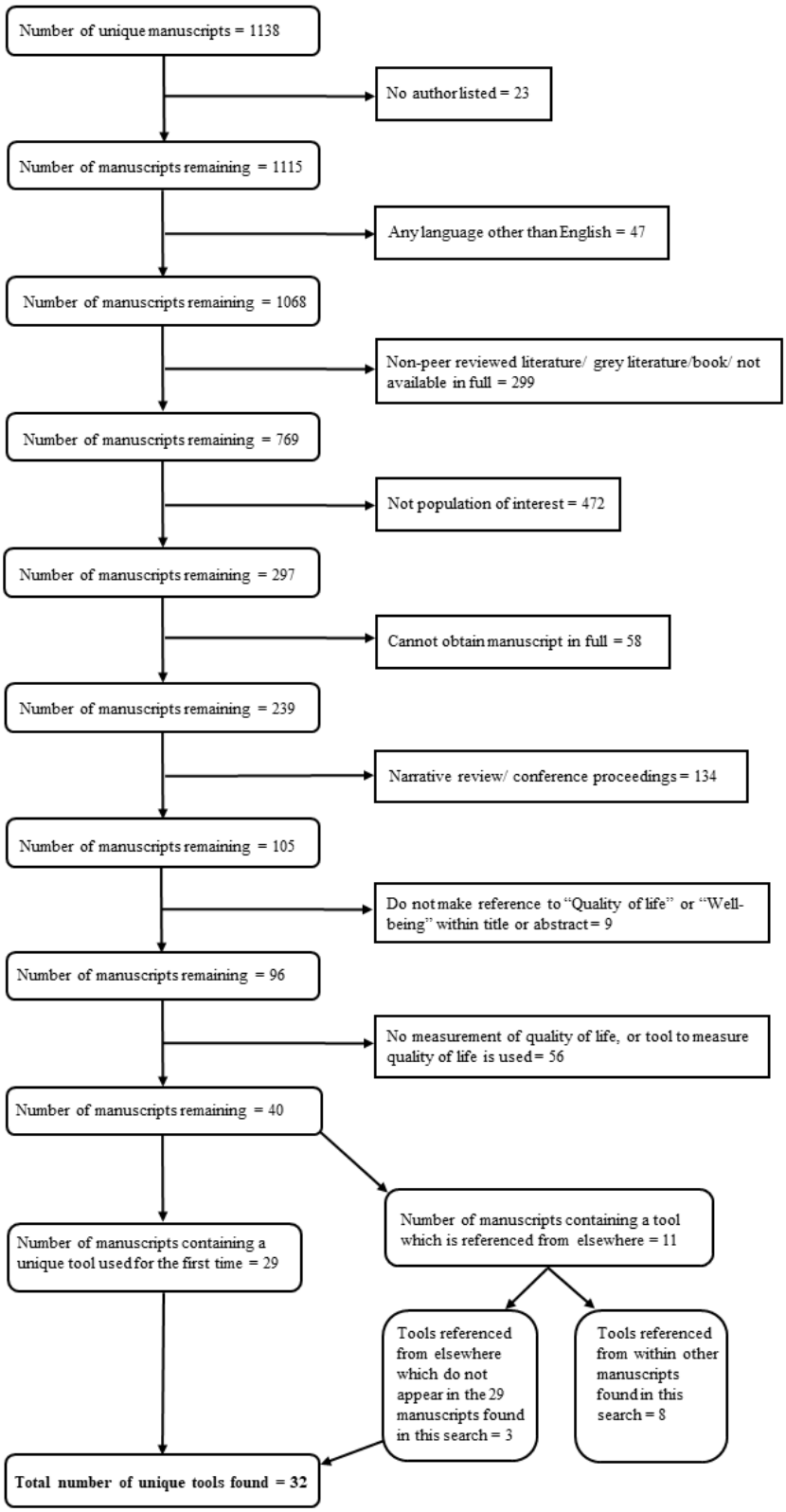


Figure 4.1: The number of manuscripts included and excluded at each stage of the systematic review process, and the reasons for these decisions. The numbers of quality of life assessment tools extracted from the manuscripts included in the review is also shown.

4.5.1 Manuscripts identified containing quality of life assessments

Of the 96 manuscripts included, 40 (42%) were found to contain some form of QoL tool or assessment (Figure 4.1). Within the 40 manuscripts containing an assessment of QoL, we found 32 unique tools or assessment methods which could be clearly identified. Twenty-nine of these appeared within a manuscript detailing their first use. An additional three unique tools appeared within the remaining 11/40 manuscripts. However, for these three, the manuscript describing their origin or first use did not appear within our search results.

Within the remaining 8/40 manuscripts, seven referenced tools that were already found within the 32 unique tools, and the final manuscript described a paper which was insufficiently described and referenced for the tool or its origin to be clearly identified. Table 4.2 provides more detail on all the tools found in the 40 manuscripts where a QoL assessment was carried out, including author, administration of tool, how information was gathered for the tool, whether the tool was unique, and whether the tool was validated. The supplemental table for this chapter (Appendix 8) contains the manuscript title and a brief description of the assessment tool. The majority of the tools were owner completed questionnaires, of varying complexity. Three tools clearly explained that they included a veterinary surgeon's involvement or a physical examination. Two of these tools were validated (Adamelli et al., 2004/2005) and (Taffin et al., 2016) and one was not validated (Fox et al., 2000). Change in QoL was assessed in 12 tools, for example, before and after treatment, or time to return to "best" QoL. Of these 12, eight tools used numbered scales e.g. rate QoL 1-10 before and after treatment, three used one word assessments e.g. QoL worse or QoL improved, one recorded the number of days e.g. to return to normal QoL.

Table 4.2 The 40 papers included in this systematic review: authors, how the assessment tool found was administered, how information was gathered for the tool, the uniqueness of the tool and whether the tool was validated.

[a]By the authors name denotes one of the 12 manuscripts where a validated tool was used

Author(s)	**Administration of tool**	**How information gathered for tool**	**Unique tool used for the first time? Or reference from elsewhere?**	**Is validation of the tool described?**
Adamelli et al., 2005 [a]	Owner and veterinary surgeon	Questionnaires and physical examination	Referenced from Marinelli et al., 2001	States was previously validated by Marinelli et al., 2001
Adamelli et al., 2004 [a]	Owner and veterinary surgeon	Questionnaires and physical examination	Referenced from Marinelli et al., 2001	States was previously validated by Marinelli et al., 2001
Bass et al., 2005	Owner	Questionnaire	Unique tool, not a named tool, not referenced.	No
Benito et al., 2013	Owner	Questionnaire	Unique named tool used for the first time	No

Benito et al., 2012	Owner	Questionnaire	Referenced from Budke et al., 2008	No, in Budke et al., 2008 the tool was originally designed for dogs
Bijsmans et al., 2016 [a]	Owner	Questionnaire	Unique tool, first use	Psychometric validation is carried out and described within the paper, where two of the items are removed as a result, leading to a final 16 item tool.
Boland et al., 2014	Owner	Questionnaire	Unique tool, first use	No
Bowles et al., 2010	Owner	Questionnaire	Unique tool, first use	No
Brown et al., 2009	Owner	Questionnaire	Unique tool, first use	No

Christmann et al., 2016	Owner	Questionnaire	Unique tool used for the first time	No
Fischer et al., 2011	See Hartmann and Kuffer (1998)	See Hartmann and Kuffer (1998)	Referenced from Hartmann and Kuffer (1998)	No
Forster et al., 2010	Owner	Questionnaire	Unique tool, first use	No
Fox et al., 2000	Owner and veterinary surgeon	Questionnaire and additional evaluation, method not described	Unique tool, first use.	No
Freeman et al., 2012 [a]	Owner	Questionnaire	Unique named tool used for the first time	Yes
Freeman et al., 2016 [a]	Owner	Questionnaire	Unique tool, first use.	Validity and reliability evaluated within this manuscript.
Fritsch and Jewell, 2015	Owner	Questionnaire	Unique tool, first use	No

Gates et al., 2017	Researcher	Information gathered from clinical notes written by the veterinary surgeon	Unique assessment, first use.	No
Giuffrida and Kerrigan, 2014	N/A	N/A	Not applicable	Not applicable
Gostelow et al., 2018 [a]	See Niessen et al., 2010	See Niessen et al., 2010	Referenced from Niessen et al., 2010	States that the tool is validated
Guedes et al., 2018	Owner	Questionnaire	Not referenced but is described as if is not unique.	No
Hartmann and Kuffer, 1998	Owner and veterinary surgeon	Questionnaire and veterinary observations	Unique named tool used for the first time	No
Hung et al., 2014	Owner	Questionnaire	Unique tool, first use	No
Kooij et al., 2014	Veterinary surgeon	Questionnaire	Unique tool, first use	No
Kulendra et al., 2014 [a]	See Niessen et al., 2010	See Niessen et al., 2010	Referenced from Niessen et al., 2010	Yes

Lascelles et al., 2007	Owner	Questionnaire	Unique tool, first use	No
Lynch et al., 2011	Owner	Questionnaire	Unique tool, first use	No
Matei et al., 2017	Not clear	Not clear	Unclear as not stated.	No
Niessen et al., 2010 [a]	Owner	Questionnaire	Unique named tool used for the first time	Yes
Noli et al., 2016 [a]	Owner	Questionnaire	Unique tool, first use.	Criterion and construct validity described within the manuscript.
Pakozdy et al., 2013	Owner	Questionnaire	Unique tool, first use	No
Reynolds et al., 2010	Owner	Questionnaire	Unique tool, first use	No
Ritz et al., 2007	See Hartmann and Kuffer, 1998	See Hartmann and Kuffer, 1998	Referenced from Hartmann and Kuffer, 1998	No
Ruda and Heiene, 2012	Owner	Questionnaire	Unique tool, first use	No
Rush et al., 2015 [a]	See Freeman et al., 2012	See Freeman et al., 2012	Referenced from Freeman et al., 2012	Yes

Sabhlok and Ayl, 2014	Owner	Questionnaire	Unique assessment, first use.	No
Taffin et al., 2016 [a]	See Hartmann and Kuffer, 1998	See Hartmann and Kuffer, 1998	Referenced from Hartmann and Kuffer,1998	Yes
Tatlock et al., 2017 [a]	Owner	Questionnaire	Unique tool, used for the first time	Yes, validation is described within this manuscript
Theobald et al., 2013	Owner	Questionnaire	Unique assessment, first use.	No
Tzannes et al., 2008	Owner	Questionnaire	Unique tool, first use	No
Williams et al., 2017	Owner	Questionnaire	Unique tool used for the first time, created based on information from Tzannes et al., 2008; Reynolds et al., 2010; (Belshaw et al., 2015)	Not stated.

4.5.2 Unique tools found across the 40 manuscripts

Of the 32 unique tools found, 16 were classed as structured and 16 were considered not structured. Structured tools were identified as those in which more than one question or assessment was carried out, and the tool went into detail regarding clinical signs and/or life and/or behaviour. These were converted to scores, which were then summed to give overall totals.

4.5.2.1 Unstructured tools

The 16 unstructured tools carried out a simple assessment of QoL as a single word, number or one or two short questions (Figure 4.2). Of the 16/32 unique unstructured tools, eight tools (Boland et al., 2014; Bowles et al., 2010; Brown et al., 2009; Fritsch & Jewell, n.d.; Hung et al., 2014; Ruda & Heiene, 2012; van der Kooij et al., 2014; Matei et al., 2017) scored QoL on a Likert scale (e.g. rating of 1-3 or 5-1). In five tools (Bass et al., 2005; Lascelles et al., 2007; Pazkody et al., 2013; Theobald et al., 2013; Guedes et al., 2018) a single word was used to describe a QoL assessment, such as “poor” or “good”. In the remaining three tools, one used an owner subjective overall assessment of tumour size, eating and grooming as a proxy for QoL assessment (Sabhlok & Ayl, 2014), one looked for clinical signs and chronic diseases potentially associated with a decreased QoL from the veterinary clinical notes (Gates et al., 2017) and one asked two questions about time taken to return to best or normal QoL (Forster et al., 2010).

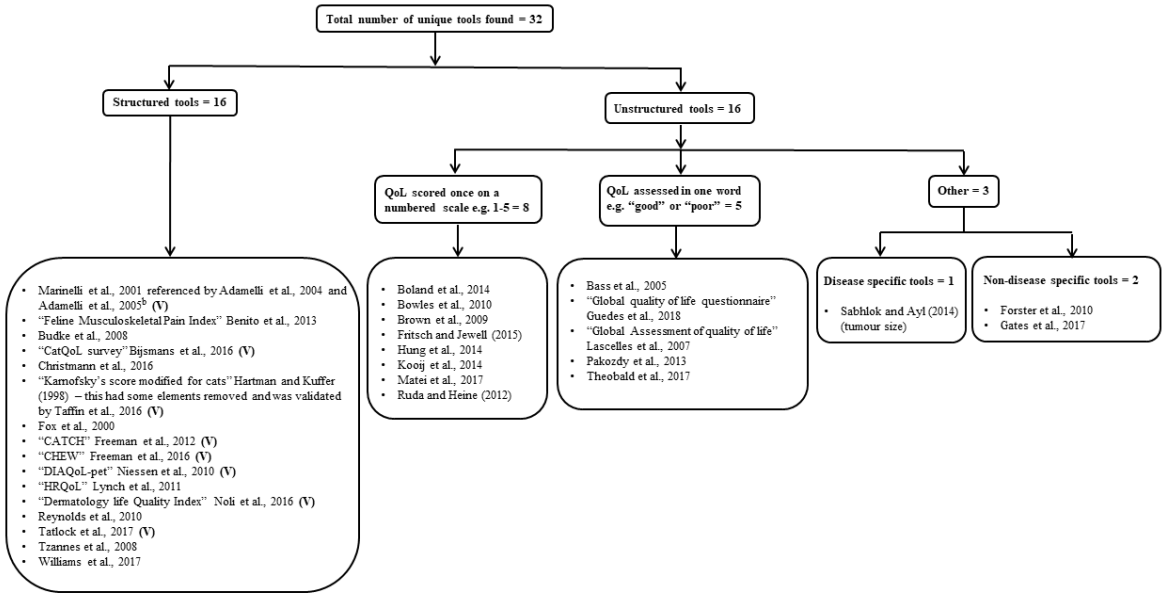


Figure 4.2: Flow chart to illustrate the balance of structured vs. unstructured tools which were found, and how quality of life was assessed in the unstructured tools.

[b] The two manuscripts by Adamelli et al were both found in the search done as part of this systematic review. They both reference the same tool, originally published in Marinelli et al., 2001. However, the manuscript by Marinelli et al, 2001 was not found in the results from this systematic review search.

(V) denotes tools which had been validated.

4.5.2.2 Structured tools

All 16 structured tools carried out a detailed assessment on a variety of aspects of the life and behaviour of the cats assessed and included a scoring system (titled disease or condition specific tools). Explored parameters included: physiological parameters such as breathing pattern, appetite and mobility and other more behavioural parameters including: hunting, grooming, sleeping, sunbathing, visiting favourite places, interacting with people, interacting with other cats, play behaviour and mood. There were parameters that fitted into both physiological and behavioural indicators, e.g. litter tray parameters which included different assessments depending on the tool. Litter tray parameters noted included: stool volume, diarrhoea, appropriate use of litter box and toileting habits.

Of the 16/32 tools defined as structured, 6/16 were named and of the tools considered unstructured (16/32), 2/16 were named. Some of the named tools appeared more than

once in the overall search results: Karnofsky's score modified for cats appeared in 4 manuscripts: (Hartmann and Kuffer, 1998; Fischer et al., 2011a; Ritz et al., 2007; Taffin et al., 2016). DIAQoL-pet appeared in 2 manuscripts: (Gostelow et al., 2018; Niessen et al., 2010) and the Cats' Assessment Tool for Cardiac Health CATCH appeared in two manuscripts: (Freeman et al., 2012; Rush et al., 2015).

4.5.3 Validated tools

Of the 32 unique tools found, 26% were validated (8/32). Validated tools were more likely to be structured (8/8; 100%) and named (6/8; 75%). The eight validated tools which were found consisted of three tools designed to assess the QoL of healthy cats (one represented in Adamelli et al., 2004 and 2005 ; one in Freeman et al., 2016 and one in Tatlock et al., 2017), one tool for assessing hospitalised cats (Taffin et al., 2016), one to assess cats with chronic kidney disease (Bijsmans et al., 2016) one to assess cats with cardiac disease (Freeman et al., 2012), one tool to assess cats with diabetes (Niessen et al., 2010), and one tool to assess cats with skin disease (Noli et al., 2016) (Figure 4.2). Figure 4.3 demonstrates the intersection of tools which were named, validated and disease specific. All these tools were detailed questionnaires, and 6/8 were only completed by the cat's owner. Of the remaining two tools, one included a veterinary physical examination which was coded and scored (Adamelli et al., 2004 and 2005) and the other (Karnofsky's score modified for cats, validated in Taffin et al., 2016) included a score from 0-5 given by the examining veterinary surgeon. Three of the validated tools appeared in more than one manuscript within this review. The same unnamed tool appears in Adamelli et al, (2004) and Adamelli et al, (2005), the CATCH tool (Freeman et al., 2012) appeared in two manuscripts, and the DIAQoL-pet tool (Niessen et al., 2010) appeared in three manuscripts. This made a total of 12 manuscripts where one of the eight validated tools was used. This was 30% (12/40) of all manuscripts included in this review. Appendix 8 contains full details of all 40 manuscripts.

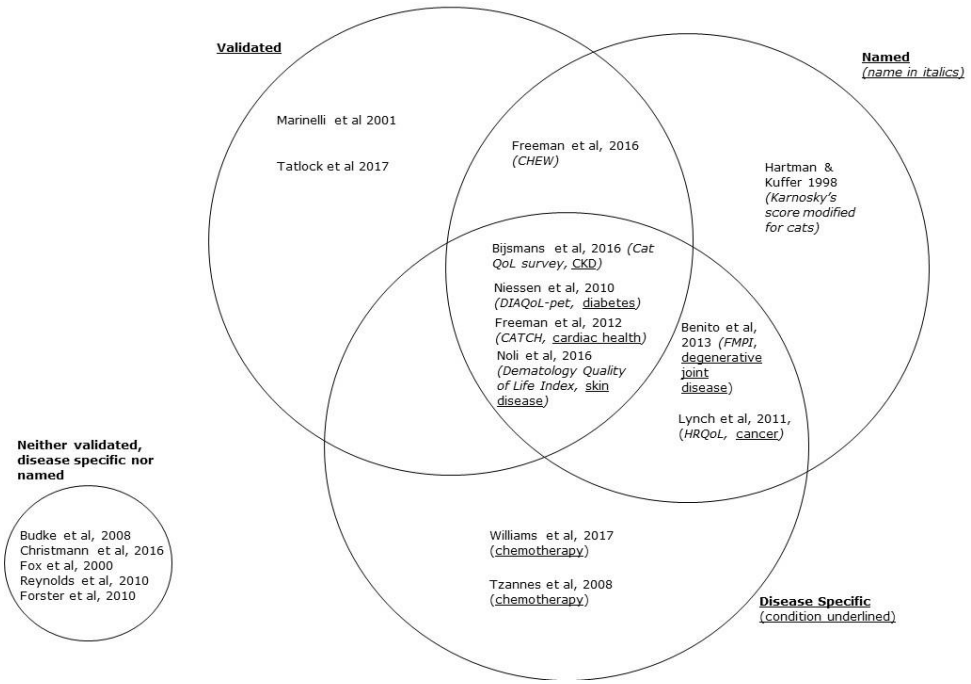


Figure 4.3 The intersection between different groups of assessment tools for those which were validated, named and disease specific.

The number of items examined in each validated tool ranged from 17 items (CATCH tool, Freeman et al., 2012) to 100 items (CHEW, Freeman et al., 2016) (Appendix 8). In some tools these items were divided into domains, for example play, mood, energy, appetite, physique, coat (Freeman et al., 2016), and in all tools the items were scored numerically to give an overall QoL result. The number of items assessed in the tool used in both Adamelli et al, (2004) and Adamelli et al, (2005) was not stated, nor was the number of items assessed in the tool used in Taffin et al, (2016). Most of the tools found contained an additional question to assess the assessor's impression of the QoL of the cat overall. The only stated recall periods were seven days (CHEW, Freeman et al., 2016) and the preceding 4-week period (Tatlock et al., 2017). For the other assessment tools the recall period was described as one of the following: during the study, or since the intervention, or since the previous visit, or was not stated.

4.5.4 QoL assessment tool for cats with CKD

Bijsmans et al., 2016 developed and validated the CatQoL tool for assessing the QoL of healthy cats and cats with CKD. This tool assessed 16 items, divided into four domain groups: general health, eating, behaviour and management. Each item was scored for frequency or severity (from -3 to +3) and importance of that item to the cat as an individual (from 0 to +3) to create average weighted impact scores (AWIS). These scores were then compared between groups of young healthy cats, older healthy cats and cats with CKD, and also compared between domains. The manuscript authors reported significant differences in the score results between eating and management domains of CatQoL for older healthy cats and cats with CKD. Cats with CKD scored significantly lower in both domains and the manuscript authors advised that this signals that these QoL aspects are more vulnerable to the negative effects of quality of life in cats with CKD. They explain that cats with CKD have been observed to have poor appetites in other studies. The eating domain included: liking food, appetite, difficulties eating and the management domain covers going to the vets and medication. In addition, in the behaviour domain (happiness, stress, interactivity, playing, hunting, grooming and scratching), both old healthy cats and cats with CKD scored significantly lower than young healthy cats (Bijsmans et al., 2016). The authors stated that their assessment tool worked best for longitudinal repeated use on the same cat, so that each cats score's can be compared to its own previous scores.

4.5.5 Unvalidated tools

Unvalidated tools designed to assess the QoL of cats with a particular disease condition were identified for degenerative joint disease (Benito et al., 2012), osteoarthritis "FMPI" (Benito et al., 2013) and cancer "HRQoL" (Lynch et al., 2011). An additional three unvalidated tools were found to assess QoL associated with chemotherapy or the presence of tumours: (Sabhlok & Ayl, 2014; Tzannes et al., 2008; Williams et al., 2017). One unvalidated tool was found to assess the QoL of healthy cats: Karnofskys' score modified for cats (Hartman and Kuffer, 1998) although this was later validated (Taffin et al., 2016).

4.6 Discussion

This is the first structured literature review focused on assessment tools for QoL of cats in all circumstances, whether healthy or unwell. This review found that although QoL or well-being was mentioned in many manuscripts, actual assessment of QoL with some form of tool was carried out in less than half. Some papers mentioned the importance of QoL or discussed how a new treatment has the potential to improve QoL, without any actual assessment of QoL alongside this. Assessment with a validated tool was carried out in just over a quarter of manuscripts. Many tools used a Likert scale or one word to assess QoL and these very simple, unstructured tools were not validated. One tool was found for QoL assessment in cats with CKD (Bijsmans et al., 2016)

The only other review of QoL tools for cats found was a systematic review by (Giuffrida & Kerrigan, 2014) looking at tools for QoL of cats (and dogs) with cancer. This review aimed to understand what tools are currently available for decision makers and researchers for assessing cat QoL and specifically if any tools were published for assessing the QoL of cats with CKD. Defining QoL is very complex and no universally accepted definition yet exists (Gaynor and Muir 2014). The aim was to find out whether any assessment of QoL was carried out in manuscripts which discussed QoL, whether a simple or structured tool was used, and whether that tool was validated. In human medicine, Carr and Higginson (2001) discussed how evaluation of QoL can be very specific to an individual patient. Therefore, it is possible that without an agreed definition of QoL or any validated tools, QoL may not be well assessed. Independent assessments using different tools may come to different conclusions about QoL.

4.6.1.1 Tool validation and the complexities of QoL assessment

QoL is a very complex construct (Scott et al., 2007) so it is likely that it would not be possible to validate many of the tools found in this review where only a single Likert scale of one

word were used to assess and describe QoL. These tools are likely to not capture enough complexity to assess QoL well. Bijsmans et al. (2016) in developing their QoL assessment tool for cats with CKD compared a general QoL overview question to their own 16 item tool and found a moderate correlation between the two results. This suggests that asking only one question may provide an incomplete assessment of patient's QoL (Bijsmans et al., 2016). Assessing this important concept so simply in research studies, particularly clinical trials, may risk missing subtle differences between patients. This would reduce the useful contribution that these trials could make to the evidence-base for treatment decision-making. Quality of life assessment in cats may be more than a single construct. It may incorporate specific characteristics within different contexts, likely to have a common set of characteristics that may apply to all contexts. Even within the validated tools found, there is wide variability in the number of items assessed by each tool, and so each tool may produce a different quality of life assessment.

The validation of tools to measure QoL is important, as without validation we cannot be certain that a tool is truly measuring what it has been designed to measure (Belshaw et al., 2015; Scott et al., 2007). Assessment of the validation process used for these tools should now be carried out and if validation is found to have been conducted rigorously, users can be more reassured as to how well the validated tools measure QoL and how comparable the results gained from assessments with each tool may be. Assessment of the validation process should be carried out according to the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) (Prinsen et al., 2016). The next step for this work should be to look at both the validity and reliability (Spofford et al. 2013) of the QoL assessment tools, and specifically the tool for assessing QoL in cats with CKD (Bijsmans et al., 2016). Both validity and reliability are important for determining how well a tool assesses what it is supposed to in a consistent way. However, this process may be complicated by the lack of definition of QoL for animals Gaynor and Muir (2014) and (Belshaw et al., 2015).

Prior to assessment of the validity of QoL assessment tools, or for the development of new tools if required, it will be important to understand clearly what the concept of QoL means for cats with CKD and what a tool for QoL for cats with CKD would need to capture. Cats will

need advocates to represent them in this process, with owners and carers being well placed for this role, potentially with the addition of veterinary surgeons and veterinary nurses. Conceptual clarity is important in quality of life because differences in meaning can lead to differences in outcomes for research and clinical practice (Ferrans, 1996). The concept of quality of life can be examined in terms of a conceptual framework. This is important because it has explanatory power and provides a firm foundation for measurement. The framework takes the concept forwards from concept to a construct with associated measurement properties (Schalock et al., 2008).

Methodology for building a framework could follow a recent publication from veterinary healthcare for QoL in dogs. Roberts et al. (2021) constructed a conceptual framework of indicators of health-related quality of life (HRQOL) for dogs with osteoarthritis, focusing on the subjective experience of the dog. Indicators of osteoarthritis and its impact on QoL were extracted from a systematic review and used to generate items and domains which were assessed at a workshop where hypothesised directional interactions between the domains were identified, and a visual representation of the conceptual framework was produced. They advise a future qualitative concept elicitation study with veterinarians and dog owners to provide additional evidence to validated whether the HRQOL domains and interrelations they describe in their model is reflective of real world experiences.

As many existing QoL tools for cats have not been validated, this limits what individuals involved in QoL assessments on a daily basis (e.g. veterinary surgeons, animal owners and managers) can utilise for decision-making in relation to the animals under their care, be they assessments of positive or negative QoL in healthy animals, or those suffering from a disease. It has been reported that the most common method used to assess QoL in veterinary practice is a single broad question, for example, “How is your cat getting on?” (Yeates & Main, 2009). For decision making in the veterinary clinic, the FMPI tool (Benito et al., 2012) is now accessible on a website for vets to use for assessing musculoskeletal pain. This may increase awareness and use of this tool. However this tool is unvalidated for QoL assessment. It is hoped that this review will highlight the validated tools which do exist, to encourage future researchers and clinical practitioners to use them. It is hoped that these validated tools will provide a more thorough and appropriate QoL assessment than unvalidated tools. However, given the assessment of the validation process and reliability of

the tools has not yet been carried out, users should note that further recommendations may be made after this process is completed.

4.6.1.2 Potential limitations

There are some potential limitations to the work carried out in this review. The search strategy used only covered the databases Medline and CAB Abstracts. These databases should have good coverage of the literature relating to animals, as research has identified that CAB Abstracts covers 90% of journals relevant for veterinary medicine (Grindlay et al., 2012). However, it is possible that further searching with additional databases and hand searching the grey literature may have found more results and it is possible that more tools may have been published since this review was carried out. Since the search was carried out an additional manuscript has been identified (Noble et al., 2019) which was likely not indexed at the time of the original search. In addition, the search terms used were very specific to QoL. The term "well-being" was included and was also helpful as many authors seemed to use this interchangeably with QoL. The search terms used in this review were the same as used in a review of QoL assessment tools for dogs (Belshaw et al., 2015). It is possible that using additional search terms, for example "welfare" could have returned more results, as some consider the terms "welfare" and "QoL" to be synonymous (Mullan, 2015). However, welfare can also include practical welfare measurement, which is most usually concerned with ensuring minimum standards of care are provided (Scott et al., 2007). Therefore, including this term may have made the results much broader, covering more general practical aspects of a cat's life, and less applicable to the specific assessment of QoL. In addition, the manuscripts in this review only met the inclusion criteria if they were in English. If more languages had been included in the scope of this review, it is possible that additional QoL tools may have been identified.

In addition to the tools identified in this review, it is possible that veterinary surgeons and researchers use other tools to assess QoL of cats with or without CKD, which are neither published nor validated. These tools could be identified by questionnaires or by examination of patient consultation history notes. Once all possible methods for assessing QoL of cats with CKD are identified, (Williamson et al., 2017b) recommend assessment of their

properties and a further consensus process to agree the best tool for measuring each outcome in a COS.

4.7 Conclusions

Only a small number of validated tools were identified for assessing QoL in cats and few researchers appeared to use them. A wide range of unvalidated tools were identified alongside the validated tools found in this review. A validated tool was identified for cats with CKD and further assessment of the reliability and validation process carried out on this tool is now required. The suitability of this tool for assessing QoL as part of the COS for CKD treatment trials (Chapter 3) needs to be decided by consensus, including representatives of all decision makers for cats with CKD.

Researchers assessing QoL for healthy cats or cats with medical conditions apart from CKD should aim to use existing validated tools where they are appropriate. However, they should be aware that work assessing the quality of the validation process carried out on these tools and the reliability of the tools has not yet been completed. The results of this further work once completed may impact on future QoL assessment tool choices. All QoL assessments of cats whether healthy or unwell would benefit from the development and agreement of a universally accepted definition for cat QoL. Reaching this definition is likely to be difficult, due to the complexity of the QoL construct (Scott et al., 2007).

Reporting guidelines:

The information presented in this chapter has been reported according to the PRISMA 2020 checklist (Page et al., 2021) and all items are present, except for those relation to a risk of bias assessment. This has not been carried out as it was not thought to be appropriate for the type of results extracted in this study. In addition, the checklist points relating to data synthesis (e.g. statistical analysis) are not included as considered not appropriate for the types of results extracted in this study.

5. Chapter 5: Obtaining and preparing veterinary practice clinical data for research

5.1 Context

Chapter 3 identified a core outcome set (COS) for CKD. On a daily basis, veterinary surgeons diagnose, treat and assess the outcomes of cats with CKD and as part of this, clinical notes are recorded in a patient record. Data representing large numbers of patients is recorded in this way. If this data can be accessed and analysed and the outcomes from the COS found within it, then there is the potential to use patient records as a data source for future treatment trials, adding to the existing evidence base. This study aimed to explore the feasibility of accessing patient records, extracting the required data and storing it in a way that allowed straightforward interrogation to extract information of clinical interest.

5.2 Introduction

Cats with chronic kidney disease (CKD) are seen commonly in first opinion veterinary practice in the UK (Conroy et al., 2019; Marino et al., 2014). Their presenting signs, diagnostic test results, treatment choices and treatment outcomes are recorded in their electronic patient record (EPR) when they are seen for veterinary consultations (Robinson et al., 2015). CKD is a chronic condition, so if patients are diagnosed early on in the disease process, they may make many visits to the veterinary practice over the years as their condition progresses. If the information recorded in the EPR about these patients could be extracted and the data shown to be relevant and in a useable format, then EPRs could become a valuable source of information for clinical trials for these patients. This is especially if outcomes from the core outcome set for feline CKD generated in Chapter 3 are found to be routinely assessed and recorded. This could increase the data contribution by veterinary practices as a whole in trials, as effectively little or no extra effort would be required for clinicians to participate. The cats represented within the EPR dataset are similar

to other, normal cats. Their data and recorded treatment outcomes may provide relevant and useful information on treatment effectiveness, which is how a treatment performs under real world conditions (Revicki & Frank, 1999). This information could help address current feline CKD treatment uncertainties and provide veterinary surgeons and cat owners with a larger evidence base for decision making because it mirrors cats like those they care for.

5.2.1 The recording of patient data within the electronic patient record

5.2.1.1 Overview

Over 98% of veterinary consultation records are held electronically in the UK within Practice Management Systems (PMSs) (Robinson & Hooker 2006). The EPRs for all veterinary patients are held within databases. As a result, EPRs represent the majority of the animal population seeking veterinary care in the UK. These are managed and maintained by a Practice Management System (PMS), of which there are many in the United Kingdom (UK). Some veterinary corporate groups have their own bespoke PMS which they require all their veterinary practices to use. Other PMSs are used by a variety of veterinary practices, both independent private veterinary practices, and those within larger corporate groups.

5.2.1.2 Potential datasets

Within each PMS the EPR is held within a bespoke database structure. The structural design and the number and type of fields provided in the interface where users input the data varies between PMSs. The location and format in which different data are recorded is influenced by the interface. The data held in EPRs is divided into a variety of field types. Some are fixed fields, for example dates or species information, where the type and amount of data which can be inputted is restricted (formatted and validated) or even pre-specified. Some fields contain written free text, for example detailing the patient's clinical history, or general notes about the patient or owner (J. S. Jones-Diette et al., 2016).

5.2.2 Methods for obtaining patient data from electronic patient records

5.2.2.1 EPRs and veterinary research

Several research groups in the UK are already working with veterinary EPR data. The Small Animal Veterinary Surveillance Network (SAVSNET) at the University of Liverpool work on disease surveillance, disease risk factors, antimicrobial resistance and use and infection risks (A. Radford et al., 2010). They achieve this using real time patient data from veterinary consultations and additional embedded short questions within the PMS to further classify detail of the main reason the patient was brought to the practice for the consultation.

The Veterinary Companion Animal Surveillance System (VetCompass) at the Royal Veterinary College in London also use veterinary EPRs. They collect from over 1,800 veterinary practices in the UK for epidemiological research purposes and make the data available to participating practices for their own research and audit (www.rvc.ac.uk/vetcompass/papers-and-data/original-publications). The research interests of VetCompass include antimicrobial stewardship, disease predispositions and risk factors and heat stroke among others. In addition, they have recently begun an eClinical Trials project, which aims to analyse EHRs with novel statistical methods to evaluate the effectiveness of clinical interventions (www.rvc.ac.uk/vetcompass/research-projects-and-opportunities/projects/projects/vetcompass-eclinical-trials). To date this is the only use of veterinary EPRs for trials which exists.

At the University of Nottingham the Veterinary Clinical Trials Network (VCTN, www.nottingham.ac.uk/cevm/practice-based-research/the-veterinary-clinical-trials-network-vctn/the-veterinary-clinical-trials-network-vctn) are a group of veterinary practices who are interested in participating in veterinary trials by using clinical practice data, and who participate in questionnaires, surveys and other forms of practice-based research with the Centre for Evidence-based Veterinary Medicine (CEVM).

The VCTN, VetCompass and SAVSNET use EPRs which were not originally created for veterinary research. However, another initiative, the Banfield Applied Research and

Knowledge (BARK) initiative developed by the Banfield Pet Hospital in the USA is a bespoke data recording system which does specify, capture and records data fields of relevance to clinical research, e.g. blood test parameter measurements (www.banfield.com/en/pet-health/State-of-pet-health, (cat & banfieldcom, 2014)).

Within the UK and USA, private veterinary practices and veterinary corporate groups will use their own EPRs for clinical audit and quality improvement purposes (e.g. (Leicester et al., 2023).

5.2.2.2 Deidentification of patient records

Within the EPR, the unstructured, free text fields contain crucial data on patient history, investigations, diagnostics, treatments and outcomes, all of which have real potential to inform clinical research. The free text is non-structured which means specialised methods are required to find and extract relevant data of interest (R. J. Turner et al., 2022). Manual analysis alone of free text can be laborious and time consuming due to the size of these fields and the detail contained within them (Duz et al., 2017). In addition, research has shown that free text fields within EPRs are likely to contain Potential Personal Identifiers (PPI) about the owner or the patient, (Newman, 2018 PhD Thesis) and to be compliant with GDPR regulations these need to be removed before the data is held, handled or used for research, as otherwise consent from the person identified by the PPI would be required for that purpose. PPIs likely to be found include phone numbers, names, addresses or email addresses. There are written into the free text for the information of the veterinary professionals treating the patient. However, in order to be GDPR compliant, these records need to be anonymised. PhD work at the University of Liverpool (Newman, 2018 PhD Thesis) has developed a method for deidentifying veterinary practice clinical notes from the SAVSNET database. Called 'Clancularius' it is written in Python and successfully redacts human names (99.7% sensitivity), locations (94.7% sensitivity) and microchip numbers (100% sensitivity) from clinical notes (Newman, 2018 PhD Thesis).

XML schemas

The PMS interface and the database structure underlying the PMS result in differences in the patient data recorded by each PMS, meaning that combining patient data from differing PMSs is potentially difficult (J. S. Jones-Diette et al., 2016). In addition, the original purpose of the PMS database structure is clinical record keeping and billing, not research (J. S. Jones-Diette et al., 2016). The database structure facilitates information storage and retrieval on patients or patient owners individually. It is not designed for the simultaneous data extraction of cohorts of patients, either retrospectively or prospectively.

One method of transferring veterinary patient data from the EPR between differently structured databases, via a format which can be read by both, is by the use of XML schemas. This has been pioneered by the VetXML Consortium (www.vetxml.co.uk) , established in 2006. Their aim is to 'improve the sharing of data through the development of an industry standard data format, in order to maximise the service provided by the veterinary profession' (www.vetxml.co.uk/en/aims-of-the-consortium). Their members are research groups, veterinary PMSs, insurance companies, microchip companies, veterinary laboratories and others. They have created and endorsed schemas for transfer of patient information for insurance claims, microchip registrations etc. The Clinical Evidence Schema v1.0.5 (Jones-Diette et al., 2016) was endorsed and published by them for the transfer of patient data for research. It was successfully used in the extraction of patient data from the PMS Vet-One, from one demo veterinary practice over nine days, and from one real veterinary practice over eight weeks (Newman, 2018 PhD Thesis)

An XML schema is a document which can be used to describe the structure of a data extract, from a source database, written in the language XML. XML is an eXtensible Markup Language, which can be easily read by humans or computers (Klipp et al., 2008). The XML schema protocol provides user friendly interpretation. Data fields from the source database are represented by elements within the schema and special characters show where an element starts and finishes. Elements are described by name, number of occurrences and data format. The meaning of the data is retained alongside the data, for example <Breed>Persian</Breed>. Within the schema, an element would be written like this:

<xs:element name="DateOfBirth" type="xs:date" minOccours= "0" maxOccurs="1">

This element describes the data field from the PMS, “DateOfBirth”, which has a similar name in the XML schema. The data type is “date” and this element occurs a minimum of zero times (date of birth data might be missing) and a maximum of once, (each animal can only have one date of birth). This also allows for a NULL entry, that is, one where the data exists but is not available but may be in the future, and is not the same as an entry which reads “0”, as this is still an ‘entry’ (https://learn.microsoft.com/en-us/dotnet/framework/data/adonet/sql/handling-null-values). Other data types included in a schema could be: “string” which is alphanumeric characters, “DateTime” which is date and time, “Boolean” which is true or false. If an element can have a maxOccurs “unbounded” then there is no limit on the number of times that element could be repeated in the XML document produced conforming to the schema. This has the potential to work well for clinical trials, where each patient may have many clinical history entries recorded. This structure allows for them all to be collected.

The schema may be written in a nested structure with parent and child elements and these relationships are demonstrated by indenting. For example, a parent element might be a veterinary consultation and nested within that are the child elements consultation date, notes taken in the consultation and diagnosis made. One animal may have many consultations nested within it, and many animals may be nested within a veterinary practice. Using an XML schema format enables data from multiple disparate sources to be easily formatted to the requirements of a new destination database because the structure, content and format of the data is standardised. The XML data files can be validated against a schema before entering into the destination database to ensure the data types are compliant with the destination database, and all information required for the primary keys is included. A primary key is a unique identifier for each record in a table, the value must be unique and cannot be NULL. Each table in a database can only have one primary key, which can either be from one column alone or multiple columns (fields) making a composite primary key (www.w3schools.com/sql/sql_primarykey.ASP).

Clinical Evidence Schema v1.0.5 and other schemas published by the XML Consortium work well for extracting data from PMS databases for individual patients for insurance claims, microchip registration and for other reasons (www.vetxml.co.uk/en/vetxml-schemas/) To the authors knowledge, none of the schemas published by the VetXML Consortium have

been used for extracts of cohorts of patient's data simultaneously from within each PMS. In addition, the existing clinical evidence schema does not include an element to describe which PMS the data originated from, nor does it allow for data from more than one veterinary practice to be included per data export. This is because it was designed to be embedded within the Vet-One PMS only, and each data extract sent directly to researchers from each individual veterinary practice, not as a batch of data for multiple practices sent from the central PMS. Veterinary practices are identified by numbers, not names, and the same practice numbers might be used by two or more PMSs. The clinical evidence schema requires updating to allow data from multiple practices to be contained within a single data extract direct from a central PMS database. It also needs to identify the PMS of origin of each data extract, so that veterinary practices from different PMSs are not confused with each other when the data from multiple extracts is combined by researchers.

5.3 Aim

To create a framework for extracting patient data from the clinical notes of patients with feline CKD from within PMSs, with the view to establishing the usefulness of this data for conducting clinical research.

The objectives of this work were:

1. Establish an agreement with one or more veterinary PMSs to share veterinary EPRs for a research study.
2. Write a new schema for extraction of clinical evidence which is capable of identifying data extracts from multiple veterinary practices and PMSs.
3. Create a database to structure and store the data in a format from which it can be easily queried and extracted to answer research questions.
4. Create a method for deidentifying the free text from the veterinary EPR.

5.4 Methods

5.4.1 Methods 1: Agreement with PMSs to share veterinary EPRs for research

PMSs who were part of the VetXML Consortium were approached directly by email, at the Consortium's regular meetings and at BSAVA Congress, to identify if they wanted to contribute to the study. These PMSs were approached because they were already familiar with transfer of data using XML schemas. The data requirements of a potential new schema for clinical evidence were discussed and an example data file of imaginary patient data was shared with the PMS (Figure 5.1. Follow-up emails were sent and virtual meetings were held to discuss all details with the research team. Once involvement was approved, bespoke data sharing agreements were set up for each PMS. The vision for the flow of data from the patient EPR to the destination research database is shown in Figure 5.2.

```
<?xml version="1.0" encoding="UTF-8"?>
- <ClinicalDataBatch xmlns="http://www.vetxml.org/schemas/Schema_Rev_23.xsd" BatchEnds="2016-06-01" BatchBegins="2015-08-19" PMS_ID="ce
  - <Practice>
      <PracticeID>HD1</PracticeID>
    - <Animal>
        <AnimalID>123456</AnimalID>
      - <Overview>
          <Species>Bear</Species>
          <Breed>Brown</Breed>
          <DateOfBirth>2008-07-03</DateOfBirth>
          <DateOfDeath/>
          <Gender>Male - Castrated</Gender>
          <Dangerous>0</Dangerous>
          <Insured>0</Insured>
          <Notes>Exits stage left</Notes>
          <RegistrationDate>2009-02-13</RegistrationDate>
        - <ChronicCondition>
            <DateRecorded>2016-01-01</DateRecorded>
            <Description>Arthritis</Description>
          </ChronicCondition>
        - <ChronicCondition>
            <DateRecorded/>
            <Description/>
          </ChronicCondition>
        </Overview>
      - <ClinicalHistory>
        - <History>
            <HistoryDateTime>2016-05-23T09:19:11.000+01:00</HistoryDateTime>
            <EnteredByID>678</EnteredByID>
            <ClinicalNotes>Not so well</ClinicalNotes>
            <Diagnosis>Heart Cardiac Failure</Diagnosis>
            <DiagnosisVeNomCode>679</DiagnosisVeNomCode>
          </History>
        - <History>
            <HistoryDateTime>2016-05-23T09:19:13.000+01:00</HistoryDateTime>
            <EnteredByID>678</EnteredByID>
            <ClinicalNotes>1 x sConsultation repeat 3/Short consult </ClinicalNotes>
            <Diagnosis>Heart Cardiac Murmer (functional)</Diagnosis>
            <DiagnosisVeNomCode>948</DiagnosisVeNomCode>
          </History>
        - <Parameters>
            <ParametersDate>2016-02-22</ParametersDate>
            <Weight>70.2</Weight>
            <WeightUnit>kg</WeightUnit>
            <WeightNotes>Increasing</WeightNotes>
            <BodyConditionScore>3</BodyConditionScore>
            <MuscleConditionScore>3</MuscleConditionScore>
          </Parameters>
        </ClinicalHistory>
      </Animal>
    </Practice>
  - <Practice>
      <PracticeID>HD2</PracticeID>
    - <Animal>
        <AnimalID>654321</AnimalID>
```

Figure 5.1 Example of imaginary patient data extracted and arranged conforming to the schema. This demo extract was validated against the schema in Microsoft Visual Studio

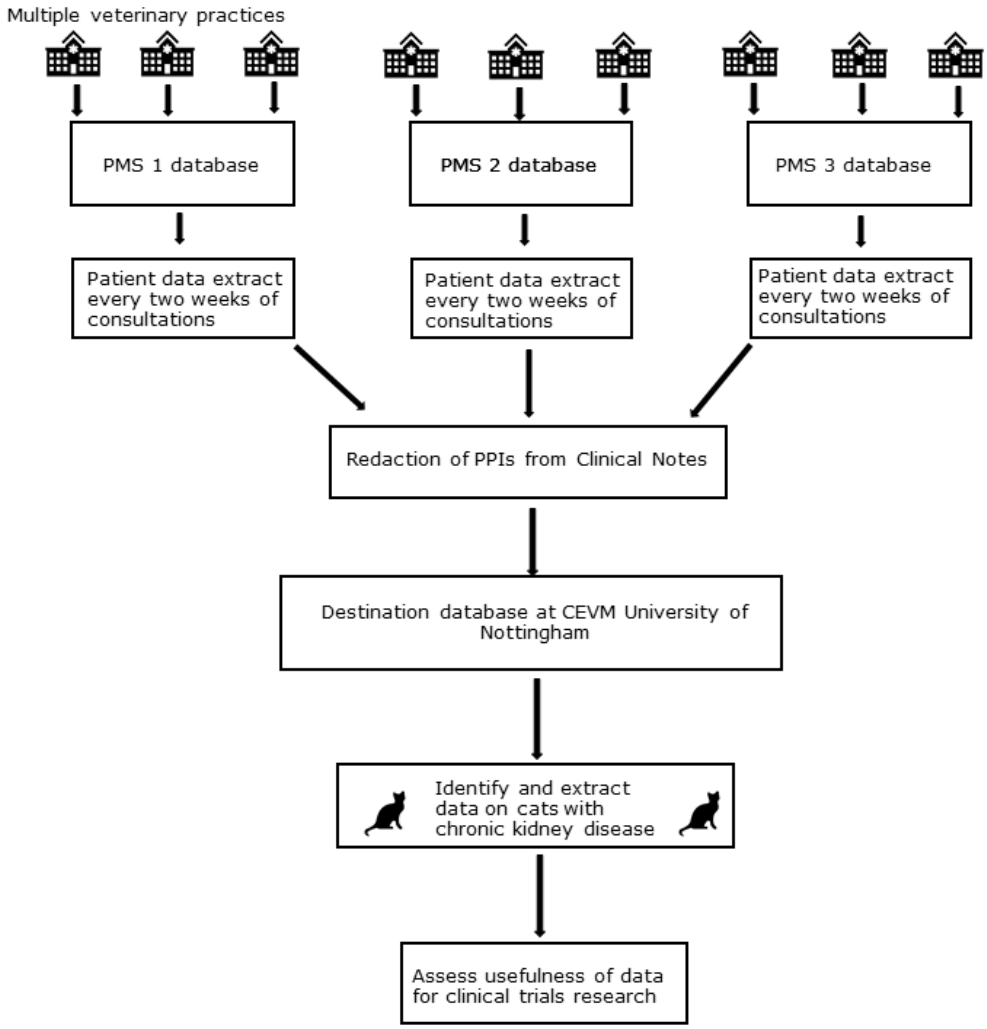


Figure 5.2 Overview of planned flow of patient data from veterinary practices to researchers, and cats with CKD to be identified and their data examined in more detail

5.4.2 Methods 2: New schema for clinical evidence

The Clinical Evidence Schema v1.0.5 (J. S. Jones-Diette et al., 2016) was used as the basis for the new schema. The previously published schema required several adaptations to meet the requirements of this current study, so that it could be used to extract cohorts of patient data into one destination database for clinical research from multiple disparate PMS systems. The adapted schema would be used to describe the format and content of the data extracts from each PMS database to be sent to the research group on a two-weekly basis, detailing the veterinary consultations which had taken place during the two weeks. The changes made were as follows:

- The maximum number of occurrences of PracticeID was changed from '1' to 'unbounded'.
- The PMS of origin for each data extract was added to the schema as 'PMS_ID'.
- The dates of the data extract were added to the schema as 'BatchBegins' and 'BatchEnds'.
- An unlimited ('unbounded') number of veterinary practices could be included per data extract and each veterinary practice could include data on an unlimited number of animals, who in turn could have an unlimited number of parameter measurements included.
- Each animal had a unique AnimalID number.
- The element 'Remarks' from Clinical Evidence Schema v1.0.5 was changed to "Notes" as this terminology was found to be more widely used and recognised for this field across PMSs.
- Weight measurements were moved from being nested within 'AnimalDetails' (J. S. Jones-Diette et al., 2016) to a separate part of the schema.

5.4.2.1 Validation pilot

The schema was written in XML. Schemas can be held locally or on a webpage and data extracts which are supposed to conform to the schema can be validated against the schema automatically, to look for missing or incorrectly presented data. To ensure that this process worked successfully for the newly created schema, a test file of imaginary patient data (Figure 5.1) which was created conforming to the schema, was validated against the schema in Microsoft Visual Studio.

5.4.3 Methods 3: Create a database to structure and store the data

A relational database was built in MySQL (SQL: Structured Query Language) in preparation to hold the EPR data.

5.4.4 Methods 4: A method for redacting identifiers from the free text fields.

5.4.4.1 Overview of redaction method

After some preliminary investigation of the data within the free text entry field 'ClinicalNotes' where the veterinary consultation notes were written, it became apparent that this field particularly was at risk of containing Potential Personal Identifiers (PPIs). A script was created in Microsoft Visual Basic to identify and redact PPIs from the text where they occurred.

An overview of processes required to obtain patient data from the PMS and prepare it for analysis can be seen in Figure 5.3.

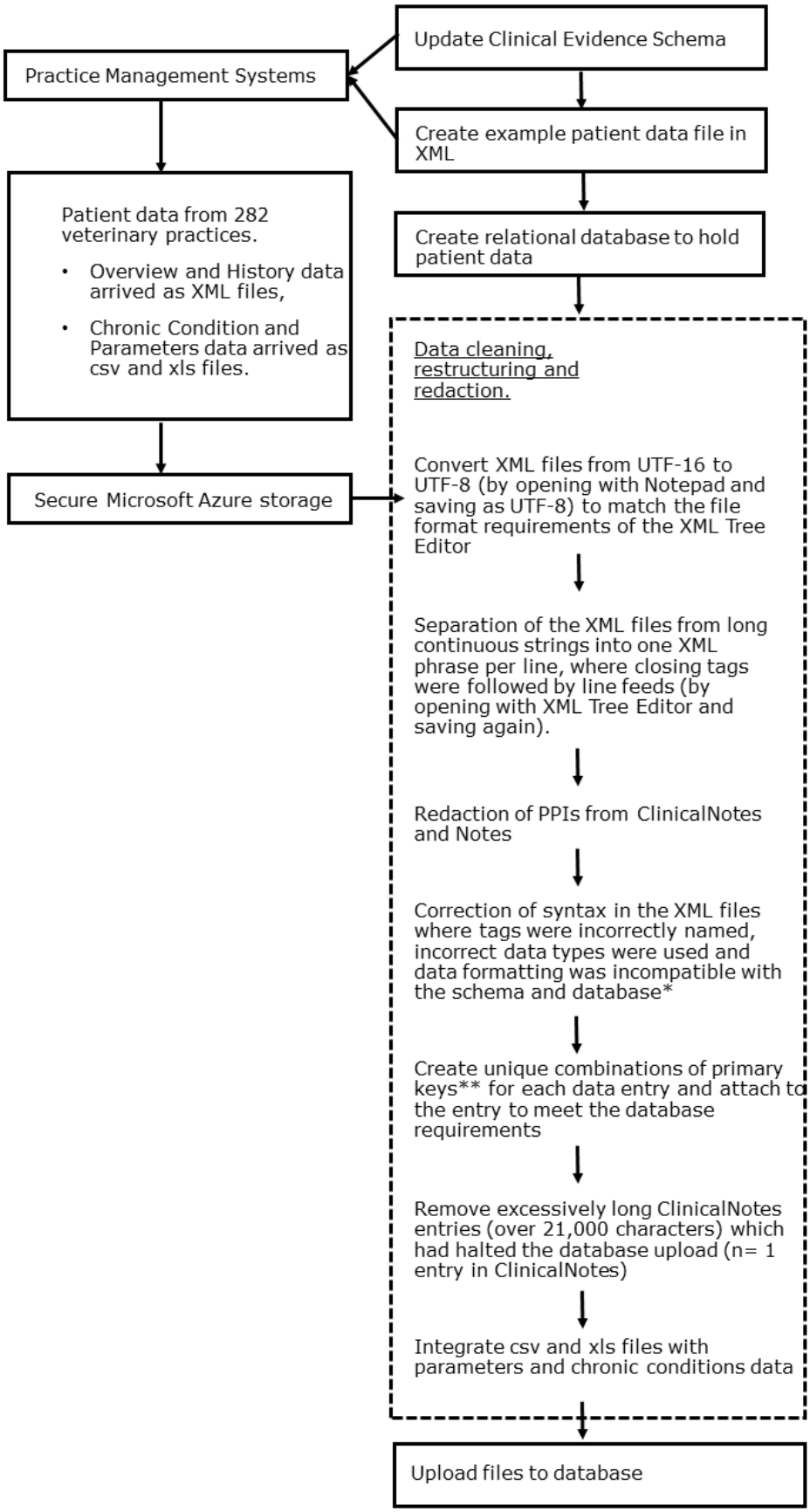


*Figure 5.3 Flowchart to show tasks and processes required for obtaining patient data from PMS, the movement of data from PMS to research database and then preparing data for analysis. *changes to tags can be seen in Appendix 10. **see tables and primary keys in fig.6.*

5.5 Results

5.5.1 Results 1: Agreement with PMSs to share veterinary EPRs for research

5.5.1.1 Covid-19 impact

The Covid-19 pandemic had a large impact on this study. Four PMSs were in regular discussions during the PhD study to discuss the possible process, the data required and to set up data sharing methodology for this study for automated data extraction. Out of all PMSs in discussion, only one PMS was able to contribute data, and changes were made to which data was obtained, the timescale represented by the data and the method of data transfer. So that the data extracted was as representative as possible to normal veterinary consultations under normal working conditions, the data extracted was from the pre-pandemic period. Any data generated during the Covid-19 lockdown, while veterinary practices were using more telemedicine and not allowing clients into the practice building for consultations, was unlikely to represent normal practice, (Caney et al., 2022; Owczarczak-Garstecka et al., 2022) and SAVSNET Reports (http://www.liverpool.ac.uk/media/livacuk/savsnet/Impact,of,COVID-19,on,companion,animal,veterinary,practice,report,6.pdf) . A data sharing agreement was agreed and signed with the Contracts Department of the PMS before data files were transferred (Appendix 9).

5.5.1.2 Data extract

A single data extract covering all consultation records from 282 veterinary practices serviced by the same PMS, from January 1st 2019 to June 30th 2019 was obtained. This data file was too large to be processed as a single unit and was separated into 282 files, each representing the data from a single veterinary practice. Each of the 282 PMS XML files contained the information required on patient overview and consultation histories. Data on chronic disease conditions and weight measurements were provided as .xls files. These files

were then converted into XML format before loading into the database. All data files were transferred to the University via secure Microsoft Azure Storage.

5.5.2 Results 2: New schema for clinical evidence

The schema went through 23 revisions before being finalised (Figure 5.4 = whole schema. Appendix 11 highlights features of the schema and changes made).

Key features included:

- The data in each batch could come from an 'unbounded' number of veterinary practices, each practice was described by one ID.
- Each veterinary practice could included data from an unlimited ('unbounded') number of animals.
- Each animal had one 'overview' where the species, breed, date of birth and other data for the Overview table in the database were described.
- Each animal could have an unlimited number of chronic conditions. The data for this included date recorded and description.
- An unlimited number of History entries could be included for each animal. History data included date and time of data entry into the PMS database, who entered the data, the clinical notes, any diagnosis given and diagnosis VeNom Codes if used.
- Each animal could have an unlimited number of parameters recorded. Data for these included date of recording, weight, weight unit and weight notes (if it was a weight) and body condition and muscle condition score given if used.
- The data batch closed by defining the PMS of data origin and the start and end dates of the data batch.

```
<xs:schema xmlns:xs="http://www.w3.org/2001/XMLSchema" targetNamespace="http://www.vetxml.org/schemas/Schema_Rev_23.xsd" elementFormDefault="qualified" attributeFormDefault="unqualified">
▼<xs:annotation>
  ▼<xs:documentation>
     Schema_rev_23 revised 16th March 2020.
     <br/>
     The following dates can be empty: DateOfBirth, DateOfDeath, RegistrationDate, DateRecorded.
     <br/>
     The following default values within the schema allow null entries for non-string elements: Dangerous=0, Insured=0, DiagnosisVeNomCode=0, Weight=0.0, BodyConditionScore=0, MuscleConditionScore=0.
     <br/>
     To be useful to a normalised database, PMS_ID, PracticeID and AnimalID are required.
     <br/>
     In addition, HistoryDateTime and ParametersDate are required but only if History and/ or Parameters are recorded.
   </xs:documentation>
  </xs:annotation>
▼<xs:element name="ClinicalDataBatch">
  ▼<xs:complexType>
    ▼<xs:sequence>
      ▼<xs:element name="Practice" maxOccurs="unbounded" minOccurs="0">
        ▼<xs:complexType>
          ▼<xs:sequence>
             <xs:element type="xs:string" name="PracticeID" maxOccurs="1" minOccurs="0"/>
            ▼<xs:element name="Animal" maxOccurs="unbounded" minOccurs="0">
              ▼<xs:complexType>
                ▼<xs:sequence>
                   <xs:element type="xs:string" name="AnimalID" maxOccurs="1" minOccurs="0"/>
                  ▼<xs:element name="Overview" maxOccurs="1" minOccurs="0">
                    ▼<xs:complexType>
                      ▼<xs:sequence>
                         <xs:element type="xs:string" name="Species" maxOccurs="1" minOccurs="0"/>
                         <xs:element type="xs:string" name="Breed" maxOccurs="1" minOccurs="0"/>
                        ▼<xs:element name="DateOfBirth" maxOccurs="1" minOccurs="0">
                          ▼<xs:simpleType>
                            ▼<xs:union memberTypes="xs:date">
                              ▼<xs:simpleType>
                                ▼<xs:restriction base="xs:string">
                                   <xs:enumeration value=""/>
                                 </xs:restriction>
                               </xs:simpleType>
                             </xs:union>
                           </xs:simpleType>
                         </xs:element>
                        ▼<xs:element name="DateOfDeath" maxOccurs="1" minOccurs="0">
                          ▼<xs:simpleType>
                            ▼<xs:union memberTypes="xs:date">
                              ▼<xs:simpleType>
                                ▼<xs:restriction base="xs:string">
```

```
            <xs:enumeration value=""/>
          </xs:restriction>
        </xs:simpleType>
      </xs:union>
    </xs:simpleType>
  </xs:element>
  <xs:element type="xs:string" name="Gender" maxOccurs="1" minOccurs="0"/>
  <xs:element type="xs:boolean" name="Dangerous" maxOccurs="1" minOccurs="0" default="0"/>
  <xs:element type="xs:boolean" name="Insured" maxOccurs="1" minOccurs="0" default="0"/>
  <xs:element type="xs:string" name="Notes" maxOccurs="1" minOccurs="0"/>
▼<xs:element name="RegistrationDate" maxOccurs="1" minOccurs="0">
  ▼<xs:simpleType>
    ▼<xs:union memberTypes="xs:date">
      ▼<xs:simpleType>
        ▼<xs:restriction base="xs:string">
            <xs:enumeration value=""/>
          </xs:restriction>
        </xs:simpleType>
      </xs:union>
    </xs:simpleType>
  </xs:element>
▼<xs:element name="ChronicCondition" maxOccurs="unbounded" minOccurs="0">
  ▼<xs:complexType>
    ▼<xs:sequence>
      ▼<xs:element name="DateRecorded" maxOccurs="1" minOccurs="0">
        ▼<xs:simpleType>
          ▼<xs:union memberTypes="xs:date">
            ▼<xs:simpleType>
              ▼<xs:restriction base="xs:string">
                  <xs:enumeration value=""/>
                </xs:restriction>
              </xs:simpleType>
            </xs:union>
          </xs:simpleType>
        </xs:element>
        <xs:element type="xs:string" name="Description" maxOccurs="1" minOccurs="0"/>
      </xs:sequence>
    </xs:complexType>
  </xs:element>
 </xs:sequence>
</xs:complexType>
</xs:element>
▼<xs:element name="ClinicalHistory" maxOccurs="1" minOccurs="0">
  ▼<xs:complexType>
    ▼<xs:sequence>
      ▼<xs:element name="History" maxOccurs="unbounded" minOccurs="0">
        ▼<xs:complexType>
          ▼<xs:sequence>
```

```
                    <xs:element type="xs:dateTime" name="HistoryDateTime" maxOccurs="1" minOccurs="0"/>
                    <xs:element type="xs:string" name="EnteredByID" maxOccurs="1" minOccurs="0"/>
                    <xs:element type="xs:string" name="ClinicalNotes" maxOccurs="1" minOccurs="0"/>
                    <xs:element type="xs:string" name="Diagnosis" maxOccurs="1" minOccurs="0"/>
                    <xs:element type="xs:integer" name="DiagnosisVeNomCode" default="0" maxOccurs="1" minOccurs="0"/>
                  </xs:sequence>
                </xs:complexType>
              </xs:element>
            ▼<xs:element name="Parameters" maxOccurs="unbounded" minOccurs="0">
              ▼<xs:complexType>
                ▼<xs:sequence>
                    <xs:element type="xs:date" name="ParametersDate" maxOccurs="1" minOccurs="0"/>
                    <xs:element type="xs:decimal" name="Weight" default="0.0" maxOccurs="1" minOccurs="0"/>
                    <xs:element type="xs:string" name="WeightUnit" maxOccurs="1" minOccurs="0"/>
                    <xs:element type="xs:string" name="WeightNotes" maxOccurs="1" minOccurs="0"/>
                    <xs:element type="xs:integer" name="BodyConditionScore" default="0" maxOccurs="1" minOccurs="0"/>
                    <xs:element type="xs:integer" name="MuscleConditionScore" default="0" maxOccurs="1" minOccurs="0"/>
                  </xs:sequence>
                </xs:complexType>
              </xs:element>
            </xs:sequence>
          </xs:complexType>
        </xs:element>
      </xs:sequence>
      <xs:attribute type="xs:string" name="PMS_ID" use="required"/>
      <xs:attribute type="xs:date" name="BatchBegins"/>
      <xs:attribute type="xs:date" name="BatchEnds"/>
    </xs:complexType>
  </xs:element>
</xs:schema>
```

Figure 5.4 Finalised updated schema written in XML. Allows for multiple PMSs, multiple veterinary practices and multiple patients to be identified. Weight measurements moved out of the animal details and more parameter measurements are included.

5.5.2.1 Validation pilot results

The test file of imaginary patient data was successfully validated against the schema, using Microsoft Visual Studio.

5.5.3 Results 3: A database to structure and store the data

The resulting database structure with four tables can be seen in Figure 5.5. Primary key attributes are notes by a key symbol. Non-key attributes for each table had unique names. PMSs and veterinary practices were identifiable within the dataset by unique numbers and each patient had an AnimalID number. Patients were uniquely identified across the dataset by a composite primary key consisting of their AnimalID, PracticeID and PMS_ID (all of these were also primary keys). All non-key attributes were solely dependent on the keys. The attributes within each database table can be seen in Table 5.1.

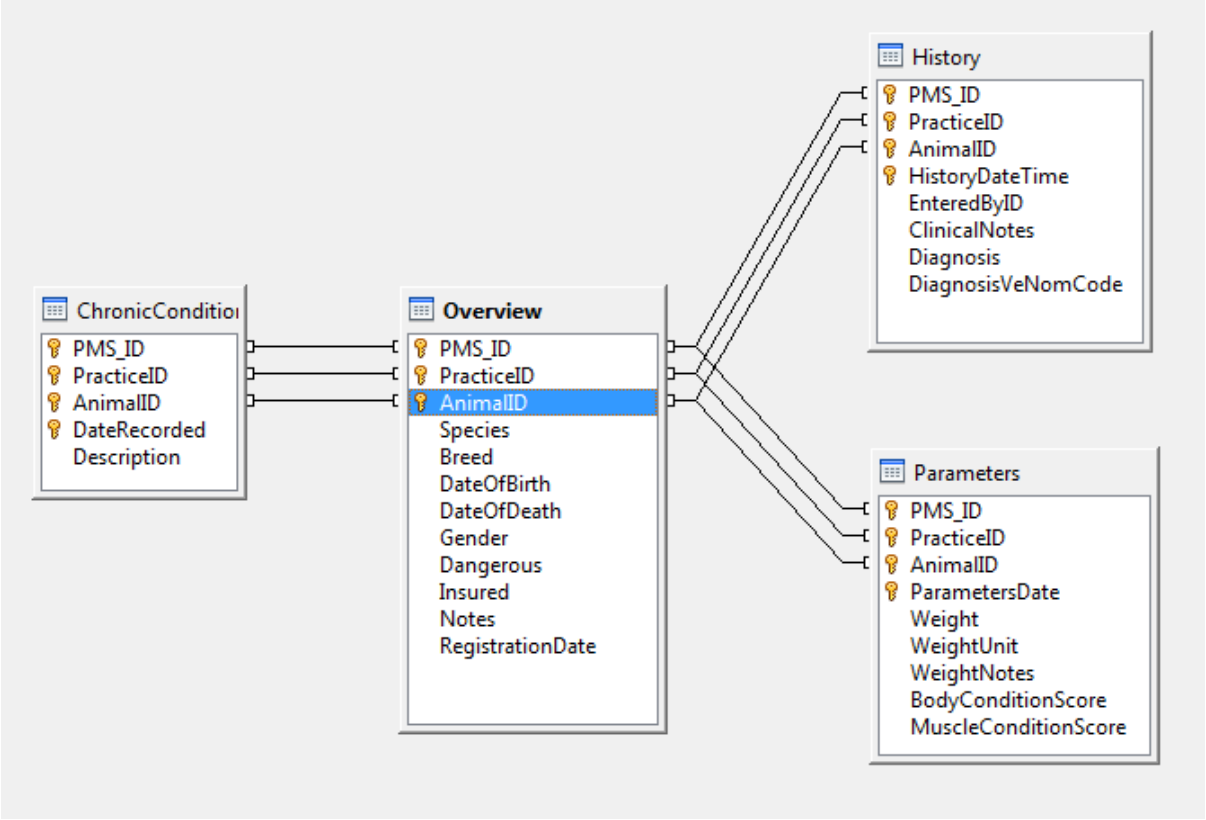


Figure 5.5 Relational database structure as created, taken from a screenshot from Microsoft Access.). This same structure was then replicated in MySQL. Key symbols represent primary keys for each of the tables. Non key attributes have unique names. The one-to-many relationships between tables are demonstrated by the connecting lines between the tables.

5.5.3.1 Database tables

"Overview"

Contained attributes about each patient which were mostly static, have only one entry per patient and are not added to cumulatively over a prospective time period. For example, a patient will only have one breed or species. There was only one record for gender for each patient, this would be updated in the source database and subsequently the destination database, if the patient was neutered. The notes field also had a single entry, which could be updated when additional notes were added. The information recorded in the notes field varied between PMSs. This field was not used to store the record of the veterinary consultation.

"History"

Contained information about veterinary consultations. Each time the patient had an interaction with the PMS, (this could be a veterinary consultation, a nurse consultation, phone call or discussion with reception staff) where notes were written, a new entry was made in the history table. This had a unique date and time stamp "HistoryDateTime" which was part of the primary key for that entry. EnteredByID contained the unique ID number of the person entering the record on the PMS, the person was not identifiable within the research dataset via this number.

"Parameters"

Contained records of weight, body condition or muscle condition measurements which had been entered within each specific field within the PMS. A unique date and time stamp formed part of the primary key for each entry in this table. WeightUnits denotes the unit of weight measurement. WeightNotes was used for the EnteredByID to leave comments, e.g. "losing weight".

"ChronicConditions"

Contained information captured about chronic conditions by a specific field within the source PMS. A chronic condition e.g. diabetes, was entered into the PMS and the date and time stamp of that entry was created for each entry. In meetings with PMSs where the

schema was discussed, it was found out that some PMSs prepopulated this field with a predefined list of conditions and for some PMSs this was a free text field.

Table 5.1 Description of all attributes within the database and which tables they belonged to.

Database table	Attribute	Description
All	PMS_ID (primary key for all tables)	Name of the PMS of origin of the data extract
	PracticeID (primary key for all tables)	A unique number, given to the veterinary practice by the PMS, to identify the practice within the PMS dataset. PracticeID numbers were not unique to individual branches of a veterinary practice, one number represented all branches within one veterinary practice business
	AnimalID (primary key for all tables)	A unique number allocated to identify each animal within the PMS dataset. This number was allocated either at the level of the PMS or the level of the veterinary practice, and varied between PMSs
Overview	Species	Animal species
	Breed	Animal breed
	DateOfBirth	Date the animal was born, if known.
	DateOfDeath	Date the animal died, if applicable.
	Gender	Gender and neuter status
	Dangerous	Information field, yes or no
	Insured	Information field, yes or no
	Notes	May be used for animal related notes that are not the clinical history notes from the veterinary consultation
	RegistrationDate	Date of registration of this animal with the PMS

History	HistoryDateTime (also a primary key for this table)	The date and time stamp when the clinical notes were entered and saved into the PMS interface.
	EnteredByID	The identity of the person entering the clinical notes, usually identified as a unique number.
	ClinicalNotes	The free text field where the consultation information and data were recorded by the veterinary surgeon or veterinary nurse.
	Diagnosis	Diagnosis made during the veterinary consultation, if known.
	DiagnosisVenomCode	A coded entry as designed by the Venom coding group (https://venomcoding.org/venom-codes/) for the diagnosis reached.
Parameters	ParametersDate (also primary key for this table)	The date and time stamp when the parameter entry was made.
	Weight	The weight measurement
	WeightUnit	The unit used for recording the weight, e.g. kg
	WeightNotes	Free text field for commentary on the weight, e.g. 'losing weight'
	BodyConditionScore	Body condition score, entered as a number.
	MuscleConditionScore	Muscle condition score, entered as a number.
ChronicConditions	DateRecorded (also primary key for this table)	The date and time stamp when the chronic condition entry was made.
	Description	Description or diagnosis of the chronic condition, e.g. 'arthritis'.

5.5.4 Results 4: A method for redacting identifiers from the free text fields.

Identifying information was found in the 'ClinicalNotes' field and contained information relating to phone numbers, email addresses, names and other PPSs. A script was written in Microsoft Visual Basic, in Microsoft Visual Studio to redact PPIs (Table 5.2) from the field. This redaction was carried out on the data extract files written in XML. First, the 'ClinicalNotes' field was identified by reading each line of the file in turn, searching for the tag '<ClinicalNotes>'. Next the end of the string was identified by finding the closing tag '</ClinicalNotes>'. The "string" was everything that appeared between the opening and closing tags. The opening and closing tags were removed and a selection of common XML mark-up tags and other characters were removed from the string. These tags were initially identified by manual examination of free text and during the data cleaning process. They were tags used for formatting the text within the PMS interface but have no role in the destination research database and had the potential to cause problems with assessment and redaction, causing the meaning of the text or be misread either by eye or when querying the database. Tags were removed and replaced as described in Appendix 10.

Following this, the string was split into individual words and each word in the string was examined in turn by the redaction process against each redaction test (Table 5.2). After the redaction process was complete, each word would either: be given a "flag", or be redacted, or left alone. If a "flag" was set with a test result, no further tests were carried out on the word.

Following the redaction, the words in the string were concatenated and then the original string was rebuilt, with all words either protected (Table 5.3), redacted or left alone by the process. Finally, the '<ClinicalNotes>' and '</ClinicalNotes>' tags were re-attached to either end of the string and the modified string was replaced back into the XML data file.

Table 5.2 Explanations of each test applied to words to assess whether the word required redacting. Explanations are given in italic text. Grey boxes describe the process but are not in themselves things to look for or redaction methods.

Test	**Look for**	**Action to take**
Email address	'@'	Replace the word with 'email_address' (and set flag)- once a flag is set, no more tests are done, this makes the process more efficient.
Webpage address	'http' or 'www'	Replace the word with 'webpage_address' (and set flag)
Phone number and microchip number	If the second character of the word is a number	
	If last character is a full stop	Remove
	If the word contains a decimal point	Do not redact (and do set flag). This protects weights and urine specific gravity measurements.
	If the word is longer than three characters	Check the first three characters and if they are not all numbers, do not redact (and do set flag). This protects weights, blood pressure measurements and urine specific gravity measurements from accidental redaction.
	If neither of the two rows above apply	Redact all characters (replace all characters with #) (and set flag)
Postcode	If the word is all lower case	Do not redact (and do set flag).
	If the word contains 3 or 4 characters, check to see if it is part of a postcode	
	If the first character is a number and the second and third are letters	Redact as "###" (and set flag)

	If the first and second characters are letters and the third is a number	Redact as "###" (and set flag)
Name	First, remove any character which was not a letter from the end of the word, e.g. '.'	
	Check the word against the two lists, 'short word list' (Appendix 12) and 'long word list' (Appendix 13) for matches. *These lists were created to prevent useful clinical words or acronyms being redacted mistakenly as names.*	If a match is found to either list (according to each list's individual rules), then set flag and protect from further redaction.
	Words remaining unprotected after comparison with the short and long word lists were examined to see if they were names of people, animals or places.	
	If the word starts with a capital letter it is classed as a name	Alternate characters in the word removed and replaced with '#'.
	At the end of this process, any characters (e.g. '.') which had been removed at the start of the name test were replaced.	

Table 5.3 The rules applied for words to match the short word list and long word list. These were lists of protected words, introduced to reduce the accidental reduction of clinical meaning from the text by redaction. Matching words were flagged and protected.

Lists of protected words	**List rules**
Short word list	Words have to be exact matches (including upper/lower case match) to be flagged and protected, e.g. BID, SDMA, TLI.
	If the word is written in capital letters, the match has to be in capital letters, even if it is inside another word (this protects acronyms). Acronyms containing characters

	like hyphens were not set up to be protected in this way. Words containing hyphens words were put onto the 'Long word list' where only partial matches were required.
Long word list	Words only have to be partial matches in order to be flagged and protected, e.g. Biochem, Kidney, Interpret.
	Words on this list do not have to match upper/lower case.
	The script looks inside the word being examined for partial matches to words on the list. For example: "urin" was on this list. This would make a partial match with any of: urine, urinate, urination, urinated, during, maturing, or any other word containing "urin".

The program created to redact PPIs from the clinical notes appeared to work well and after demonstrating the effectiveness of the program to a PMS, they were willing to provide EPRs for the study. Example clinical notes with redacted text can be seen in Figure 5.6.

Although the redaction performed as it had been designed to, approximately 40 microchip numbers were found within the data extract provided by the PMS which had not been redacted by the process described. The numbers had been retained as they were written in a way which had not been anticipated; the numbers contained either "." or "-" characters to separate groups of numbers. For example: 981.0000001234.123. The redaction program had recognised the additional characters inside the numbers and mistakenly flagged them as weight measurements or specific gravity measurements and protected them from redaction.

First entry	#r#b#e# : Old cat, gradual weight loss; vacant episode yesterday, today better; #D#P# for a while; Eating ++; had dia last few days . BAR. BS 3/9 Diet : #e#i#r Exm : MM pink, CRT 2s; teeth mouth good. #o#e ok. #y#s ok, #a#s ok. LN ok. No palpable thyroid #b#o NAD, no pain or mass. HR 240 regular, no murmurs RR 20 clear. Coat fair. Mobility fair, #i#c#s# : 1 gettign old 2 heart - poss Hypert/HCM 3 PD - HyperT, CRF, DM, others 3 diarhoea - nutrional, metabloic, lyphoma. #p#i#n# of work up to get better idea. O elect not for now #L#N support treatmetn re diarrhoea. BB if not improving. O aware may need euth soon
Second entry	Heart failure, with dyspnoea ++++; O elct euth; to bury at home

Figure 5.6 Example of two redacted clinical notes entries for the same patient. Redacted words have all or alternate letters replaced with '#'.

5.6 Discussion

This study met its four objectives for obtaining and using veterinary EPRs for clinical trials research: 1) acquisition of real veterinary patient EPRs from a six-month period for analysis, 2) creation of a schema capable of allowing and identifying data from multiple PMSs and multiple veterinary practices, 3) creation of a bespoke database to structure and store the data for analysis, and 4) redaction of PPIs from the free text fields of the dataset.

5.6.1.1 The data extract from the PMS

The original plan for the research was to involve multiple PMSs. All data would be extracted in XML format, conforming to the schema, and the XML files would have been validated against the schema, and automatically transferred and uploaded to the dataset. The Covid-19 pandemic caused time constraints on many veterinary PMSs who had been approached and discussions started about contributing to the study. Two PMSs who were in discussion with researchers by the later stages of the study then had new commitments and development projects as a result of responding to the needs of their veterinary practices. One of these PMSs was a small organisation and the company director (the study liaison)

was occupied with developing software to meet the needs of the PMSs veterinary practices for remote consulting. This PMS was unable to provide data for the study. The other PMS had reduced staff availability due to the demands of the Covid-19 pandemic, to support this project. Despite this, the researchers were able to obtain some data. However, the automation of the extraction and upload processes for the datasets could not be developed and tested. It was hoped that part of the automated process would include validation of the XML data extracts against the schema, as validated extracts would require less cleaning and restructuring before use in the destination dataset. Automating the transfer and upload process would save time and reduce workload in the future for clinical trials, especially if large datasets were being extracted on a regular basis. Future work should explore this in more detail.

5.6.1.2 The schema

Once the alterations were made to the pre-existing published schema it appeared that the new schema would have functioned correctly for defining the structure and content of cohorts of patient data extracted for clinical trials. It was used by the PMS who participated in this PhD work to guide the required content for their data extraction, and used to validate the demonstration data file provided to the PMSs. However, due to constraints caused by the Covid-19 pandemic, it could not be used to validate the final XML data file produced by the PMS, as the PMS provided only a partial file in XML with additional data provided as other file types. Subsequently, some problems with the data file were later discovered (further detail provided in Chapter 6). Future work should explore the validation of the full XML data extract by PMSs and determine how feasible it is for PMSs to perform a full data extract conforming to the schema in the updated design.

The pre-existing published schema (J. S. Jones-Diette et al., 2016) held weight measurements as part of the animal's details (now called 'Overview' in the updated schema). In order to monitor weight change over time in clinical trials, it would be necessary to retain all weight measurements made on a patient. The pre-existing schema only extracted the last weight recorded. If a patient was frequently weighed over a period of time (e.g. once a week), then only extracting the last weight instead of all weights recorded would miss potentially clinically important data. In addition, if the elements as described in the pre-existing schema were translated directly into database fields then the previous

weight history could be overwritten each time the patient's weight was extracted using this schema. To overcome this issue, the updated schema separated out weight and other parameter measurements into a separate part of the schema, and multiple weight or parameter measurements could be included per patient. This was then recorded in the database with a date stamp, so that new weights would be added to, rather than replace, the information already recorded in the database.

5.6.1.3 The database

The database for this study was written in MySQL. Structured Query Language (SQL) consists of data definition and data manipulation commands which are commonly used for database writing, due to its ease of use and high functionality (Ricardo, 2002). Each PMS may be used by many veterinary practices. Each veterinary practice will have many patients and each patient will have many consultations and parameter measurements recorded over time and potentially visit more than one practice. The database structure needed to be relational to reflect and accurately represent these relationships so that individual patients could be uniquely identified within the database, their attributes linked together, and their clinical history and parameters added to continuously. In a clinical trial, it is vital that individual patients can be identified and tracked over time and in human medicine there is a recognised risk of 'duplicate subjects' and 'professional patients' when individual patients enrol in various clinical trials contemporaneously (Pinho et al., 2021). It is anticipated that the research database for a clinical trial would be an aggregated database, contributed to by many PMSs, veterinary practices and patients. Each patient needs to be uniquely identifiable. To achieve this, a combined primary key was built to identify each patient. If a patient moves to a new veterinary practice during a trial, that patient should still be identifiable as themselves, for continuity of records and to prevent that patient being incorrectly added to a trial twice. The PMS contributing to this study actually allocated AnimalID numbers per PMS, not per practice. Therefore, within all patients from this PMS, the AnimalID number should serve to uniquely identify each patient.

Within other PMSs (not involved in this study) unique AnimalID numbers can be allocated at the level of each individual veterinary practice. Therefore, within that PMS it is possible to have two or more patients with the same AnimalID number. To create unique identifiers for these patients, the veterinary practice ID needs to be combined with the AnimalID.

However, within some PMSs, the PracticeID may be a number instead of a name, for anonymity. If multiple datasets from multiple PMSs were combined, it is possible that multiple practices would have the same ID number. To ensure that patients remain uniquely identifiable despite practices having the same ID number, the PMS of origin was included as part of the primary key for each patient. Each patient will have multiple consultations and multiple parameter measurements taken within a trial. When new information about a patient is added to the record, it needs to be captured and uniquely identifiable within the database.

For each measurement and each set of clinical notes added to the dataset, the DateTime of each recording was designated a unique identifier and a primary key for this information. The PMS used in this study recorded data locally at each veterinary practice, however the main dataset held centrally at the PMS headquarters was updated every 30 minutes, and the DateTime for all recorded interactions was added at this stage to the main dataset. This main dataset was the source from which data for this study was extracted. Some patients would have multiple interactions with the practice within the same 30 minutes period, e.g. sales, clinical notes entries, decisions and test results. This then created multiple DateTime entries for some patients which were not unique, which then could not be loaded into the database as the primary key created from them was not unique. As part of the data cleaning process during this study, the time stamps were compared between each entry and the entries immediately before and after it, if the time recorded was identical and the other primary key information matched, the time stamp was incremented by one second, to prevent the times being identical. This time stamp duplication is something to be aware of for future versions of the database and for further study with PMS data. Establishing the method and timing by which time stamps are added to data within the PMS database is an essential part of understanding the data which will be extracted, and how best to handle, store and use it, so that no important clinical data is lost when the primary keys are applied.

5.6.1.4 Redaction of potential personal identifiers

The system created for this study for the redaction of PPIs appeared to work well, although there were limitations in relation to some microchip numbers not being redacted as they contained hyphens or decimal points. The redaction system did not redact numbers which contained decimal points, in order to protect weight measurements or urine specific gravity

measurements within the free text. Some refinement of this process is required in the future if microchip numbers are not being redacted, especially as there is a risk of phone numbers being noted in a similar way.

Weight measurements in the free text were protected by the system checking for decimal points within the first three characters, e.g. 13.4kg. However, this was designed for small animal weight measurements and would not protect weight measurements greater than 100 kg, nor would it protect drug doses (e.g. 1500mg), so future work is needed to further refine this part of the redaction.

The postcode redaction would redact a word in which either the first character was a number and the second and third were letters (e.g. 8DL), or the first and second characters were letters and the third was a number (e.g. LE9). This would only partially redact a postcode such as with the case of 'G13 1BX', the '1BX' would be redacted but not 'G13'. Despite the fact that this would later be redacted as a name as it starts with a capital letter, some further refinement may be required for better anonymity.

If redaction could have been carried out at the source PMS, a more complete redaction of names from the free text could have been achieved by the system referencing a list of known client names and redacting them from the free text. However, by agreement with the PMS in this study, the redaction was carried out immediately upon arrival of the data files before any further processing was done. Therefore, the resulting system, designed to assume that names would start with a capital letter and redacting all non-protected names, was effective. It is possible that non-capitalised names were missed and some further words redacted than were required, so some clinical meaning may have been lost from the text. Some conditions or pharmaceutical products may start with a capital letter or may begin a sentence, and these could have been lost from the text using the existing redaction system. For future use, more clinical meaning could be retained by making the 'long list' of protected words more comprehensive.

5.6.1.5 Limitations

Further to the limitations already mentioned, only one PMS contributed data to this study so it is not known whether other PMSs would have been successful in supplying data to fulfil all fields of the newly revised schema. It was also not possible to test whether the PMS

identification element added to the XML extracts would reliably distinguish between PMS extracts in the destination dataset. The automation of data extraction, validation and uploading was not tested during this study and the manual upload and data transfer system which was used instead will likely prove to be intractable for large datasets in future clinical trial work.

In the following chapter (Chapter 6), the extracted dataset will be explored and the feasibility of using SQL to query the MySQL database for extracting clinical data required for research trials examined. It will also explore whether the data contained within the patient EPR is sufficient for informing research trials.

5.7 Conclusions

Although many PMSs are interested in contributing data to clinical research, their involvement in this study was limited due to the Covid-19 pandemic. Data which were reflective of normal, pre 'lockdown' veterinary practice was obtained by the generous cooperation of one PMS. An XML schema was generally successful in describing the required data extract. A MySQL relational database and MySQL queries appeared to work well for handling patient data, due to the databases relational nature. The database was designed to allow the integration and incorporation of future data extracts from additional PMS sources, although not tested in this study. The next stages of this work will explore the clinical usefulness of the patient data which was extracted and structured according to these methods.

6. Chapter 6: Identifying cats with chronic kidney disease in electronic patient records and identifying and extracting core outcomes for trials.

6.1 Context

In chapter 5 the feasibility of accessing, extracting, storing and querying patient records was explored. This next study aimed to establish whether cats with chronic kidney disease (CKD) could be found within the dataset and their treatment outcomes could be extracted from the data. A core set of treatment outcomes for these patients was established in chapter 3. The patient dataset was reviewed for cats with CKD, their associated clinical notes and other fields where outcomes might be recorded. The dataset was interrogated for the presence of the outcomes identified from the COS to establish the potential contribution that these patient records could make to future practice-based treatment trials.

6.2 Introduction

6.2.1.1 Consultation data within Electronic Patient Records (EPRs)

Demographic and clinical information about animal patients treated by veterinary professionals is stored electronically within Practice Management Systems (PMSs) in Electronic Patient Records (EPRs). These data are collected from patients treated in veterinary clinical practice, both for routine preventive healthcare consultations (J. Jones-Diette et al., 2017) and for a range of clinical conditions (Robinson et al., 2015). Historically, patient data were stored for billing purposes to ensure every procedure and drug dispensed was appropriately charged for (J. S. Jones-Diette et al., 2016).

6.2.1.2 EPRs and research

An advantage of extracting data from EPRs for research is that it facilitates inclusion of a large number of animals into trials, likely from multiple different clinics. In human healthcare research, using routinely collected data means that trial sample sizes can far exceed the number of patients typically seen in sample sizes for clinical trials (Hemkens et al., 2016). However, this advantage may be mitigated by the quality of the information available in the EPRs. As the data are not collected for research purposes, the information contained may be subjective or limited.

6.2.1.3 EPRs and pragmatic trials

In pragmatic trials the treatments given, assessments carried out and the data recorded should reflect standard routine practice as far as possible so that the data generated reflects real world treatment effectiveness (Patsopoulos, 2011). Veterinary practice EPR data could be an ideal data source for pragmatic trials because the patients represented in the EPR are real-world patients, with potential comorbidities, treatment constraints and owner constraints. The resulting treatment outcomes recorded in the EPR directly reflect real world patient responses to treatments and treatment effectiveness. This patient information held within EPRs could be invaluable in expanding our knowledge on how treatments perform beyond the original efficacy trial studies and increasing our knowledge of treatment effectiveness.

6.2.1.4 EPRs and human pragmatic trials

Routinely collected electronic patient data has already been established as a data source for pragmatic trials in human medicine. The CPRD (Clinical Practice Research Datalink) collects anonymised patient data, including data for 60 million patients, from GP practices across the UK and link this to other health data for research. They have published over 3000 times on a variety of areas including drug safety, medicines use, risk factors for disease and health care delivery (https://cprd.com/cprd-enabled-research).

6.2.1.5 Novel initiatives in veterinary research with EPRs for clinical trials

In veterinary research, a recently started project by VetCompass is investigating methods for using routinely collected EPRs for clinical trials in dogs. The aim is to generate evidence of a comparable level to randomised controlled trials, for the treatment of canine osteoarthritis, otitis externa, chronic diarrhoea and cruciate ligament rupture (https://www.rvc.ac.uk/vetcompass/research-projects-and-opportunities/projects/projects/vetcompass-eclinical-trials). It is logical therefore to investigate routinely collected veterinary patient data, to see if it could be a useful data source for veterinary pragmatic trials to address research questions for feline CKD. When these patients are seen by clinicians in veterinary consultations, their presenting clinical signs, diagnostic test and examination results, treatment strategies and outcomes are likely to be recorded within their EPRs (Robinson et al., 2015). This information is normally used to inform the veterinary professionals caring for the patient of their progress, so that they can be monitored and treatment success for each patient can be ascertained. Important decisions around length of treatments, patient success or deterioration and often eventually, euthanasia decision making, can all be supported by the information recorded in the EPR.

As part of their practice-based research, the Centre for Evidence-based Veterinary Medicine (CEVM) at the University of Nottingham have established their Veterinary Clinical Trials Network (VCTN), a rapidly expanding group of over 70 veterinary practices (https://www.nottingham.ac.uk/cevm/practice-based-research/small-animal/index). They are working with veterinary surgeons, veterinary nurses and clients from these practices, who provide input on research prioritisation, outcomes consensus building and the practicalities of trials research using PMS data. By working with the veterinary surgeons and veterinary nurses and owners who care for patients and make their healthcare decisions, the CEVM ensure their research is as relevant as possible to clinical practice. Small animal research work includes preventative healthcare consultations, quality of life of dogs with arthritis, appropriate use of antibiotics in dogs, cats with lymphoma and feline CKD; unanswered questions on CKD treatment and management (Dean, 2014) and parameters to measure in CKD treatment (Chapter 3 and Doit et al., 2021.

6.2.1.6 Feline CKD

Chronic kidney disease (CKD) is a commonly reported condition in cats causing significant morbidity and mortality, impacting on the patient's quality of life (Bijsmans et al., 2016). There are many uncertainties and unanswered questions on CKD treatment and the top ten most important unanswered questions were recently published (Dean, 2014). The questions included uncertainties around the 'single best treatment on a limited budget' and whether different treatments already in use would 'improve the life of cats with CKD'. Pragmatic trials would be well suited to address these types of uncertainties around treatment effectiveness.

6.2.1.7 EPRs as a data source for CKD trials research

Extracting cohorts of data from the EPRs of multiple feline patients across multiple veterinary practices and PMSs could collectively provide the information required on large sample sizes of patients for feline CKD trials, if key research outcomes of interest are routinely recorded. A core outcome set for feline chronic kidney disease (CKD) trials has already been established (Chapter 3) and if the outcomes from this core set are recorded routinely in patient EPRs, this could be useful for future trials research.

6.3 Aim

The aim of this study was to investigate whether patient EPRs for cats with CKD could be extracted from veterinary patient data, and whether these EPRs contained data relevant to clinical trials, specifically outcomes from the CKD Core Outcome Set.

Study objectives:

1. To see if patients recorded as cats (with any or no health conditions) could be identified within patient data extracted from the EPRs of veterinary practice
2. To see if cats with CKD could be found within this dataset using Structured Query Language.

3. To see if outcomes of interest to future trials (Chapter 3) could be identified within, and extracted from, the EPR of cats with CKD, namely, i) bodyweight, ii) survival time (for which extracting the date of death is required), iii) the fluid therapy part of the outcome 'endpoint for renal survival' (defined as ''the need for parenteral fluid therapy or euthanasia or death of the cat because of renal failure" King et al., 2006) and, iv) blood pressure.

6.4 Methods

6.4.1 Dataset preparation

Six months of patient data from January 1st 2019, to June 30th 2019 were extracted from the EPRs of all patients seen at 282 veterinary practices in the UK which all used the same PMS (Chapter 5). The data was uploaded to password protected Microsoft Azure storage for transfer from the PMS to the research group. The majority of the data provided by the PMS was in XML format, however the data provided for the ChronicConditions and Parameters tables was provided in the .csv and .xlsx file format. The database was prepared as previously described and personal identifying information redacted (Chapter 5).

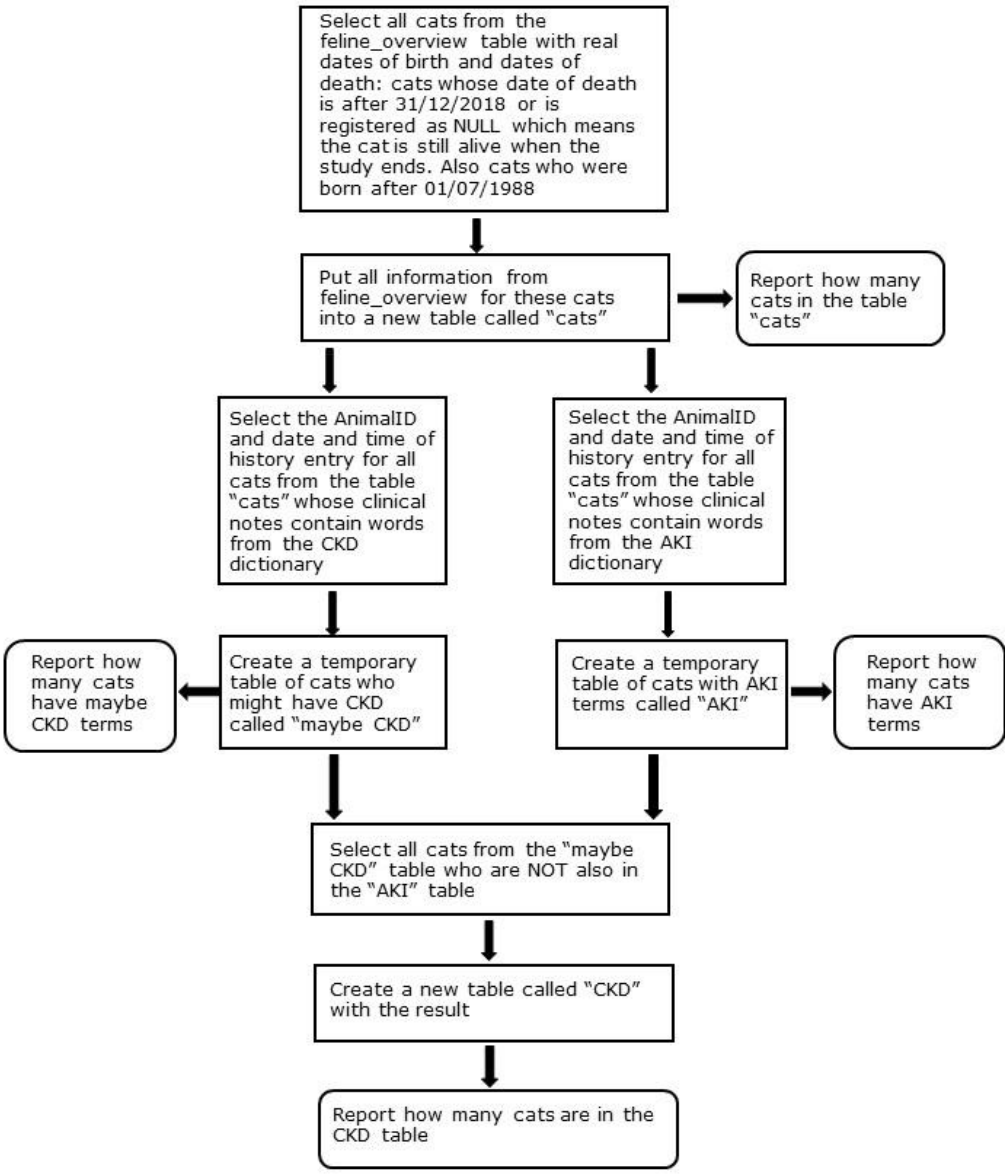


Figure 6.1 Overview of the process whereby the CKD script was used to identify cats with CKD.

6.4.2 Identifying cats with chronic kidney disease

Terms for CKD and acute kidney injury (AKI) were identified by listing all words from all clinical notes in the dataset using code written in R, according to a methodology validated on veterinary EPRs (Duz et al., 2017). Briefly, all words from the free text were extracted, listed alphabetically and the frequency of occurrences for each word were calculated. This

list of all words in the dataset was then examined manually for words which appeared to describe CKD and AKI. This included all misspellings and abbreviations. An inclusion dictionary of all these words was then examined with each word in the context of its surrounding words, and the most frequently appearing words for CKD discussion and diagnosis were extracted. Dictionaries for CKD and AKI were then created. The dictionaries can be seen in Table 6.1. The process by which these dictionaries were used by the CKD script to find cats with CKD can also be seen in Figure 6.1. All the AnimalID numbers for cats whose free text clinical notes matched with terms in the CKD dictionary were collated in one table 'maybe CKD' and all cats with matches to the AKI dictionary were collated in another table, 'AKI'. The AnimalID numbers were then examined by the script, and all cats whose AnimalID numbers appeared in the AKI table were removed from the 'maybe CKD' table, leaving a final table which was then renamed as 'CKD'.

The CKD table contained the AnimalID number and the HistoryDateTime of the earliest ClinicalNotes entry for that cat where CKD had been identified.

Table 6.1 Terms searched for by the script in the clinical notes of each cat, to identify cats with chronic kidney disease and cats with acute kidney injury

Dictionary	**Terms to match**	**Notes**
CKD dictionary terms	_CKD _CRF _CKF	Leaving a space before these acronyms means that CKD is not identified as part of another word
	Do NOT match " _CRF__s"	Some clinical notes were found where CRF 2s or CRF 3s was written to represent capillary refill times. Defining that CRF__s should NOT be a positive match for CKD, aimed to rule out these false positives, while not stopping inclusion of cats with CRF as capillary refill time, providing additional CKD terms were included in their notes. The character "_" is a wildcard which can represent a space or any character. In this instance, one wildcard "_"

		was inserted before the C, and two wildcards "__" were inserted between the F and the s.
	kidney dx kidney dz kidney dis kidney deteriorate kidney fail kidney ins also the following misspellings of "kidney" followed by the same words as above (dx, dz etc): kideny kiddney kidnay kidny kidnies kidey renal	The words chosen to look for as inclusion terms following each spelling of kidney or renal, were chosen as they were the most commonly found words paired with kidney and renal in notes where CKD was diagnosed. These misspellings of the word kidney were chosen as these were the most common misspellings (out of 20 misspellings found). Each occurred seven times or more, meaning they were found associated with the records of greater than 0.1% of all cats. There was only one other spelling of renal found which was "renail" and occurred only once, with an insurance claim, so it was decided that this would not be necessary for the dictionary.
AKI dictionary terms	AKI	Acute Kidney Injury
	ARF	Acute Renal Failure
	pre_renal post_renal acute kidney acute kiddney acute kideny acute kidey acute kidnay acute kidnies	The same misspellings were used as selected above. Pre and post renal were also included here to try to exclude non-renal causes of kidney terms being mentioned in the notes from the finally selected CKD dataset.

	acute kidny acute renal	

6.4.3 Validation of the CKD script

6.4.3.1 Validation step 1: Comparing the diagnostic accuracy of a veterinary surgeon (gold standard) and the CKD script

To validate how well the CKD script could identify cats with CKD compared to manual examination of the ClinicalNotes by a member of the Royal College of Veterinary Surgeons (MRCVS), a two-stage process was used. All clinical notes entries for a random sample of cats from the "cats" table (Figure 6.2), a table including all cats in the whole dataset, with no filtering for disease status, were examined manually to identify for each cat: a) whether the CKD terms were present and the AKI terms were absent as specified by the script and b) whether a diagnosis of CKD was made or referred to within the notes. The output of the manual examination of these cats was compared to the CKD script output, by determining whether cats diagnosed with CKD manually also appeared within the CKD table or not (Figure 6.2).

A random sample of 384 AnimalID numbers were extracted from the "cats" table, with all ClinicalNotes entries for each cat, and the results stored in a word file. The sample size of 384 was calculated using https://epitools.ausvet.com.au/oneproportion for a 5% precision estimate, a 95% confidence level, 50% estimated proportion and a population size of 139,672 (the total number of individual cats within the dataset). All ClinicalNotes for the 384 AnimalID numbers were read manually, and the AnimalID number was noted for all cats where a diagnosis of CKD had been found in the ClinicalNotes. A diagnosis of CKD was reached if the Clinical Notes included terms from the CKD dictionary in addition to contextual notes diagnosing the cat with CKD or referring to a previous CKD diagnosis. Examples included:

- Previously diagnosed with CKF
- On renal diet for CKD
- Has a history of CRF

- CKD checkup
- IRIS stage II kidney failure written

The diagnosis of CKD had to be made by reading the content of the clinical notes and could not be inferred, for example if there was suspicion of CKD because of urine test results within the ClinicalNotes, without the diagnosis being made by the treating veterinary professional the cat would not count as a positive CKD diagnosis.

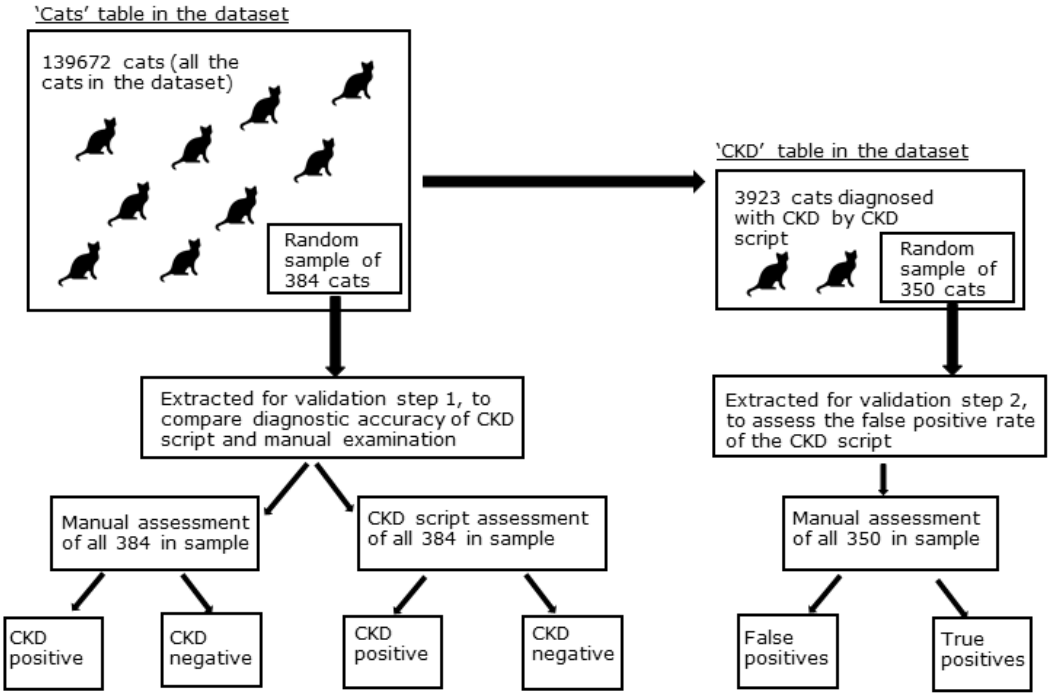


Figure 6.2 Validation sampling protocol to assess the effectiveness of the CKD script

Next, sensitivity and specificity were calculated, along with positive and negative predictive value, treating the CKD script as if it were a diagnostic test for detecting CKD in veterinary clinical notes. The following formulae were used for the calculations (www.msdvetmanual.com/multimedia/table/v15788146):

6.4.3.2 Calculations:

Sensitivity= a/(a+c)

Specificity= d/(d+b)

Positive Predictive Value (PPV)= a/(a+b)

Negative Predictive Value (NPV)= d/(c+d)

Table 6.2 Calculating test sensitivity and specificity, taken from the Merck Veterinary Manual (https://www.msdvetmanual.com/multimedia/table/v15788146)

		Gold standard		
		Disease present	Disease absent	Total
Test result	Positive	A	b	a + b
	Negative	C	d	c + d
	Total	a + c	b + d	

6.4.3.3 Validation Step 2: Examination of a sample of records from the CKD table

All ClinicalNotes from a random sample of 350 individual cats were extracted from the CKD table (Figure 6.2. This sample size was calculated using https://epitools.ausvet.com.au/oneproportion for a 5% precision estimate, a 95% confidence level, 50% estimated proportion and a population size of 3923 (the total number of individual cats within the CKD table). The CKD table contained all cats positively identified by the CKD script as a cat with CKD. The AnimalID for each cat and the HistoryDateTime of the earliest dated ClinicalNotes entry containing the CKD terms was included in the 'CKD' table. The sample was then manually examined for (a) the terms used to positively identify cats with CKD and exclude cats with AKI by the CKD script, and (b) false positive CKD identifications. False positive results in this context were defined as cats whose records appeared in the CKD table but who were not definitively diagnosed as having CKD after manually checking the ClinicalNotes. A definitive diagnosis of CKD was defined as one or

more terms from the CKD dictionary appearing within the clinical notes, in addition to contextual notes diagnosing the cat with CKD or referring to a previous CKD diagnosis (as above).

False positives were cats who either:

1. Were suspected of having CKD but had not yet had investigations carried out to confirm/ investigations not completed/ investigation results diagnose another condition and rule out CKD.
2. CKD was one of a list of differential diagnoses for the cat, but no further testing was done before the cat was either euthanased, died or the study period ended.
3. The cat was on a renal diet and CKD terms had been discussed but a CKD diagnosis was not referred to or reported.
4. Clinical Notes state “unable to rule out CKD” or “not CKD” or “hyperT4 can unmask CKD” or “warned signs of CKD to watch out for” or “in cases of kidney disease metacam is contraindicated” or “CKD risk low” or similar.

6.4.4 Running queries on the dataset

To query the database the mysql.exe executable was run using the Windows Command Prompt. Scripts Table 6.3) were written in Data Manipulation Language (DML). These scripts were run on the dataset via the SQL Command Prompt and written direct to local file types as required. Query access to the dataset was password protected.

All scripts began the same way, selecting for analysis all of the cats in the dataset with plausible age data. To do this, the script would select cats whose date of birth fell after 1st July 1988, as some cats were found in the dataset with dates of birth much older than this. It was suspected that they would have died before the study began, their data had been supplied in error, and their date of death was missing from the dataset.

Table 6.3 Overview, purpose and explanation of the various scripts written in Data Manipulation Language and run on the dataset. Scripts are available in appendices as detailed.

Script designed to identify	Overview of what the script does	Appendix number
How many cats visited more than one practice during the study.	The dataset was from a single PMS and this PMS allocated AnimalID numbers which were unique within the PMS and transferred with the patient if the patient changed veterinary practice. Counts the number of unique entries in the feline_overview table and then counts how many times each unique AnimalID appears in the feline_overview table in combination with a new PracticeID number. Then groups the cats by the number of PracticeID numbers they are associated with and calculates percentages.	15
Most common cat breeds recorded in feline overview table.	Counts the total number of unique AnimalID numbers in the cats table (the total number of cats in the study). Checks which breed is recorded in feline overview for each AnimalID number and then groups cats with the same breed together, counts the number in each group and calculates percentages.	16
Gender and neuter status of all cats which die during the study	Finds all cats with a date of death recorded during the study period and calculates their age at death from their date of birth	17

(and their age at death in years.)	and date of death, then cross references their gender and neuter status from the overview table and reports how many died at each age in each gender and neuter status category. The gender and neuter status of each cat is updated if the cat is neutered and there is no date stamp on this attribute. The gender and neuter status of each cat is reported by this script as it was recorded by the PMS at the end of the study period, which would equate to the most recent information about the cat's status. As this would not be changed after death it can be assumed that gender and neuter status as recorded was correct on the date of death, unless the cat died during neutering surgery.	
Number of cats with chronic kidney disease (CKD) in the dataset	(Figure 6.1) Identifies cats whose ClinicalNotes contain matches to words in the CKD dictionary, then removes from this group any cats whose ClinicalNotes contain matches to words in the AKI dictionary.	18
All breeds of cats with CKD, sorted in descending order from most common to least common.	Counts the number of cats which appear in the CKD table in each recorded breed entry variation, then reports this as a percentage of all cats in the CKD table.	19

Age at death for cats who died during the study, for cats with and without CKD.	Selects all cats from the CKD table whose date of death is recorded within the study timeframe, uses their date of birth to calculate their ages and then groups them into age at death in years. To find cats who died without CKD, creates a table of all cats who die within the study period from the cats table. It then selects cats from this table who are also not in the CKD table, then calculates the remaining cats ages at death (from their date of birth) and groups them by age at death in years.	20
Age in years when CKD terms first appeared in the ClinicalNotes.	Selects the date when CKD terms first found in the ClinicalNotes alongside each AnimalID, also the date of birth for each cat. Finds differences between date of birth and date of CKD terms first being mentioned, converts into years and considers this the 'age at diagnosis'. Groups cats by age at diagnosis in years and puts groups in ascending order by age.	21a, 21b
Age in years when death recorded for cats with CKD, also known as 'risk of death'	Selects all cats whose date of death falls within the study period, and convert into a percentage. Then looks for the AnimalIDs of cats from the dead group in the CKD table, counts these and converts to a percentage. Then does the same process for cats who don't appear in the CKD table. Then looks up each cat's date of birth and	22

	compares to date of death to get age at death. Groups ‘all cats’, ‘ckd cats’ and ‘not ckd cats’ by age at death in years and puts in ascending order by age.	
Age in years for cats who have CKD terms mentioned in their ClinicalNotes on three or more dates: age when CKD mentioned and age at death.	Counts all cats alive at the beginning of the study and creates temporary table from all the cats in the CKD table containing their AnimalID, age in years (created from their date of birth), gender, and HistoryDateTime for all unique combinations of AnimalID and datetime in the ckd table (which is all clinical notes with CKD terms in). Counts the number of unique HistoryDateTime and AnimalID combinations in the table, grouped by AnimalID, to see how many times each AnimalID is matched with a HistoryDateTime, then selects out all those which appear 3 or more times and reports the result. The resulting group of cats had CKD terms found in their clinical notes on three or more dates. As date of birth is known for these cats, this can then be used to calculate their age the first time CKD terms were found in their notes.	23a, 23b

	For cats in this group whose date of death has been recorded, their age at death can then be calculated by comparing date of birth and date of death. (Three or more dates was investigated as a comparison to one or more dates. This was chosen to reflect the chronic nature of CKD and it was thought that cats who had terms in their histories on three or more dates were more likely to be living with an ongoing CKD diagnosis, whereas cats with CKD terms on one date only might have had CKD terms as part of a differential diagnosis which was later discarded. Cats with CKD terms in their notes on three or more dates were termed cats with 'ongoing CKD')	
Deaths with CKD at all ages, as a percentage of all deaths at each age. Both as absolute numbers and as a percentage of all deaths at each age.	Finds all cats whose date of death falls within the study period and calculates their age at death from the date of birth and date of death. Then looks up which of these cats' AnimalIDs are in the CKD table (to find those who died with CKD) and reports number dying with CKD terms in their clinical notes at all ages, and all cats who die and the ages at which they die.	23b

Sixty day survival: survival rate for cats with CKD at 60 days after the CKD terms were first mentioned in their notes, for cats who in addition to CKD terms have keywords for CKD interventions in their notes at any time during the study.	Selects cats whose earliest HistoryDateTime for their ClinicalNotes matching CKD terms falls within March and April during the study. It is expected these cats may be newly diagnosed with CKD because CKD terms were not matched in their clinical notes in January and February. Specific interventions (renal prescription diets, angiotensin receptor blockers, medication for hypertension, angiotensin-converting-enzyme-inhibitors and intravenous fluid therapy) were then searched within the clinical notes. It is important to note that the list of intervention terms searched for was created from a list of product names and abbreviations thought to be most likely to be used, by the researchers. No misspellings were searched for and a full dictionary of terms was not created from within the clinical notes in the same way that the CKD dictionaries were created. In addition, only the free text notes were searched, no treatment or billing information fields were available to search for prescriptions.	24

	All cats whose free text contains a positive match for an intervention was counted. Their AnimalIDs were then cross referenced to see if their date of death was: a) less than 60 days after the intervention was mentioned b) b) greater than 60 days after the intervention was mentioned c) c) not recorded, meaning they did not die during the study. The number of cats receiving each intervention who survive 60 or more days from the date of the intervention was then calculated. This was a very simplified pilot style search in which interventions were searched for individually, however no account was made for cats being on multiple interventions, e.g. renal prescription diet was searched for, and separately intravenous fluid therapy was searched for. The same cats may have appeared in the results of both searches.	
Number of times weighed during the study for all cats and cats with CKD.	Within the parameters table, counts the number of times each AnimalID occurs with a new date stamp for a weight entry, groups by the number of times and reports	25a and 25b

	in ascending order. Then cross references the AnimalID numbers for each cat to see which ones appear in the CKD table, and separates out 'all cats' from 'CKD cats' and reports the numbers of weightings.	
Percentage weight change (as a percentage of each cat's own average weight) for cats with CKD who were weighed frequently (more than 10 times) and died during the study, and the same for CKD cats who did not die during the study.	A convenience sample was manually extracted of the AnimalID numbers from the results of the script in the row above, for cats with more than 10 weight entries each during the study. Each AnimalID number was manually inputted into a new script which looked up the date stamp of each weight entry and the weight entry recorded. The weight measurements were then normalised by converting each weight entry into a percentage of the last weight recorded for each cat and then reported each percentage weight and the accompanying date. Not all cats were included here, eight cats were chosen from each group to illustrate how weight trends could be followed over time. For all cats included in this analysis, the ClinicalNotes were manually checked to ensure that all cats were correctly identified as having CKD and there were no false positive diagnoses included.	26a, 26b, 26c

Blood pressure measurement results written into the free text ClinicalNotes, for cats who had blood pressure measurements done on four or more dates.	Finds cats already classified as having CKD, and then looks for a match for “mmHg” within their ClinicalNotes. Counts how many individual cats have this match. Then counts the number of different dates that this match is found for each cat and makes a subset of the AnimalID numbers of all cats who have a count of greater than 3 dates. Then makes a temporary table of all cats with CKD who have “mmHg” within their notes, this new temporary table contains the AnimalID, HistoryDateTime and ClinicalNotes for each time “mmHg” was matched. Then the script selects from this temporary table all cats whose AnimalID matches the AnimalID numbers in the “greater than 3 dates” list. Finally, for all of these matches, the HistoryDateTime and ClinicalNotes for every time mmHg appears in the ClinicalNotes is written into an excel file, from which the blood pressure measurements can easily be extracted either manually or using an excel formula which finds “mmHg” and then copies this match and the three preceding characters to a new cell.	27

6.4.5 Increasing the tractability of working with the dataset

When queries were first run on the dataset they were found to be intractably long, taking many hours to complete. To improve tractability for running queries on the dataset, the primary keys were removed from the final SQL tables which had been created, and a new index based on the AnimalID alone was implemented. This removed the requirement for the lengthy cross checking of all primary keys whenever the database was queried, which improved the running time of processing a query. This modification was possible because the dataset in this study came from a single PMS, meaning the same PMSID was present for all data entries and so the PMSID did not need to be checked on every query. In addition, the PMS in this study used unique AnimalIDs per patient which were allocated per PMS, not per veterinary practice and so were unique to each animal within this dataset. Therefore, the AnimalID alone without additional primary keys provided a unique identifier for each single animal patient. In addition, this study was focussed on cat patients alone. To further improve tractability, an additional subset of tables was created containing only data from cat patients. This also decreased the running time of processing the queries on the database.

6.5 Results

Please note, all AnimalID numbers and PracticeID numbers and any other potentially identifying information has been redacted from the results.

6.5.1 Descriptive data: Cat numbers, breeds and deaths

The complete PMS export contained the patient EPRs for 403,119 individual animals, of which 139,672 were cats. Approximately seven percent of the cats (n=9434) had visited more than one practice within the corporate practice group during the study (Table 6.4). The maximum number of practices visited was six (n = 3 cats). The patient records for patients visiting many practices was manually checked to ensure that this was truly one

patient and not multiple patients registered at the same moment across the country and given the same AnimalID in error. The patient's date of birth and other Overview information (except PracticeID) was seen to match exactly, no matter which PracticeID was recorded, suggesting that this was really the same patient, visiting multiple practices. The dates of the visits were all different and the timeline of the patient's travels could therefore clearly be seen.

Table 6.4 Number of cats visiting one or more veterinary practices within the same corporate practice group during the six-month study period

Number of veterinary practices visited	**Number of cats**
1	130328
2	8470
3	888
4	63
5	10
6	3

6.5.2 Gender and neuter status

Gender and neuter status were unknown for 0.8% of all cats in the dataset (n=1129/139672) and the ratios of entire: neutered cats were roughly similar for males (1:4.8) and females (1:4.5;Table 6.5). Both the gender and neuter status of the patients were held within the same field in the PMS, and date of neutering was not captured within the data extract. This means that the results seen are a snapshot in time, likely from the end of the data batch time period, and some patients may have started the study period not neutered, finished the study neutered, but only be shown in the results as neutered. This would be important

to consider if neuter status was important to the design of a clinical trial and this dataset was used for this in the future.

Table 6.5 Gender and neuter status of cats

Gender and neuter status	Number of cats	Percentage of total cat population
Female neutered	57095	40.88
Male neutered	56936	40.76
Female entire	12689	9.08
Male entire	11823	8.46
Unknown	1129	0.81

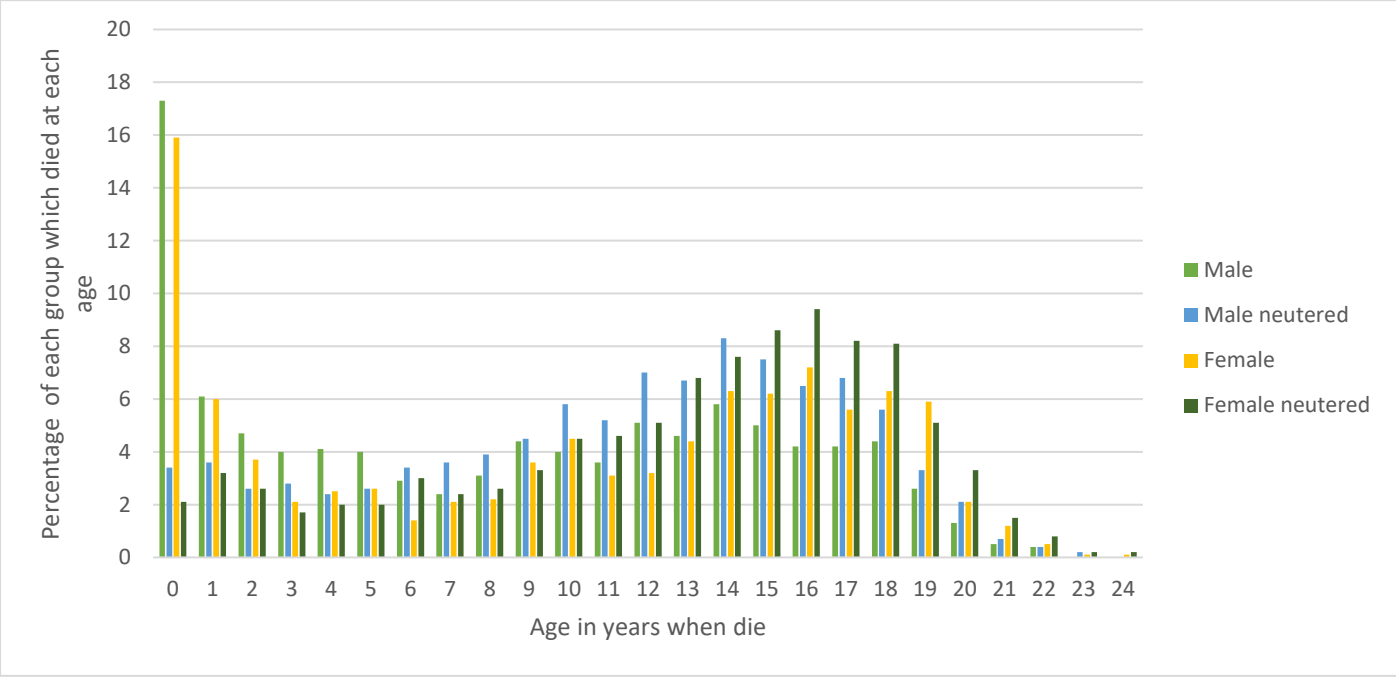


Figure 6.3 Age at death for cats who died during the six-month study, grouped by gender and neuter status

6.5.3 Identifying cats with chronic kidney disease

6.5.3.1 CKD script results

The CKD script reported 4702 cats who had CKD dictionary terms in their clinical notes on one or more dates during the study. The number of cats who had AKI terms in their clinical notes was 247. After removal of cats with AKI, there were 3923 cats identified as having CKD, which was 2.8% of all cats in the dataset.

6.5.3.2 Validation step 1: Comparing the diagnostic accuracy of a veterinary surgeon (gold standard) and the CKD script

Within the random sample of 384 cats extracted from the 3923 cats identified as having CKD, manual examination of records identified six cats as CKD positive, and 378 cats as CKD negative. Of the six cats identified as CKD positive, five of these cats were also identified as CKD positive by the CKD script Table 6.6 One cat identified as CKD positive on manual investigation was not found by the CKD script. The reason for this was because the text “CRF as” appeared, which the script recognised as being related to capillary refill time. However, this demonstrates that the CKD script performed as it was designed to do.

The CKD script identified seven cats as CKD positive and 377 cats as CKD negative. The additional two cats identified as CKD positive by the CKD script were manually classified as CKD negative for the following reasons;

- AnimalID “x”: CKD was suspected as a differential diagnosis alongside other conditions at the annual health check. Diagnostic tests were discussed but not carried out during the period of the data collection. The term ”CKD” was found by the script in these notes.
- AnimalID “y”: The cat had urine tests done and was advised to be likely to have CKD, blood tests to confirm or rule this out were advised, but CKD was not confirmed during the period of data collection. The term ”CKD” was found by the script in these notes.

A high level of specificity was seen (99.5%; Table 6.6), meaning there was a high probability that the script would not mistakenly identify a cat with CKD when the cat did not have CKD.

The sensitivity was lower (83.3%), with proportionally more cats with CKD considered as not having CKD by the script.

The positive predictive value was 71.4%. The negative predictive value was much higher at 99.7%. This suggests the validity of the negative results (cats not diagnosed with CKD by the script) is higher than the validity of the positive results (cats diagnosed by the script and entered into the CKD table).

Table 6.6 Comparing the diagnostic accuracy of the CKD script to the results of manual examination

		Manual examination results (gold standard)		
		CKD	Healthy	Total
CKD script results	CKD	5	2	7
	Healthy	1	376	377
	Total	6	378	384

Sensitivity = 83.3%

Specificity = 99.5%

Positive Predictive Value = 71.4%

Negative Predictive Value = 99.7%

6.5.3.3 Validation Step 2: Examination of a sample of records from the CKD table

All ClinicalNotes from a random sample of 350 cats from the CKD table were examined. All 350 contained CKD terms as defined by the dictionary (and did not contain AKI terms as defined by the dictionary). However, out of 350 cats all identified as CKD positive by the CKD script, manual examination found 209 CKD positive cats and 141 CKD negative cats, which

means 40% of the cats (141/350*100) were falsely classified as positive for CKD. Therefore, of the cats identified as positive by the script, approximately 60% were truly positive.

The common reasons cats were identified as negative on manual examination were:

1. CKD included within a list of differential diagnoses (48%)
2. ClinicalNotes state “unable to rule out CKD” or “not CKD” or “hyperT4 can unmask CKD” or “warned signs of CKD to watch out for” or “in cases of kidney disease metacam is contraindicated” or “CKD risk low” or similar (21%).
3. CKD was highly suspected but not confirmed during the study period (20%)
4. CKD was one of a list of differential diagnoses but the cat was euthanised or the study period ended before further testing was carried out (9%).
5. The cat was on a renal diet and CKD terms had been discussed but a CKD diagnosis was not referred to or reported (1%).

Due to the false positive rate found, it is important to note that from here onwards, ‘cats with CKD’ or ‘CKD diagnosis’ or similar terminology refers to cats diagnosed with CKD by the script. Numbers of ‘cats with CKD’ for all results at any stage in the following results should be considered in the light of the false positive rate and sensitivity and specificity of the script as described above. It is possible that the prevalence of cats with CKD within this dataset has been overestimated by the existing script and therefore some results (e.g. common breeds or weight measurements) may not have been extracted from patients with true CKD.

6.5.4 Most common breeds for cats with CKD

Of the whole population of cats with CKD within the dataset, Domestic Short Hairs were the most common (71.58% of all cats with CKD), followed by Domestic Long Hairs (10.83%) and Burmese (2.06%; Table 6.7).

The highest prevalence of CKD was in Birman (6.37% of all Birman cats in the dataset), Burmese (6.25%), Tonkinese (5.94%), Exotic short hair (3.94%) and Abyssinian (3.69%) cats. Interestingly Burmese cats were both the third most commonly identified breed in the dataset and the breed with the second highest CKD prevalence per breed.

Table 6.7 Cats with CKD (n=3923) split by the top 20 most common breeds in the dataset. Total number of cats found (those with CKD and those without) was n=139672

Breed	**Number of cats of this breed with CKD (n)**	**Number of cats of this breed in dataset (n)**	**Percentage of cats in the dataset (n=139672) which are this breed (%)**	**Percentage of this breed which have CKD (%)**	**Percentage of all cats with CKD (n=3923) who are this breed (%)**
Domestic short hair	2808	99261	71.07	2.83	71.58
Domestic long hair	425	14419	10.32	2.95	10.83
Burmese	81	1297	0.93	6.25	2.06
British short hair	75	3754	2.69	2.00	1.91
Siamese	69	1334	0.96	5.17	1.76
Bengal	46	2079	1.49	2.21	1.17
Persian	45	1392	1.00	3.23	1.15
Birman	39	612	0.44	6.37	0.99
Ragdoll	36	2345	1.68	1.54	0.92
Maine coon	27	1392	1.00	1.94	0.69
British	13	466	0.33	2.79	0.33
Tonkinese	12	202	0.14	5.94	0.31
Abyssinian	9	244	0.17	3.69	0.23

Exotic short hair	8	203	0.15	3.94	0.20
Domestic medium hair	6	523	0.37	1.15	0.15
Norwegian forest cat	6	352	0.25	1.70	0.15
British blue	5	224	0.16	2.23	0.13
Domestic cat (hair length unspecified)	5	471	0.34	1.06	0.13
Bengal cross	4	464	0.33	0.86	0.10
Sphynx	3	333	0.24	0.90	0.08

6.5.5 Age at death for cats with CKD

For all cats (with or without CKD) a date of death was recorded for 9361 cats, 6.7% of the total cat population during the six-month study period. The highest incidence of mortality for any age group seen was in male and female entire cats less than one year old. When clinical notes were examined for cats dying at under a year old, many seemed to die in accidents as very young kittens.

Of all CKD cats, 1082/3923 (27.5%) died during the study. The percentage of cats dying under five years old was much higher for cats without CKD than with CKD. The median age at death was higher in cats with CKD than in all other cats (

Table 6.8), however the interquartile ranges (IQRs) of age at death for all cats and cats with and without CKD overlapped.

Table 6.8 Age at death; median and interquartile range

Age at death (years)	All cats	Cats with CKD	Cats without CKD
Median	13	15	12
Interquartile range	7-16	12-17	6-16

Between six years old and 12 years old, and then between 22 and 24 years old, the percentage of cats dying in each group (Figure 6.4)was very similar between all three groups (all cats, cats with CKD and all cats minus those with CKD). However, between 13 and 19 years of age there appeared to be an increase in percentage deaths for cats with CKD, peaking at 16 years of age when 12.6% of all CKD cat deaths were reported.

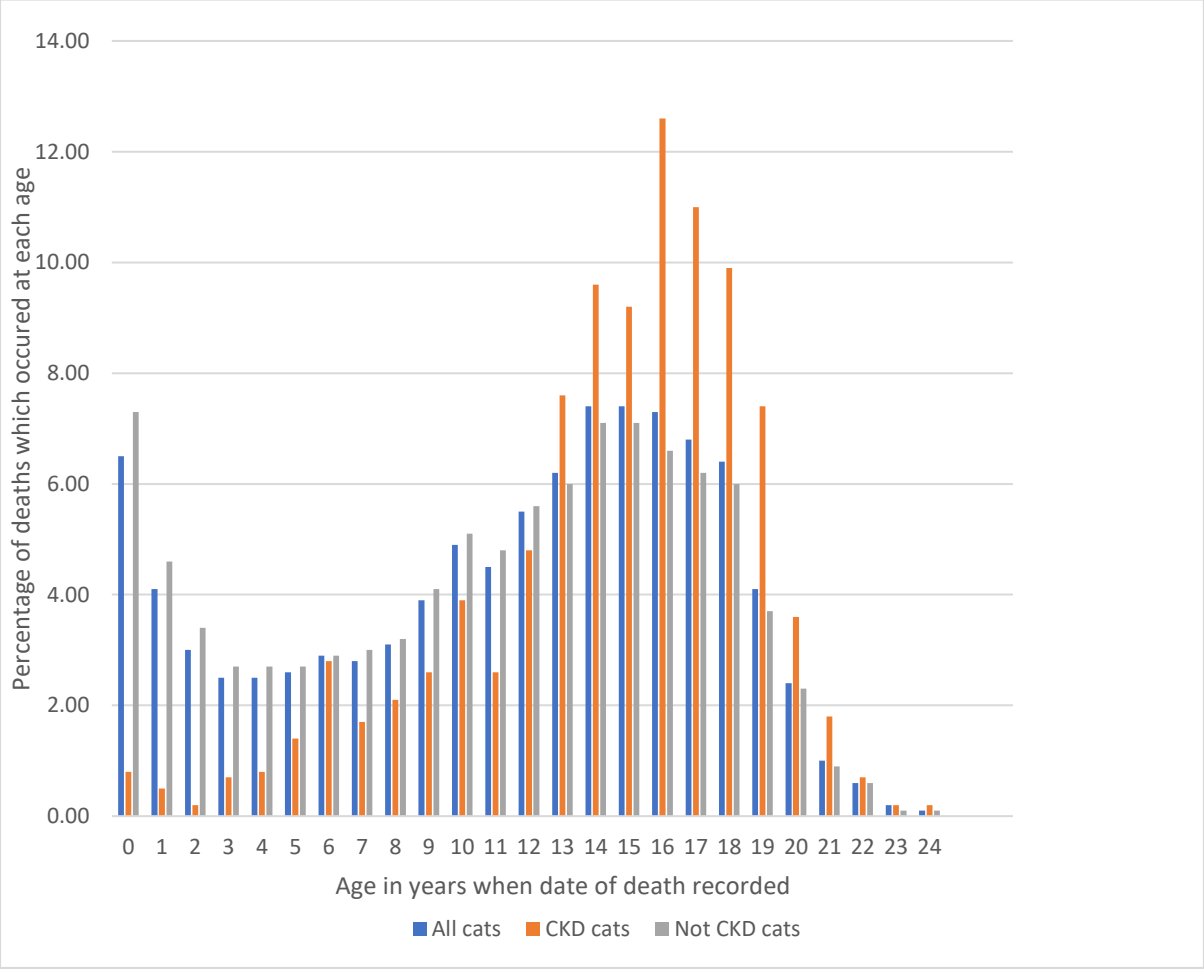


Figure 6.4 Cats which died during the study: percentage of deaths recorded at each age for cats with and without CKD terms in their notes on one or more dates

While the median age at death for cats with CKD was 15 (IQR 12-17), the median age at CKD diagnosis was 14 years (IQR 11-17). This one-year interval between age at diagnosis and age at death was broadly reflected for deaths and diagnosis of CKD at all ages. The highest percentage of CKD diagnoses was seen at 15 years and the highest percentage of deaths was seen at 16 years. There was a peak in the number of deaths between 14 and 19 years old for cats with CKD which was also broadly reflected in the wider population.

6.5.6 Sixty-day survival

Of a small subset of cats examined more closely (those cats visiting practices in March and April 2019), survival at 60 days appeared to be longest for cats for whom renal prescription diet intervention terms were found, at 82% survival (n= 167/203) (Table 6.9) and the lowest percentage survival was seen for cats for whom intravenous fluid therapy terms were found (n= 76/144, 52%). The percentage survival for all other interventions found was broadly similar, 76-79%. Survival of all cats without searching for any intervention terms was74%.

Table 6.9 Sixty-day survival for cats with CKD whose clinical histories mention CKD interventions.

Intervention (based on occurrences of specific terms searched for)	**Number of cats seen in March and April 2019 whose clinical history mentions the intervention**	**Number surviving 60+ days**	**Percentage survival at 60+ days (%)**
All CKD cats seen in March and April, regardless of intervention (no intervention words searched)	1188 cats seen in March and April	882	74
Kidney diet or renal diet or renal dry	203	167	82

Semintra or telmisartan	93	71	76
Amlodipine or amodip or istin	63	48	76
Fortekor or benazepril or benazecare or benefortin or nelio	59	47	79
IVFT or intravenous fluids or drip or IV fluids or IV drip	144	76	52

6.5.7 Weight measurements

Over the six-month data collection period, 31% of all cats had no weight measurements recorded, 42.9% of all cats were weighed more than once, and 68.4% of cats with CKD were weighed more than once. The data was not normally distributed and showed a right skewed distribution, with high numbers of cats either not being weighed at all or being weighed once or twice only (Table 6.10). Cats who lived were weighed more times during the study than cats who died (median). Cats with CKD who died during the study were more likely to have not been weighed at all (13.9%) than cats who lived (5.6%).

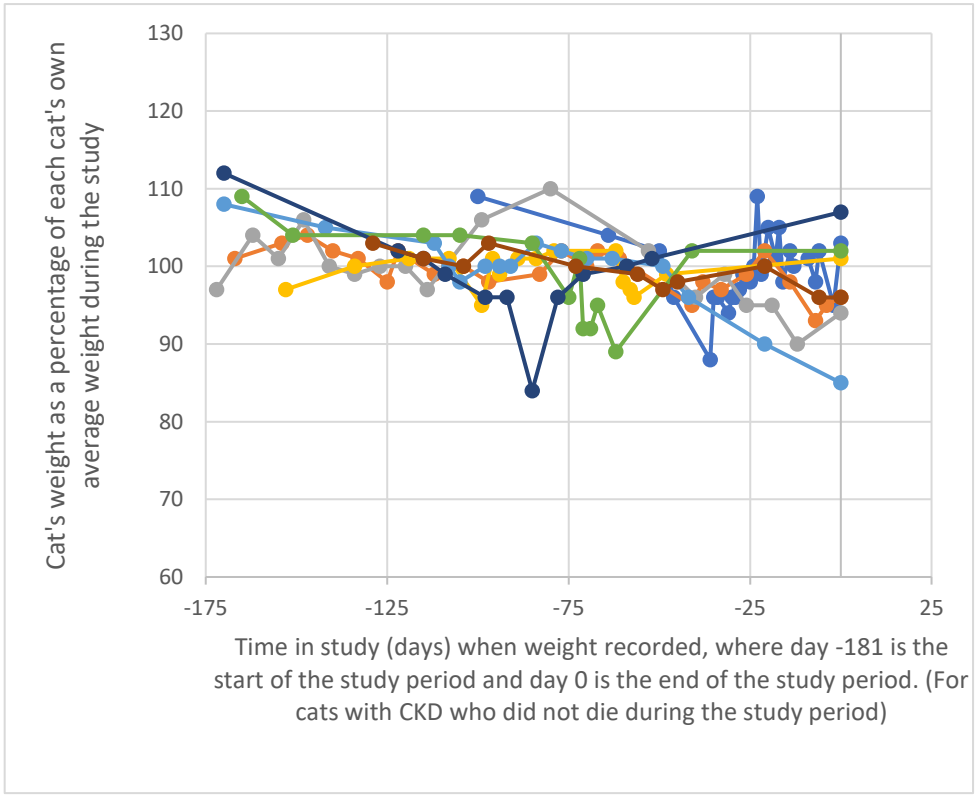
Table 6.10 Number of weight measurements recorded during the study including averages (median) for all cats, cats with CKD, and cats with CKD who lived or died during the study

	All cats	**Cats with CKD**	**Cats with CKD who did not die during the study**	**Cats with CKD who died during the study**
Number of cats	139672	3921	2845	1078
Number of cats weighed once or more	96398	3611	2685	926
Percentage of cats with no weights recorded	31.0	7.9	5.6	13.9
Largest number of times weighed	100	29	29	24
Median number of times weighed	1	2	2	1
Interquartile range	0-1	1-3	1-3	1-2

Most cats were weighed once during the study period. When cats with CKD who lived were compared with cats with CKD who died during the study, cats who lived were weighed more times, and were more likely to have been weighed at all.

6.5.8 Following weight measurements over time

A convenience sample of cats (n=16) was examined to see whether multiple weight measurements could be extracted for each cat and changes in weight followed over time (Figure 6.5). Cats who lived appeared to stay within 85% and 115% of their own average weight, whereas cats who died showed a noticeable decrease in their weight before death. The change in average bodyweight seen in cats who died ranged from 26% to 62% decrease in their own average weight. Much more rapid weight loss was seen in the cats who died.



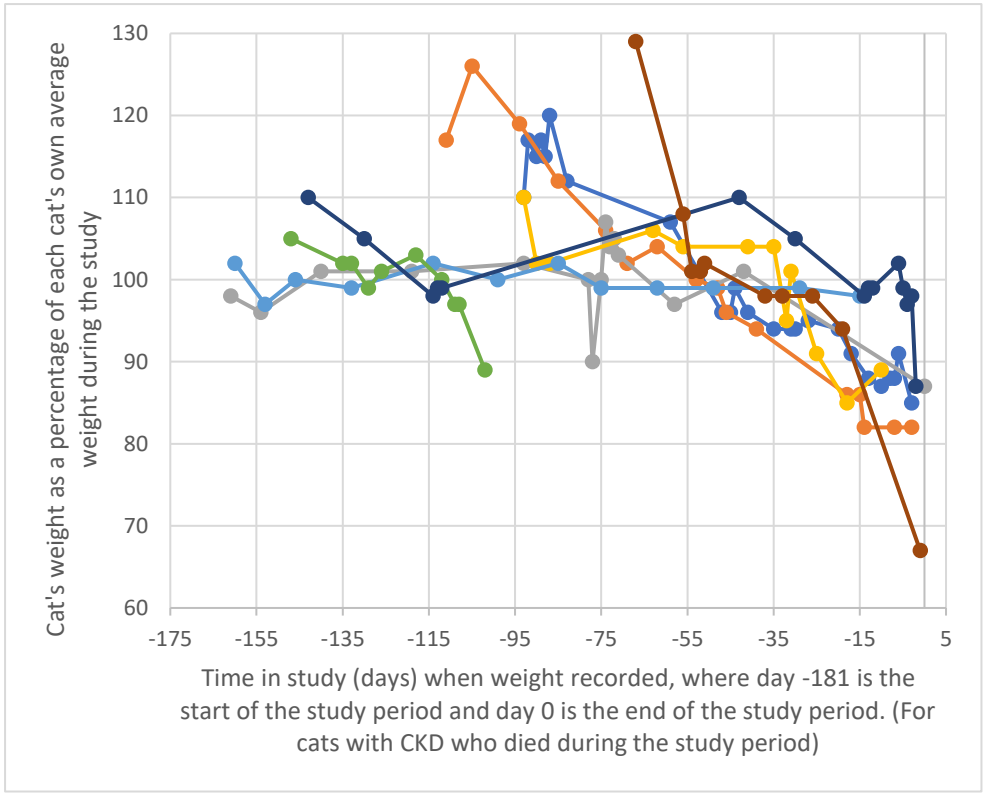


Figure 6.5 Demonstrating that weight measurements can be extracted over time and compared for two example cohorts: cats with CKD who did not die (left graph) and cats with CKD who did die (right graph). Each patient's measurements are represented by a different colour. Their AnimalID numbers are not included.

6.5.9 Blood pressure measurements

A total of 306/3923 cats (7.8%) were identified by the CKD script as having CKD and additionally having a match in their ClinicalNotes with the term “mmHg” representing blood pressure. Only nine cats had a match with this term on four or more dates during the study period, and one cat had a match on five dates. In Figure 6.6, the blood pressure measurements for each of the nine cats are shown against days since the start of the study period. For most of these cats their blood pressure appears to decrease overall during the study, however one cat shows a sharp increase in blood pressure (shown by orange line- number has been redacted)) and another shows a gradual increase (shown by lime green line, number has been redacted). For 7/9 cats their initial blood pressure measurement falls within the ‘severely hypertensive range at ≥ 180mmHg (www.iris-kidney.com/education/hypertension.html) and only two reach ‘normotensive’ levels of 140mmHg during the study period.

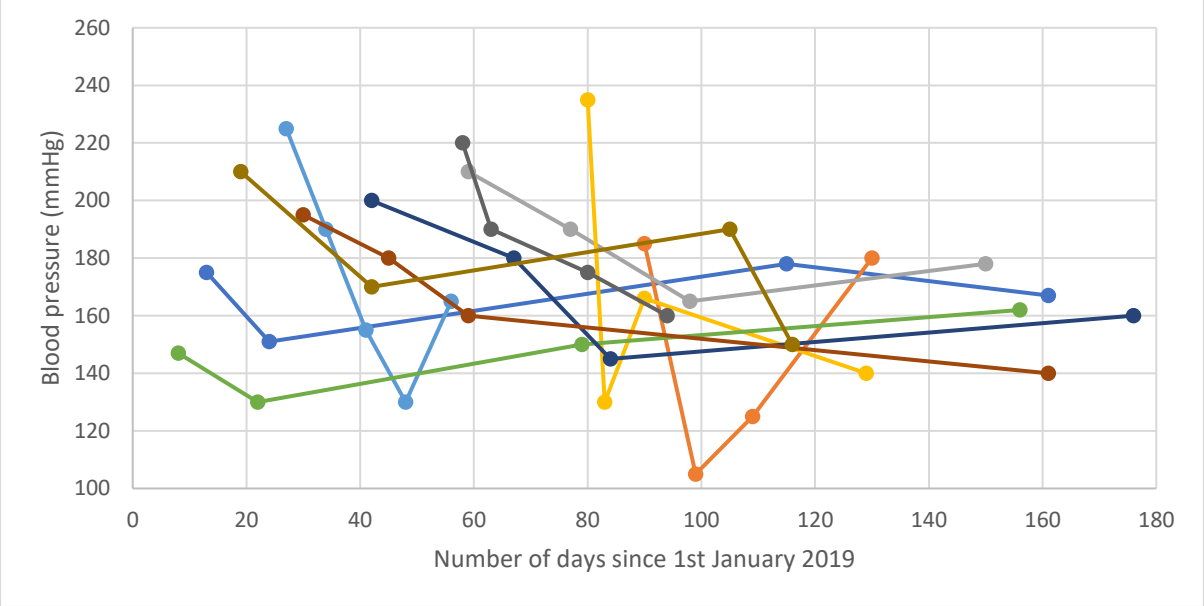


Figure 6.6 Blood pressure measurements (mmHg) extracted from the ClinicalNotes for cats with CKD who had blood pressure measured on four or more dates during the study. Each patient is shown by a different colour. Their AnimalID numbers are not shown here.

6.6 Discussion

6.6.1 Overview

In this study the EPRs of patients from 282 veterinary practices, representing a single PMS and recorded under normal working conditions were uploaded into a relational database for analysis. Cats with CKD were identified using scripts written in DML. It is not known how other research groups in the UK also working with small animal patient data define their data fields of interest or query their datasets, this information has not been published. The scripts developed in this study successfully extracted data about cats and were used to diagnose cats with CKD with reasonable success. However, the rate of false positives generated by the script was high and therefore improvements are needed to aid more accurate identification of CKD patients for trials.

A selection of outcomes from the core outcome set for CKD trials (Chapter 3) were successfully identified within the patient records, extracted, and could be followed over the six-month study period, namely bodyweight and blood pressure measurements, endpoint for renal survival (the use of parenteral fluid therapy) and survival time. It was possible to begin to identify when specific interventions were written into the ClinicalNotes, although this was only done by a free text search of correctly spelled interventions and no validation of the success of identifying interventions by this method was carried out. Some interventions may have been missed or false positive identification of interventions may have been achieved. Future work should seek to develop this method further and validate the outputs. Once fully validated, combining intervention dates and core outcome data could be extremely valuable for clinical trials. Further work could now use these outcome data together with intervention dates to input into a pragmatic trial. Survival time (another core outcome) can be calculated if the date of diagnosis and date of death are known; both these parameters were successfully extracted from the EPRs. These results preliminarily suggest that data for the core outcome 'endpoint for renal survival' (King et al., 2006 & Chapter 3), defined as the time when intravenous fluid therapy is required for renal support can potentially be provided from identification of this intervention in the ClinicalNotes (although as discussed, extraction of this outcome has not yet been validated).

All patients were uniquely identified within the dataset and could be followed, and their data still extracted when they moved between different veterinary practices within the PMS, reducing the risks of data duplication or of patients being lost to follow up in a trial. The relational structure of the database and the method for querying the database worked well in combination, allowing information to be extracted as required.

6.6.2 Finding cats with CKD in the dataset

6.6.2.1 CKD script results

To the authors knowledge this is the first time that scripts written in DML (and executed via the SQL Command Line) in combination with dictionaries created in R have been used for clinical text mining to identify patients with a condition of interest.

This study found a 2.8% prevalence of CKD. The CKD patient finding script was found to have a high negative predictive value, meaning few false negatives would be found, but a higher positive predictive value, meaning more false positives are likely to be found. A detailed manual examination of the patient records whom the CKD script had classified as having CKD found 40% had been incorrectly classified. If this proportion is extrapolated to the rest of the dataset, then of the 3923 CKD cats found, only 60% of these would be true positives (60/100*3923) i.e. 2354 cats. This would equate to an overall prevalence in this data sample of 1.69% ((2354/139,672)*100).

A recent study (Conroy et al., 2019) found similar numbers with an overall CKD prevalence of 1.2%. They also searched free text clinical notes for terms relating to CKD and renal failure, however their list of terms was shorter, no misspellings were discussed and cats matching terms relating to AKI were not removed. In addition, they use VeNOM codes to identify patients with CKD and were able to search for CKD treatments. These differences in techniques may account for the slight differences in prevalence found. It is possible that the additional detail in the free text searching as described in this chapter has helped to improve the accuracy of identifying feline CKD patients. Results found in this study were similar to (Conroy et al., 2019) in relation to: breed showing the highest prevalence (Burmese), overall number of all cats for whom bodyweight was recorded, and median age

at CKD diagnosis. However, the current study found much higher incidence of weighing in cats with CKD (68.4%). Conroy et al. (2019) found an association between bodyweight and survival of at least one day following CKD diagnosis. The current study suggested that cats with CKD who died lost weight dramatically before death or euthanasia. These findings should be further investigated, with weights monitored for a properly sampled cohorts of cats, in order to ascertain whether weight loss or rate of weight loss could be used as a prognostic indicator for cats with CKD, and whether it could be used to predict likely survival time.

6.6.2.2 Future improvements to the CKD script

Although the false positive diagnostic rate found was higher, there are several potential explanations for it:

1. CKD prevalence is low

CKD prevalence is low within this dataset (2.8%) and within the wider cat population. This means the absolute numbers of cats found within the validation sample is also very low. This has an impact on the positive predictive value of the script, so finding just one or two more cats within the sample would have had a large impact on the false positive rate. One solution to obtain a more accurate validation of the CKD script could be to examine a sample of cats taken from age groups where the CKD prevalence has been found to be higher. This would increase the likelihood of finding cats with CKD within the sample and would increase the reliability of the validation calculation.

The requirement for cats to have a clear CKD diagnosis made or referred to within the clinical notes left many cats in a grey area where CKD was suspected but unconfirmed. Although it is preferable to have confirmed cases if conclusions about the patients are to be drawn from the results, this strict requirement may have narrowed the number of cats with CKD (and therefore the prevalence found in this study) to be smaller than it could otherwise have been.

2. Study time frame was short

This study had a relatively short time-period of data collection (6 months). Diagnosis of CKD may take a few days for collection and analysis of blood and urine samples (Cannon, 2016). Cats may live for weeks, months or years with CKD (Boyd et al., 2008). The results from this study show longevity of several months or more. However, with a relatively short data collection period it is not guaranteed that all Clinical Notes made pertaining to an individual cat will fall within the short study time frame so not enough information was always available to confirm a CKD diagnosis. Often cats in this study would have suspicion of CKD recorded, but investigations and test results may not have been recorded until after the end of the study period and so were not available for analysis. The chronicity of CKD in some patients also means that the Clinical Notes obtained during a short study time frame may contain little or no reference to CKD if it was diagnosed prior to the study period starting. Data collected over a longer period, ideally several years, would allow for mitigation of these issues as more of the CKD journey could be represented in the dataset. One script aimed to more correctly identify cats with CKD by finding those whose notes mentioned CKD > three times. However, it's possible this may instead have diagnosed cats who were undergoing CKD diagnostic testing, and further manual examination of these patient's notes would be required to confirm this.

In addition, a lifelong clinical history or a data collection period of two to three years would help to investigate further survival time after diagnosis and be better placed to compare age at death for cats with and without CKD. The low prevalence of CKD in the dataset meant that results for age at death for 'cats without CKD' and 'all cats' were very similar. A data collection period of two to three years or longer would further investigate the one-year time gap between diagnosis and age at death which appeared to be suggested by some results in this study. In addition, the patient unique ID's between both groups should be compared. Alternatively, a lifelong clinical history for patients diagnosed with CKD would be better placed to more fully investigate survival time after diagnosis.

3. The design of the CKD script

The CKD script used for the majority of the results (with the exception of the 'ongoing CKD' cases) only required the inclusion of CKD dictionary terms on one occasion for a positive diagnosis to be made. If CKD was listed as a differential diagnosis or note contains e.g. "CKD ruled out" or "risk of CKD", these were identified as positive matches for CKD. Future solutions to reduce these occurrences and reduce false positives could include manual examination of all script results to confirm diagnosis. This is likely to be extremely time consuming, however it would not be as time consuming as examining all Clinical Notes in the whole dataset. Alternatively, common phrases used in contexts where CKD has been ruled out could be identified using Keywork in Context (KWIC) search methods in either WordStat or R. These could then be incorporated into the next version of the script so that Clinical Notes containing them are removed from the CKD results table, in the same way that ClinicalNotes containing AKI terms were removed. A potential third solution would be to recognise that CKD is often a condition that patients live with for months or years, and require that CKD dictionary terms be identified on more than one date or over a specific time period in the Clinical Notes for each cat, before a positive CKD diagnosis is made by the script. It is likely that this would increase the true positive diagnostic capability of the script.

4. Older cats euthanased before diagnosis finalised

Some older cats Clinical Notes appeared to describe a cat presenting for examination at an advanced stage of disease, usually polyuric and polydipsic, with weight loss and a number of other clinical signs. These patients would have a number of diagnoses listed, usually CKD, hyperthyroidism, diabetes mellitus, neoplasia. However, due to the poor condition of the patient or the owner's preferences, testing was not carried out and the final diagnosis was not known before the patient died or was euthanised

These cases may have been identified as false positives on manual examination. There is probably little which can be done to mitigate for the way these are identified by the script, and they are likely candidates for true CKD diagnosis. If a future trial wished to identify a retrospective cohort of cats for examination of risk factors or treatment methods then the date and cause of death and the date of CKD diagnosis could both be extracted from the

dataset and where they are both the same date or separated by only one to two days, the possibility that CKD was not fully diagnosed in these cats should be considered.

5. Blood and urine test results not recorded within the free text so diagnosis not known

Some Clinical Notes contained reference to CKD as a potential diagnosis for the patient, and blood and urine testing was recorded to have been carried out. The ClinicalNotes then described that "test results discussed with owner" however the results were not written in the notes and the patient was then either euthanased or not treated. These cats would be positively diagnosed by the script but then recorded as false positives on manual examination. Recording of clinical notes is required under the code of conduct for veterinary surgeons (https://www.rcvs.org.uk/setting-standards/advice-and-guidance/code-of-professional-conduct-for-veterinary-surgeons/supporting-guidance/clinical-and-client-records/) and recording diagnosis and treatment plans accurately is helpful to colleagues. Some PMSs and research groups also use VeNOM codes (https://venomcoding.org/venom-codes/) to add diagnostic accuracy for researchers and veterinary colleagues so the use of these could be encouraged in PMSs joining future research trials. Additionally, the importance of detailed clinical note recording to include trial specific data could be emphasised to veterinary surgeons participating in any future trials. However, in human healthcare trials it has been suggested that detailed data collection in addition to the usual workload, may be too much for general practitioners or smaller hospitals (often treating the patient population of interest to the study) to cope with (van Staa et al., 2014).

It is likely that a combination of all these suggested improvements would result in a script with higher accuracy and fewer numbers of false positives. Future work should look to improve the script and then re-evaluate the subsequent results within this study, in light of the improved accuracy of diagnosis.

6.6.3 Finding CKD core outcomes in the dataset

6.6.3.1 Sixty-day survival post intervention

Endpoint for renal survival (the timepoint when an intervention such as intravenous fluids is required, King et al., 2006) was recently identified as a core outcome for future CKD treatment trials (Chapter 3). Cats requiring this intervention within this study may have been the most unwell, so although the group identified as having intravenous fluid terms in their notes had the lowest survival rate at 60 days (52%), the low survival may be more reflective of the severity of illness instead of being related to the fluid therapy. Future work should create a more detailed dictionary for intervention terms to include all misspellings, product and active ingredient name using the same methodology as described for creating the CKD dictionary. Validation of this improved method should then be carried out, in the same way as the CKD identification script was done. Future work could then investigate whether patients were on more than one intervention, the interventions with the longest survival time, whether combinations of interventions changed the survival seen, and also whether finding the intervention named within the notes is indicative of the intervention being given or just of discussion of the intervention as an option.

Future work should also clarify whether an additional data field to capture all treatments given is required for more accurate analysis on which interventions have been given, for example treatment or billing information fields. Very little prescription information was seen when analysing records in this study and although pharmaceuticals appeared by name within some ClinicalNotes, little information on pack sizes, doses or treatment duration was seen. VetCompass extract a data field called ‘treatment’ (O’Neill et al., 2021) which could be useful to include in future revisions of the clinical evidence schema. With these improvements made and appropriate cohorts of patients selected, the results suggested by the current study could be further investigated to establish whether they are reflective of real-world treatment effectiveness. Until this additional work has been carried out, no clinical conclusions should be drawn from the results found here. This preliminary work has shown that interventions can be identified in the free text and that the survival time of patients can also be identified and extracted. Survival time is another core outcome for CKD

trials (Chapter 3). This data has real potential as a data source for clinical trials and survival analysis.

6.6.3.2 Weight measurements

The analysis performed in this study used weight measurements which had been recorded in the specified weight field within the PMS and were then inputted to the parameters table in the database. However, this may not contain all patient weight measurements undertaken by veterinary practices. During creation of the dictionaries for CKD and AKI terms, when all words from the free text were listed, it appeared that some of the free text contained weight measurements also. It was not clear at this stage whether these were patient actual weights, target weights or weights of products e.g. '5kg bag of prescription diet'. Further work could look at these measurements in context and establish a method to extract weights from the free text if required.

Despite having a consultation recorded at their veterinary practice during the six-month study period, 31% of cats were not weighed at all (or if they were, the weight was not recorded in the dedicated weights field in the PMS). However, these consultations histories could have been from insurance claims or telephone advice, there is no guarantee that the cat actually attended the premises of the veterinary practice for each consultation, which could explain this finding.

When cats with CKD who lived were compared with cats with CKD who died during the study, cats who lived were weighed more times, and were more likely to have been weighed at all. Some possible explanations for this finding are that cats who died may have been euthanised on their first consultation and the recording of the weight measurement in a field separate to the Clinical Notes may have not been prioritised as it would not have been information which was required about the cat for future treatment. Alternatively, cats who were weighed frequently may have been treated by clinicians who were familiar with the importance of bodyweight assessment in thin cats. In addition, cats who were living with CKD could have been weighed more simply because they survived to be weighed and their condition monitored.

The main objective in extracting and calculating the weight change (relative to average weight) for cats who lived vs. cats who died during the study was to establish whether it was possible to extract this information so that trends in weight change could be followed, and rate of change in weight could potentially be calculated. As this was a convenience sample results should be interpreted with caution. Weight is another core outcome for CKD trials (Chapter 3) so being able to extract this information easily from the EPR is very useful and this work suggests that veterinary practice clinical notes could be a valuable resource for collecting data on this important outcome. The subset of patients investigated here were those weighed very often and there may be many health related or other reasons why this was done. These may affect the results seen, so although it appears that cats who died appeared to lose weight before death, whereas cats who lived did not, these results must be interpreted with caution, and may be unlikely to represent cats living 'normally' with well managed CKD who would be unlikely to be weighed so often.

Data collection over a longer time frame would allow more cats, more representative of all stages and severities of CKD to contribute to the weight assessments and tracking. With carefully sampled data from a longer time frame, these measurements could potentially be used to inform a prognostic indicator which could predict longevity relative to change or rate of change in weight. This could be useful for clinicians and owners, who are often asked 'how long' a patient might live for. Freeman et al. (2016) also studied weight measurements in cats with CKD. Theirs was a smaller sample of veterinary practices (n=6) and cats (n=569) but a longer timeframe of data collection (2006-2014). Their inclusion criteria were more detailed than in this study, as they required a pinpointed date of diagnosis, and IRIS stage, alongside the cat's age. For inclusion in their study cats were required to have at least two bodyweight measurements: one at diagnosis and one within three years before or after diagnosis. The exact method for extracting the inclusion criteria and data from the cat's clinical records was not reported. They proposed a relationship between weight loss and survival time. They found weight loss to increase progressively over time both before and after CKD diagnosis in cats, with a median -8.9% weight loss in the 12 months before diagnosis of CKD and median -6.2% weight loss in the first 12 months after diagnosis. They also found bodyweight lower than the group median (4.2kg) to be associated with shorter survival time, and cats with the highest bodyweights to have shorter survival times however

stating that the relationship between bodyweight and survival time warrants additional research.

It is hard to directly compare the results from Freeman et al. (2016) with the current study due to the differences in inclusion criteria, number of weight measurements per patient, and data collection time period. The extended timeframe for data collection means that weight measurements in their cats could be much further apart in time than the cats in this PhD study and each patient's weight may have fluctuated between the recorded data, without that information being captured. Their potential follow up time for bodyweight measurement was up to six times as long as in this PhD study. They also knew the date of CKD diagnosis and had a confirmed diagnosis for all included patients, whereas in the current study, some cats may have joined the dataset with existing CKD and this information was not known. However, it is interesting that both their data and this PhD study suggest a relationship between weight loss and reduced survival time, and results from both studies encourage the further development of weight monitoring as a potential prognostic indicator for these patients.

6.6.3.3 Blood pressure

The subset of records whose blood pressure measurements were extracted and examined in detail showed that blood pressure measurements which are a core outcome for feline CKD can be easily extracted from the ClinicalNotes free text. With larger datasets over longer periods, change in blood pressure in response to treatment interventions could be extracted and provide useful data for trials.

6.6.4 Potential limitations of the electronic patient record

Any conclusions about the prevalence of feline CKD in the dataset or any suggested results seen in the outcomes extracted in this work are purely observational in nature. However, the study has fulfilled its aim in establishing whether patients and outcomes of interest could be identified and extracted.

Not all owned animals are seen and treated by veterinary professionals. If animals who are not taken to the vet are different from animals who become patients, this creates potential for hidden bias in the EPR dataset. The EPR can only represent the patients who are seen within veterinary practices. Of these patients, the EPR has the potential to represent all cats who are seen and diagnosed with CKD. However, there are some additional challenges to identifying these patients within the EPR. Research has shown that only 60% of the content which is discussed between clinicians and owners in veterinary consultations is written into the EPR (J. Jones-Diette et al., 2017). The discussion which takes place between the owner and clinician may be affected by the questions and discussion that are initiated by the clinician, and the owner's explanations and observations of the patient's clinical signs. Some owners may not identify mild clinical signs or may not seek veterinary advice until the patient is very unwell or the disease stage is very advanced. In addition, some clinical conditions may not manifest as clinical signs until the condition is very advanced. For these reasons, and possibly also for financial and practical reasons (e.g. how quickly a veterinary consultation can be arranged), the stage of disease at which patients are presented for examination may vary between patients.

6.6.5 Patients moving between practices may be duplicated or lost from trials

The composite primary key in the database design allowed cats who had visited more than one veterinary practice within this PMS to be easily identified and tracked. However, if a patient moves to a different PMS there are no unique identifiers which would be maintained except microchip numbers. These cannot be collected as they are potentially identifying a specific animal and be used as a route for identifying the animal's owner and would therefore not comply with current General Data Protection Regulations (www.gov.uk/data-protection). Therefore, there is no way of preventing patients moving between PMSs having duplicated information on a future clinical trials database containing information from multiple PMSs. This would be risky to trials results if the same patient was registered multiple times. The CEVM aim to communicate directly with veterinary practices who would contribute to clinical trials, and it is hoped when an interventional trial is carried out, discussions with veterinary practices and patient owners will help to build good relationships with trial participants. This would ensure that patients who move between

PMSs were aware of the importance of making themselves known to the CEVM, even if only as ‘AnimalID1234’ from PMS ‘1’, to mitigate the risk of duplication.

6.7 Conclusions

Cats with CKD were identified in a dataset of EPRs and selected core outcomes for CKD trials in cats were successfully identified and extracted. Using DML scripts was a successful method for rapidly identifying patients and outcomes of interest in a large dataset and future work should further explore and refine this method. The next steps of the research should aim to improve the accuracy of CKD case identification, to look at recording of interventions and intervention combinations used and to extract data over a longer period of time, ideally two to three years. Overall, this study demonstrates that without additional work or record keeping on the part of clinicians, the standard veterinary EPR presents a valuable resource for clinical trials, from which key outcomes can be extracted for analysis.

Reporting guidelines:

Reporting guidelines:

The information presented in this chapter has been reported according to the RECORD statement (Benchimol et al., 2015) and all items are present, except for those explained within the text of this chapter and information for point (16) on variable and relative risks. This information was not applicable to this study as these calculations were not carried out as the work did not progress to this stage.

7. Chapter 7: Discussion

7.1 Broad overview of the research

The aims of this PhD work were to establish the most important outcomes to assess in trials for cats with CKD, and to investigate the feasibility of using EPRs from first opinion veterinary practice as a data source for trials for these patients. Methods used included both quantitative and qualitative approaches, with systematic reviews (Chapter 2 and Chapter 4), conducting an eDelphi and a consensus meeting (Chapter 3), data extraction from a Practice Management System (PMS), data cleaning, structuring and database design, running queries and undertaking analyses (Chapters 5 and 6). See Figure 1 for overview.

This PhD study was framed around cats with chronic kidney disease (CKD) because CKD is an important cause of morbidity and mortality in domestic cats in the UK, occurring at all ages but more commonly in older cats. As a chronic condition, it is a useful focus to investigate how measured outcomes might be recorded and potentially how they change over time. In addition, it is a condition for which many research questions remain unanswered. In this PhD, the outcomes already reported in CKD treatment trials research were systematically examined (Chapter 2). These outcomes were individually considered and rated, re-rated and discussed by a panel of stakeholders with relevance to feline CKD treatment. From the outcomes scored the highest by over 80% of the stakeholders involved, a core outcome set was created for feline CKD trials (Chapter 3). Following this, the work of establishing the tools required to assess each outcome in trials began, starting with Quality of Life (QoL), where a systematic review of all QoL assessment tools in the published literature was carried out (Chapter 4). Many published studies where QoL was discussed did not assess QoL, or only used unvalidated, oversimplified tools to assess QoL. The small number of validated QoL tools found included a tool validated for the assessment of QoL in cats with CKD.

Finally, six months of retrospective veterinary electronic patient records (EPRs) from all veterinary practices within a single PMS was obtained for analysis (Chapter 5). Many obstacles had to be overcome to successfully extract the veterinary practice data for this PhD research. These included: de-identification of the free text records, cleaning and restructuring of the data for use and building a relational database to allow the dataset to be accurately searched. Obtaining 'normal' patient data during the Covid-19 pandemic was made possible by the kind cooperation of Medivet Group Ltd who permitted access to patient records from the 2019 year. The patient records obtained from 282 veterinary practices were examined to identify feline patients, and within these patients, cats with CKD were identified. (No patient or owner or veterinary practice identifiers are included within the thesis and to maintain confidentiality any personally identifiable information has been anonymised.) Three outcomes identified from the COS generated were searched for and two were fully successfully identified and extracted from the patient records (blood pressure and bodyweight) and one was partially identified (survival time) -(Chapter 7).

This PhD shows that patients with a condition of interest can be identified and followed over time, as normal practices regarding their treatment and their outcome assessments are carried out and recorded. This demonstrates that the veterinary electronic patient record has real potential to be a valuable source of data for future veterinary pragmatic trials, and that that data can be successfully extracted for analysis. This process does not require veterinary professionals or patient owners to change their normal behaviours or clinical history recording practices, which means that lack of time and capacity is less likely to be a barrier to patients being involved in pragmatic veterinary trials.

7.2 Impact of this PhD work

There are many areas in which the results from this PhD work have current and potential future impact.

7.2.1.1 Core outcome sets

This work has demonstrated the adaptation of methods from human healthcare for early stages of development of a core outcome set (COS) for feline CKD treatment trials (Table 1).

This is a new area for veterinary medicine where only one other COS currently exists. The methods described in this work can be adapted by veterinary researchers for developing more COSs, for feline medicine and for other species and conditions. In addition, once finalised, the COS begun during this work is recommended for use in all future treatment trials for feline CKD. This will help the results of future trials to be more relevant to treatment decision makers and permits straightforward comparisons and synthesis of trials. Core outcome sets have the potential to reduce research waste and are very much needed in veterinary research to ensure more consistency in treatment trials for all conditions and species.

Table 7.1 Development of a core set of outcomes for feline chronic kidney disease trials. The table contains a summary of key findings and what these findings mean and what the next steps will be for key stakeholder groups once the COS is finalised as described in Chapter 3.

Key findings	**Stakeholder group**	**What the findings mean for this group**	**What are the next steps for this group**
The proposed list for the core outcome set at present is not small, although it can be summarised into four key areas. There are many parameters to consider when assessing treatment success and making choices for these patients. Some core outcomes for feline CKD are not represented in the current published literature. The outcomes prioritised by each of the stakeholder groups were different. Some key differences were	Cat owners	Input from cat owners really matters to this research and had a big impact on the final results. The treatment priorities of cat owners and veterinary surgeons may be different.	Discuss the COS with veterinary professionals, with a view to recording these outcomes within veterinary consultations. There are many treatment outcomes cat owners can monitor at home and may provide most accurate results when monitored at home. These are key to assessing treatment success.
	Veterinary surgeons and veterinary nurses	The treatment priorities of cat owners and veterinary surgeons may be different. There may not be published evidence available yet on the treatment outcomes that are required for patients.	Consider setting up special appointments for monitoring CKD patients and prioritise assessing the COS outcomes in these. Discuss with owners the possibility of recording some of the COS outcomes at home.

seen between cat owners and healthcare professionals and agreement was reached for these during the consensus meeting. The COS generated included many outcomes that could be recorded at home by cat owners or by vets during consultations. Some outcomes require samples to be sent to external laboratories (e.g. SDMA). If core outcome data is clearly recorded within designated fields in the PMS or the free text clinical notes, it can facilitate the contribution of this data to future trials analysis.			Discuss with the owner which treatment outcomes matter most to them. Use the COS as a template for discussion. Familiarity with the COS and clear recording of data relevant to the COS within either designated fields in the PMS or free text clinical notes, can facilitate the contribution of this patient data to future trials analysis.
	Researchers	Inconsistencies in assessing the COS in published literature makes combining existing research evidence in systematic reviews or meta-analyses difficult.	Include the COS once finalised in future treatment trials for feline CKD. The COS requires future development, both in finalising the full COS as described in chapter 3, agreeing tools or instruments to assess each outcome, and in future, the content of the COS should be revisited and updated if needed.

	Industry[1]	There are many existing evidence gaps in feline CKD treatment as the full COS is not yet assessed by all treatment trials.	Include the feline CKD COS in future treatment trials and in designing new pharmaceuticals, nutraceuticals and diets. Highlight evidence which relates to outcomes from the COS when discussing evidence for pharmaceutical interventions with veterinary surgeons. Reference outcomes from the COS when discussing nutraceuticals and diets with owners of cats with CKD.
	Journal editors	The COS highlights the treatment outcomes in feline CKD which are most important to those	Encourage researchers to use reporting guidelines when reporting research prior to

[1] 'Industry' in this context means veterinary pharmaceutical and nutraceutical companies and manufacturers, or manufacturers of veterinary diets designed for the specific needs of particular diseases or conditions.

		who design, publish and use research on feline CKD treatment.	the research beginning, and while reporting on research already carried out. Encourage the uptake of COS for future research. In future when more COS are created for more species and conditions, checking for and using COS where they exist could become part of the required protocol for designing veterinary treatment trials, as it is in human medical research.
	Educators	The COS provides a valuable guide to the most important outcomes to all decision makers in feline CKD treatment, and a guide to the most important outcomes to record in feline CKD clinical records, to provide useful clinical history for future treatment decision making.	Include the COS in veterinary and veterinary nurse training- See the 'Knowledge exchange' in the 'Future work' section for a COS dissemination plan

7.2.1.2 Quality of life research

One outcome identified in the core set was quality of life. Researchers, veterinary clinicians and cat owners who wish to assess feline quality of life using detailed, validated tools can use the systematic review in this PhD work as a starting point to find the tools they need. Quality of life assessments can be crucial for decision-making around treatment choices, management strategies and euthanasia decisions. Often in published literature or veterinary consultation records, this important outcome is assessed in very simple terms which may not capture the complexity of this important construct, may be hard to repeat, and may not be fully reliable or valid. The systematic review in this study is a starting point for those wishing to improve their quality-of-life assessment methods.

Table 7.2 Systematic review of quality of life tools for cats. A summary of key findings and what these findings mean and the next steps to take for key stakeholder groups.

Key findings	**Stakeholder group**	**What the findings mean for this group**	**What are the next steps for this group**
Published literature contains many references to quality of life (QoL) improvements, however not all publications assess quality of life using a validated tool. Validated tools for quality of life assessments for cats are published and the majority are tailored to specific diseases or conditions.	Cat owners	Owners are vital patient advocates and have a responsibility to accurately represent their cats QoL to aid treatment and management decision-making in the veterinary clinic. QoL cannot be fully assessed only within the veterinary clinic.	Discuss objective ways to assess QoL with their veterinary surgeon when making treatment decisions for their cats. Include QoL discussions and assessment throughout the patient's life, and alongside treatment and management decisions, not only at euthanasia decision making.
	Veterinary surgeons and veterinary nurses	Consider that the patient presentation in the veterinary clinic does not represent the full picture for QoL assessment. Be aware that QoL is of core importance to owners of cats with CKD, and is likely to be so for cats with other conditions also. Therefore	Discuss validated QoL assessment tools with cat owners and encourage them to use the tools to aid in objective QoL assessments. Include QoL discussions and assessment throughout the patient's life, and

The majority of QoL assessment tools found contained questionnaires which focus on cat owners completing them. Cat QoL is important to all decision makers for cats with CKD, and forms part of the core set of outcomes to be assessed in treatment trials for these patients (Chapter 3).		the impact of treatment decisions on QoL is vital as part of the decision making process.	alongside treatment and management decisions, not only at euthanasia decision making. Veterinary nurse clinics for older patients or those with specific conditions could use validated QoL assessment tools for discussion and objective assessments.
	PMS providers	QoL is an important parameter which at present is not a defined field for data entry.	Consider including QoL assessment as a data collection field to use for research. Consider whether forms for filling in detailed QoL assessment could be added to the PMS, and whether data mining could identify cats who would especially benefit from QoL assessment (those on long term treatments or those with recent diagnoses, cats becoming geriatric etc.) and flag these patients to the treating veterinary surgeon or veterinary

			nurse for starting QoL discussions with owners.
	Researchers	Validated QoL tools exist for many cat diseases and conditions which are included in trials and research.	Use validated tools to assess QoL of cats in trials where appropriate tools exist. Extract detailed information on the published validation process already carried out on the existing published tools and assess whether the tools are fully validated or whether more work needs to be done. Create new QoL tools for diseases and health conditions not covered by the existing set of validated published assessment tools.
	Educators	QoL should not be assessed in ways which over-simplify this complex concept.	Incorporate validated assessment tools for QoL into teaching for veterinary undergraduates, veterinary CPD and veterinary nurse training and CPD.

	Industry[2]	Assessing QoL is important to the owners who are investing in diets and treatments for their patients, especially cats with CKD.	Use validated tools to assess QoL of cats in trials where appropriate tools exist. Develop resources flagging appropriate validated QoL tools, and how to use them, alongside the product information literature produced for new products.

[2] 'Industry' in this context means veterinary pharmaceutical and nutraceutical companies and manufacturers, or manufacturers of veterinary diets designed for the specific needs of particular diseases or conditions.

7.2.1.3 Working with electronic patient records

This work may also be a useful reference for those wishing to work directly with veterinary patient EPRs. A relational database which captures the complexity of the data contained in the veterinary PMS source database was developed. The structure also uniquely identifies individual patients within the dataset, regardless of PMS or veterinary practice of origin. This means that within a clinical trial or observational study, individual patients can be tracked, their information is not mistakenly duplicated, and loss to follow up is reduced. In addition, once the new clinical evidence schema created from this work has been ratified and published by the VetXML Consortium, the revised edition can be used by researchers. It allows for cohorts of data to be extracted from multiple veterinary practices and identifies the PMS of origin within the extract, so that multiple extracts can be easily combined in a one dataset. It is extensible, and additional parameters of interest or additional data fields can be added in the future if required.

Table 7.3 Working with electronic patient records for research. A summary of key findings and what these findings mean and the next steps to take for key stakeholder groups.

Key findings	**Stakeholder group**	**What the findings mean for this group**	**What are the next steps for this group**
The updated Clinical Evidence schema should work for collecting cohorts of patient data from multiple practices. Inclusion of PMS identification and dates of the data batch are vital when adding new data extracts prospectively to an existing dataset. When data extracts are written in XML language with schema tags,	Cat owners	All patients have the potential to contribute to research which would help patients like them in the future.	Consider giving consent for patient records to be used in research. Discuss with veterinary practice which research they contribute to and why.
	Veterinary surgeons and veterinary nurses	Data recorded in designated fields is easier for researchers to extract (although information can also be extracted from free text).	Use fields where available Consider using the predictive text function in free text (where available) to provide a template for recording key outcomes (e.g. COS) about patients with feline CKD so none are forgotten and the notation is consistent and clear.
	PMS providers	Recording date and time stamps for changes to entries into patient overview information (e.g. gender and neuter status) makes this information easier to extract and chronologise for researchers.	Consider partnering with researchers to include additional specific fields of interest to the PMS, to facilitate data entry to clinical trials.

understanding and using the files is straightforward. Other data types (xls, cvs) can be used but require transformation into XML before upload. More data fields may be available from other PMSs. Collecting data on patient prescriptions may require adding new data fields to the Clinical Evidence schema. De-identification of free text data entries is achievable, however is not yet as fully refined as it could be.			Consider a 'trials' alert function which could pop up (similar to allergy information) when a patient record is opened, to facilitate patient recruitment for clinical trials. For example, if recruiting cats for a CKD clinical trial, an alert could be created to pop up when any cat patient record is opened, reminding the vet of the clinical trial and asking them to check whether the patient is eligible. Or in more advanced recruitment, if access could be gained to anonymised patient records for a veterinary practice and placed in a research database, the database could be searched for e.g. all cats within a certain age bracket with CKD terms in their clinical notes, or whatever the inclusion criteria for the trial was. These patients would be identified in the research database by PMS of origin, Practice ID and Animal ID, and these identifiers could then be used by the veterinary practice to manually add an alert to the patient record for their next visit, or potentially

Increasing the scope of the protected words list, and/or removing PPIs before the records leave the PMS of origin would improve this.			alerts could be autogenerated, although the methodology for this would need to be developed.
	Researchers	Patient data from the EPR has the potential to be used for identifying eligible patients for trials. Writing scripts in DML via the SQL command line works well for rapid querying of large datasets for analysis for trials. Explore which other data fields might be available for clinical research from within the PMS, and specifically whether prescription information is recorded within a field which is not collected according to the current updated Clinical Evidence Schema.	If PPIs can be removed from free text at the PMS before data transfer, then de-identification of records would be more robust, especially as the script could be directed to redact names from a known client list at source. Scripts could be written to compare words in the free text to a known list of PPIs and redact them if matches occur (in a similar way to how the 'protected words lists' were checked for matches and then protected from redaction). The redacted notes could then be transferred for research. This would comply with GDPR as long as the PPI list was known only to the PMS. However, it would take a long time and a large amount of memory to do and may prove impractical for this reason.

			Further development of veterinary clinical text mining methods will enable improvement of the CKD script, reducing the false positive diagnostic rate by filtering out patients where CKD is a differential diagnosis or has been ruled out. It could also facilitate extraction of trial outcomes e.g. bodyweight from the free text, when the weight field in the PMS has not been used to record that information correctly. Protected word lists need to be expanded to improve the retention of clinical meaning in the free text whilst retaining deidentification.
	Educators	Clinical record keeping in the EPR has wider impact and use than for the health of the individual patient.	Discuss the value of the EPR to research when teaching students about clinical record keeping. Encourage clear note taking which can be easily understood where possible (i.e. only using acronyms that are well known) and discuss the potential value of using all available fields in the PMS and VeNOM

			coding, in making translating the clinical record into research easier.
	Industry[3]	A wealth of patient data resides in the EPR, useful for analysis for treatment effectiveness around core outcomes for feline CKD, and longer term follow up of patients than is normally available from most clinical trials.	Partner with PMSs, researchers and veterinary corporate groups to fund research using patient data from the EPR.

[3] 'Industry' in this context means veterinary pharmaceutical and nutraceutical companies and manufacturers, or manufacturers of veterinary diets designed for the specific needs of particular diseases or conditions.

7.2.1.4 Including cat owners and carers in research

Finally, this work has demonstrated the valuable contribution that veterinary clinicians and cat owners can make to research, both passively when their patient records are extracted and used, and actively when involved in stakeholder panels in consensus methodologies. Those who took part found the experience interesting and rewarding. Feedback from panellists who took part in the consensus meeting was described in Chapter 3.

There is an increasing recognition in human healthcare of the importance of patient involvement in research. The Patient Participation, Involvement and Engagement (POPPIE) working group is a COMET initiative who were established to "lead and oversee the public participation, involvement and engagement work of the COMET Initiative" (www.comet-initiative.org/Patients/POPPIE). They create plain language summaries on COSs and the processes by which they are created, raise awareness of COS among patient groups, provide guidance and resources on patient and public participation and research into how to optimise patient involvement in COS (COMET Initiative PoPPIE working group terms of reference www.comet-initiative.org/Patients/POPPIE). In veterinary research, patient owners and carers are excellent patient advocates, and their involvement in deciding research outcome goals was invaluable in this PhD work. Future work on COS developments for veterinary medicine should include learning from the example of COMET and the POPPIE group and could consider development of a working group with a similar remit for the veterinary sphere.

7.3 Future work

7.3.1.1 Knowledge exchange: dissemination of the COS for feline CKD trials

The COS has already been presented at COMET VII (2019), BSAVA Congress (2019 and 2020), SVEPM Annual Conference (2020) and published in Preventive Veterinary Medicine (2021, doi: 10.1016/j.prevetmed.2021.105348). The COS has also been included in the COMET Initiative database (https://comet-initiative.org/Studies/Details/1895).

Further strategies to raise awareness of the COS once finalised could include:

More presentations to veterinary surgeons, veterinary nurses and the academic community:

- Presentation at other veterinary conferences (e.g. London Vet Show, International Society of Feline Medicine Congress, World Small Animal Veterinary Association Congress).
- An article in the Veterinary Times (veterinary magazine) to complement the published paper.
- Presentation as an online webinar to reach wider more international audiences.
- Develop literature for veterinary practices seeing feline patients on the COS, which outcomes to monitor in the veterinary consultation and highlighting outcomes of greatest important to cat owners, to facilitate discussions. Literature could be infographic style, either digitally or as a leaflet or poster for consult rooms.
- Collaboration with Vet Professionals Ltd (organisation that works to produce information for animal owners) for either an online information sheet about the COS or a webinar about the COS and how to use the COS in monitoring CKD patients for veterinary practitioners and nurses.

Feedback to participants:

- Invitation of all contributors to the eDelphi and consensus meeting of the COS, including representatives from all industry members who participated, to a dedicated online presentation to feedback results from the study and how their contribution helped to build the COS.

Raising awareness with owners of cats with CKD:

- Article in Your Cat magazine highlighting the COS
- Owner focussed evening webinar presentation with Q & A session
- Develop client literature explaining the COS and which outcomes are vital for owners to monitor at home. Potentially use an infographic style of presentation or provide infographic either as email or leaflet to hand out to owners of cats with CKD.

- Discuss with the writer of the website 'Tanyas CRF' (www.felinecrf.org, a resource very popular with cat owners and veterinary surgeons as a source of information for feline CKD) whether the COS could be linked or highlighted via this website.
- Collaboration with Vet Professionals Ltd for either an online information sheet about the COS or a webinar about the COS and how to use the COS in monitoring CKD patients would help raise awareness and use with cat owners.

7.3.1.2 Education of veterinary students and veterinary nursing students

Information about the COS could be included in curricula for both these important student groups. This could be as either lecture based or small group problem-based learning discussions with case examples or included in small animal medicine clinical rotation teaching and discussions. The key reasons would be:

- COS are a good springboard for discussion in consults relating to feline CKD cases because we know the content reflects what is important to cat owners.
- The core outcomes are important to measure and monitor because they should be reflected in future research.
- As a result of both points above, good knowledge of the COS outcomes and confidence in assessment methods for them is very important.

7.3.1.3 Potential collaboration with IRIS

In addition to the above ideas, discussion with the panel who design the IRIS kidney guidelines (www.iris-kidney.com) for diagnosis and treatment of feline CKD could be beneficial. IRIS stage, and the outcome measurements which are required for the IRIS staging process were all included within the proposed set of outcomes. Therefore, promotion of awareness of the final COS would promote awareness and potentially use of, the IRIS staging process. If it was agreed that where the online resources for IRIS guidelines are located there was also information on the COS and links to further information on the COS, then awareness and probable use of the COS would increase.

7.3.1.4 CKD core outcome set monitoring

Once the full COS has been finalised and the assessment tools have been decided and the knowledge exchange ideas actioned it will be important to follow-up the COS to assess if, when, where and how it is being used and implemented in research trials. Feedback should be invited from researchers implementing the COS in trials and veterinary professionals and cat owners using the COS for monitoring CKD patients and planning CKD treatments. Information should be gathered on the feasibility of using the COS, and any areas of CKD outcomes which users feel the COS does not fully reflect. The systematic review of outcomes in feline CKD treatment trials (Chapter 2) should be updated, and the resulting outcomes in new trials audited to see how well the COS is being implemented and whether newly published trials are more consistent in outcome measurement and reporting and whether as a result, the feline CKD treatment evidence base has changed. Care of feline CKD patients could then be audited to see whether publication and raising awareness of the COS has had an impact on patient care. Cat owners and veterinary surgeons and veterinary nurses could be surveyed to gauge awareness and use of the COS in their consultation discussions and treatment plans. The EPRs of cats with CKD could be examined to see whether mention of the COS or the outcomes from the COS appear within the Clinical Notes. The remaining outcomes from the existing COS which have not yet been searched for and extracted from patient notes should be looked for in existing patient records, to see if they can already be extracted and utilised. Any emergence of their documentation within patient notes could be monitored. Finally, the COS should eventually be revised and if necessary, updated. All COSs represent a snapshot in time. As research develops and more is known about health conditions and available treatments, and as the research priorities of end users change, the COSs themselves may also need to adapt and change. Williamson et al., 2012 recommend reviewing COS periodically as a form of validation to ensure outcomes remain relevant and important, to allow new outcomes to be added and to engage further stakeholders if appropriate. The COS has been developed in this thesis is a starting point for feline CKD research but should not be considered static or unchangeable.

7.3.1.5 Which core outcome sets should be next for veterinary medicine?

COSs are very new within veterinary medicine. To decide which conditions or areas of interest for each species to prioritise for developing more COS will require careful planning. It is vital to include all stakeholders in patient decision making, including patient owners and carers, in the prioritisation of COS to develop and the actual development process. Co-creation of research ensures that the results will best reflect the needs and priorities of those whom the research will be used by and will impact upon. To date, the James Lind Alliance user involvement approach has been successfully adapted to the veterinary field to systematically identify research priorities for canine sterilisation (Collinson et al., 2021), feline chronic kidney disease (Dean, 2014) and equine pituitary pars intermedia dysfunction (Tatum et al., 2021). It is recognised as a process which increases the relevance of research and informs researchers and research funders about priorities which increases the meaningfulness of research to those who need it (JLA Guidebook Version 10, 2021). This methodology could be key in prioritising the next species groups and research topics for future veterinary COS development.

7.3.1.6 Quality of life assessment in cats

Next steps for assessing this important core outcome in cats with CKD must include assessment of the validation process carried out on the quality of life tools found in the systematic review. The reliability of the tools should also be assessed in terms of inter-rater reliability (when scorers simultaneously score the same animal), intra-rate reliability (when one person repeat scores the same animal), and test-retest reliability (consistency in scoring when a long period of time has elapsed) (Belshaw et al., 2016).

Specifically for feline CKD, the tool found in the systematic review (Bijsmans et al., 2016) should next be assessed in terms of feasibility of use for clinical trials. Initially, cat owners, veterinary surgeons and veterinary nurses, researchers and those in industry involved in clinical trials could be surveyed to see whether they are already familiar with, or use this tool. Their opinions could be sought as to its useability to assist decision making in first opinion practice and clinical trials, via focus groups or questionnaires. As discussed in Chapter 4, the most appropriate tool for assessing quality of life for the feline CKD COS

should be established by consensus, following the COSMIN guidelines for selection of outcome measurement instruments (Prinsen et al., 2014).

Further work could then investigate quality of life assessment in first opinion consultations. Using methodology developed in Chapter 5 and Chapter 6, the clinical histories of cats with CKD could be examined to determine how quality of life is assessed in the veterinary consultation, and how that information is recorded and used. Data Manipulation Language (DML) scripts could be used to look for specific quality of life assessment tools, or grading systems recorded in the Clinical Notes. The words used to describe specific behaviours and parameters examined as part of feline quality of life assessment in the CKD tool and other tools found in Chapter 4 could also be searched for in the Clinical Notes. This could start to build a picture of how discussions and assessments of feline quality of life are carried out in first opinion consultations, for all cats and for cats with CKD. The EPR could also be queried to discover the timing of when quality of life discussions take place, with respect to the lifespan of the cat, the diagnosis of CKD and euthanasia decision making. It is possible that initiating quality of life discussions early in the disease process means this important outcome will be assessed and monitored throughout the cat's CKD journey, and may lead to more timely and welfare friendly decision making. It would be interesting also to explore further how important quality of life assessments are in the euthanasia decision making process, and how and when quality of life starts to change for the better or worse in these patients.

Further research could also explore what 'good' quality of life looks like, firstly for healthy cats, and secondly, specifically for cats with CKD. Initially this could be carried out with interviews of owners of cats with CKD, and of veterinary surgeons who treat cats with CKD. Comparing the perspectives of these two key groups of decision makers could help to show areas where there is agreement and where there are differences of opinion. These findings could then form the basis for frameworks to support quality of life discussions in the consultation, so that the perspectives of all decision makers are reflected and included.

7.3.1.7 Streamlining data extraction

Future work with the EPRs should aim to streamline the process of data extraction from the PMS dataset and upload to the destination database at the CEVM. Automation of this process so that data arrives prospectively, on a fortnightly basis from veterinary practices participating in data transfer would be optimal, with auto alerts generated if any part of the process fails to work properly. Files could be uploaded automatically to a server at the research group, then cleaned and uploaded to the research dataset. Automatic validation of the data extract against the schema could be used to check for errors in data type and missing data. An earlier version of the PMS schema was embedded within cooperating PMS (J. S. Jones-Diette et al., 2016), so that data conforming to the schema could be extracted and emailed automatically from each individual veterinary practice by selecting a command within the PMS interface at the practice. Future work could look to embed the revised version of the schema into additional PMSs, so that the same could be done either at the level of the veterinary practice, or at the level of the central PMS database, where data from a selection of veterinary practices or all veterinary practices could be extracted.

7.3.1.8 Redaction

The method developed in this work to redact personally identifying information from the free text fields could be further refined as described in the table above. In addition, the lists of words protected from redaction should be expanded to reduce the amount of clinical meaning lost from the free text notes.

7.3.1.9 Identifying trial candidates

In human healthcare pragmatic trials, routinely collected data can be used to identify people who may be candidates for future trials (Lugg-Widger et al., 2018). For future trials for feline CKD, the method developed in this study of using SQL scripts to identify cats with CKD terms in their clinical notes could be adapted to find risk factors for developing CKD, as identified previously in research (Conroy et al., 2019), or cats with existing CKD. Once their AnimalID's are known, the existing PMS interface could be used to alert the clinician treating the patient that the cat is a potential candidate for a trial. Many PMSs have an alert field, for example for patient allergies, which appears automatically when the patient record is opened. Either this field could be used or a similar one created for trials. Then the alert message, for example, 'this cat is eligible for the CEVM trial, please discuss consent with

their owner' could be written into that field at the main PMS database, or with permission at each veterinary practice, either automatically or by the research team. Alternatively, the AnimalID numbers of eligible patients could be used to generate a list of the patient names by the veterinary practice and a manual list could be used. A patient could then be identified when they enter into the trial by tagging their record by writing a key phrase into the ClinicalNotes, e.g. "CEVM trial".

7.3.1.10 Tracking individual patients

This study identified that some of the feline patients had consultations recorded at up to six individual veterinary practices within one PMS. If patients only go to practices with the same PMS, and their AnimalID is allocated per PMS (not per practice) they can still be tracked and are not duplicated or lost to follow up within a trial. However, if they move to a practice using a different PMS, without another unique identifier it would be difficult to connect their new and old records to each other. The number of patients in this study who were also seen for consultations at veterinary practices with a different PMS, during the study period, is not known. Therefore, at this time the potential impact of patients moving between PMSs during a clinical trial remains undetermined. The only existing unique identifier for cats is microchip numbers, however this cannot be extracted due to the risk of using the numbers for identifying the cat owners. Therefore, a new solution for tracking patients who move between PMSs is required.

This research has shown that key words can be reliably extracted from the free text of a patients record. If a patient was entered into a clinical trial, the veterinary surgeon could be asked to write a key word or phrase into the text, for example, "CEVM Trial". If the patient history was requested by a new PMS and attached to the patient record in the clinical notes, the key phrase could be searched for, and the patient identified. Patients could be given trial enrolment numbers which are unique per patient which would further identify them, and could also be written into the ClinicalNotes. This solution would need to be trialled and its success validated before it could be relied upon in a future trial. A small pilot trial could be carried out initially, across a small number of veterinary practices. Each of these could be given a list of AnimalID numbers for the mock 'trial' and a phrase and ID number to write into each patient's ClinicalNotes, e.g. 'CEVM Trial 12345'. The patient records would then be extracted as XML files, conforming to the updated Clinical Evidence schema and uploaded

into the research database. The trial ID numbers would be known to the researchers and could then be searched for in the Clinical Notes in the same way that keywords relating to CKD or interventions for CKD were searched for with DML scripts. The script would report the trial ID number found and the associated AnimalID number. A list of all positive hits could be compiled and then manually compared against the list which was sent to the veterinary practices, to see how many numbers had been correctly transcribed, identified and extracted. To test whether the trial numbers would still be successfully identified within the EPR if a patient moved between PMSs could be tested in the same way but with two demo veterinary practices installed on different PMS systems. The CEVM research group have previously had their own demo version of a PMS (J. S. Jones-Diette et al., 2019). Having an additional CEVM demo veterinary practice within a second PMS would enable patient data to be entered into one, and then the second one as if it was a single patient moving between practices. Data from both could then be extracted and examined via established methods, and the overview information and clinical history for the patient compared from both extracts to ensure it was the same patient with one trial ID number. To prevent trial ID numbers from being mistakenly redacted as phone numbers, each trial ID number would need to be included in the 'short words' protected list, where an exact match is required to protect the word. Numbers might also contain letters so that they are not accidently exact matches for phone numbers themselves. For example, if 'trial ID 414985' was protected then a real phone number would be accidently preserved with the Clinical Notes. However, with 'trial ID cevm414trial985' this would not be the case.

7.4 Conclusions

This PhD has used feline CKD as a model, demonstrating that core outcome set development can be begun, assessment tools identified and veterinary EPRs are a viable and feasible resource for extracting data suitable for use in pragmatic clinical trials. Good relationships between trial organisers, veterinary practices, patient carers and PMSs are vital to enable participation and accurate detailed data collection, especially if data in addition to the EPR is required. For this reason, clinical trials networks of practices may be

smaller in size that those of veterinary EPR researchers collecting observational data. In addition, all decision-making stakeholders can, and should be co-creators in veterinary trials research, ensuring the results obtained are as relevant, appropriate and generalisable as possible.

Veterinary pragmatic trials are an exciting and emerging field. Veterinary patients stand to benefit highly from further development of veterinary pragmatic trials methods, as the results produced will give insight on treatment effectiveness, for more patients like them, created from data from patients like them.

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www.msdvetmanual.com/clinical-pathology-and-procedures/diagnostic-procedures-for-the-private-practice-laboratory/clinical-biochemistry

www.nia.nih.gov/health/placebos-clinical-trials

www.vetxml.co.uk/en/

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9. Appendices

9.1 Appendix 1 Core outcome set for feline CKD paper as published in Preventive Veterinary Medicine

What outcomes should be measured in feline chronic kidney disease treatment trials? Establishing a core outcome set for research.

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ABSTRACT

Chronic Kidney Disease (CKD) is an important cause of feline morbidity and mortality. There is currently no agreement on which outcomes are most important in CKD treatment trials to assist evidence-based decision making.

Core Outcome Sets (COSs) originated in human healthcare and are an agreed set of outcomes to be measured and reported as a minimum in any trial conducted relating to a particular disease. To establish a COS for feline CKD, this study used a systematic review and two consensus methodologies (an electronic Delphi (eDelphi), and an in-person consensus meeting), with an international panel of key stakeholders.

The systematic review identified 104 unique published parameters, which were rated by panellists in round 1 of the eDelphi. Panellists were also asked to suggest additional parameters. In round 2 these additional parameters were rated and any parameters not understood by >10% of panellists in round 1 were redefined and re-rated. Parameters reaching consensus in rounds 1 and 2 were removed from round 3, when all remaining parameters were re-rated by panellists who could view their own previous rating alongside the median rating of the whole panel. To reach inclusion in the COS, parameters had to be rated 8 or 9 on a Likert scale of 1-9 (where 1 was not important and 9 was very important) by more than 80% of panellists. In the consensus meeting, panellists discussed and re-rated borderline parameters and streamlined the final COS. Borderline parameters were those that had been closest to, but not achieved, the 80% threshold for inclusion.

The eDelphi panel (n=73) rated 24/104 parameters highly enough for inclusion and proposed an additional 20 parameters, of which 3 reached the inclusion threshold. This totalled 27 parameters for inclusion. The consensus meeting panel (n=16) rated an additional 6/20 borderline parameters highly enough for inclusion. During the streamlining process, 4 parameters were removed as one was considered not an outcome, and three were already addressed by other parameters. The remaining COS totalled 29 parameters. These were grouped into 9 core themes: clinical examination, quality of life, serum biochemistry, complete blood count, urinalysis, total amount of food eaten, CKD progression, survival time and cause of death.

This is the first COS for feline medicine. In future treatment efficacy trials the COS will strengthen the evidence-base for this condition, by facilitating easier comparison of results between studies, and reduce research waste.

KEYWORDS

Feline; Chronic Kidney Disease; Core Outcome Set; Consensus; eDelphi; Trials.

INTRODUCTION

A diagnosis of chronic kidney disease (CKD) in cats can be based on evidence of chronic structural or functional damage to the kidneys of, for example, greater than three months duration (Sparkes et al., 2016). It is often stated that azotaemic CKD becomes clinically apparent when over 75% of the renal function has been lost (Brown et al., 1997). It is a common disease in cats, and cats of any age can be affected. A recent study (Conroy et al., 2019) reported an overall prevalence of 1.2% in primary care practice, with a prevalence of 0.1% in cats less than 9 years old and 36% in cats 9 years and older. Other studies have reported even higher prevalence, Sparkes et al. (2016) reported 30-40% or higher in cats older than 10 years (from Lulich et al., 1992). Marino et al. (2014) reported that CKD can affect up to 80% of cats over 15 years of age. It causes clinical signs including polydipsia, polyuria, weight loss, inappetence, hypertension, weakness, lethargy, vomiting, and anaemia (Sparkes et al., 2016). The clinical signs reported to impact on a cat's quality of life are anorexia, weight loss and depression (Bijsmans et al., 2016). Treatment strategies vary according to the stage of the disease; in the early stages the aim is to reverse the primary cause if known and limit progression of the condition. However, primary causes are only identifiable in a minority of cases whilst in most cases kidney damage is irreversible at the time of diagnosis. In the later stages of disease, the aim of treatment is to reduce clinical signs and improve quality of life and life expectancy (Cannon, 2016).

Cat owners and veterinary surgeons have to make important decisions about which treatments to administer when CKD is diagnosed and particularly, as it progresses. There are internationally recognised guidelines to support treatment decisions, published by the International Renal Interest Society (www.iris-kidney.com) and the ISFM have published consensus guidelines on the diagnosis and management of feline CKD (Sparkes et al., 2016). However, no consensus has been reached to date on which parameters are the most useful to aid the decision-making process. Published clinical trials often use several parameters to diagnose CKD and monitor its progression, but different parameters are used in different studies and information on all parameters is not available for all tested treatment options. This limits the evidence available to help with decision-making and highlights the requirement of a consensus on best practice.

It is imperative that during veterinary clinical trials the most relevant outcomes that matter to patients, clinicians and clients are measured, in order to determine the most effective treatment and management strategies for a particular disease. A Core Outcome Set (COS) can be defined as an agreed set of outcomes or outcome measures that should be measured and reported as a minimum in any trial conducted relating to a particular disease (www.comet-initiative.org). This concept originated in human healthcare and has been used most notably in rheumatoid arthritis studies, with a COS originating from the Outcome Measures for Rheumatology Clinical Trials (OMERACT) initiative. Since this COS was created, the consistency of measurement of the core outcomes proposed has been shown to improve (Kirkham et al., 2013). It is well established in human healthcare that without COSs, the outcomes reported in trials may not be reflective of endpoints that are meaningful for health service users (Williamson et al., 2012). Additionally, the use of high quality COSs is increasingly mandated by research funders and journal editors (Webbe et al., 2018). The Core Outcome Measures in Effectiveness Trials (COMET) Initiative was created to foster

methodological research, to bring researchers together, develop resources, improve user engagement and raise awareness of COSs. An internet-based resource has been created where all existing COSs and those under development can be registered (Williamson et al., 2012). The creation and use of COSs permits the robust comparison of results between studies, facilitating evidence-based clinical decision-making (Clarke & Williamson. 2018), and reducing unnecessary research waste (Hughes et al., 2019).

The Delphi process is frequently used in the development of COSs (Kottner et al., 2018). The Delphi process is a recognised and structured methodology for gathering opinions from experts and stakeholders that facilitates convergence of opinion (agreement) on decision-making on a particular topic (Williamson et al., 2017). An eDelphi is an online electronic form of a Delphi process, and is typically carried out using questionnaires or email (Hall et al., 2018). Information or questions are presented in a number of questionnaire rounds or via email to an anonymous panel (Okoli & Pawlowski. 2003). Initially the panel gives their answers independently. In subsequent rounds they are presented with the anonymised answers from the rest of the group and are allowed to change their own answers in light of that information (Williamson et al., 2017; Barrios et al., 2021). This method helps to create a group consensus of opinion, without allowing any individuals to dominate or influence the decision-making process (Sinha et al., 2011). It is recommended that a consensus meeting follows an eDelphi process, where the results are confirmed, clarified and streamlined, and any misunderstandings or disagreements in the group consensus are addressed in a chaired, structured way (Williamson et al., 2017).

The only veterinary COS the authors have identified in the peer reviewed literature was published in 2018 and relates to canine atopic dermatitis (Olivry et al., 2018). The COS was called COSCAD'18 and it contained three outcomes: veterinary assessment of skin lesions, owner assessment of pruritis and owner reported global assessment of treatment efficacy (Olivry et al., 2018). To the authors' knowledge there is no evidence in the peer reviewed literature of any COSs for the feline species.

The aim of this study was to create a core set of outcomes to measure when assessing treatment efficacy in trials for cats with CKD.

MATERIALS AND METHODS

Systematic literature review

A systematic literature review was conducted in April 2018 which focused on identifying all parameters that had been measured and reported in published CKD randomised controlled trials relating to treatments. A systematic review is a structured review that identifies published manuscripts, which are relevant to a research question of interest, using a structured search

strategy in specific literature databases and the application of inclusion and exclusion criteria. Information is then extracted and synthesised from the manuscripts in a pre-defined and structured manner (Jahan et al., 2016). For this systematic review, the databases Medline (1970 onwards) and CAB Abstracts (1910 onwards) were searched, and the first 2000 results from a Google search were also examined. Search terms included keywords and subject headings based on cats, chronic kidney disease and renal failure or insufficiency. Inclusion criteria included: owned cats with naturally occurring CKD, randomised controlled trials and cohort studies and interventions for CKD or CKD clinical signs. Studies in all languages were included, but studies on cats with experimentally induced CKD were excluded, as were studies on treatments for comorbidities in CKD patients (e.g. antibiotics for urinary tract infections or methimazole treatment for hyperthyroidism). Manuscripts were checked for inclusion by RD and NF, and the final list of included manuscripts was additionally examined and checked by HD. There were 20 publications which met the inclusion and exclusion criteria for the review. From these, 104 individual parameters were extracted that assessed treatment efficacy for CKD. These parameters were then arranged into groups according to when and how each parameter might be measured. These groups were as follows: parameters the cats' owner might notice at home (e.g. exercise tolerance), parameters examined in the veterinary consultation (e.g. body condition score), urine parameters (e.g. urine specific gravity), parameters related to CKD progression and lifespan (e.g. survival time), parameters related to being in a trial (e.g. occurrence of adverse events), blood test parameters (e.g. Packed Cell Volume) and more advanced testing (e.g. Plasma Renin Activity).

eDelphi process

The eDelphi was designed to build consensus on the most important parameters to measure when treating cats with CKD. The process used three iterative rounds of online questionnaires. The rounds were completed anonymously by an international panel of stakeholders, who represented a number of different types of decision maker involved in the treatment, management and care of cats with CKD. The first round contained two questionnaires, the second round contained one questionnaire (third questionnaire), and the third round (fourth questionnaire) consisted of individually created word documents. The four questionnaires used in the eDelphi were piloted by members of the Centre for Evidence-based Veterinary Medicine (CEVM) research group before they were used in the study. The parameters extracted from the systematic review were divided between the first two questionnaires (round 1 of the eDelphi). These were presented to the panel, arranged into groups as described above (Supplement 1 shows all parameters, arranged in the groups as described). The definition of a COS was explained. Panellists were asked to consider each parameter individually and rate the importance of including the parameter in the COS using a Likert scale (1-9; 1 being not important, to 9 being very important to include). Alternatively, instead of giving a rating they could also choose "I do not understand what this parameter is" or "I do not understand the importance of this parameter". Consensus for a parameter to be included in the COS was defined *a priori* as 80% of participants rating the parameter as 8 or 9. Consensus for exclusion from the COS was defined as 80% of panellists rating a parameter as 1, 2 or 3. It was defined in the study protocol that where greater than 10% of panellists or a whole stakeholder group answered "I do not understand what this is" for a parameter, additional definitions would be given, and the parameter re-presented to panellists for re-rating. In round 1 of the eDelphi, panellists were encouraged to suggest new parameters they felt had not already been considered.

In round 2 (questionnaire 3), the panellists were presented with two sets of parameters to rate. The first set were new parameters suggested by panellists in round 1. The second set were parameters which more than 10% of panellists in round 1 said they did not understand, with new definitions given to enhance understanding. All of the first three questionnaires were carried out using Online Surveys (https://www.onlinesurveys.ac.uk, Jisc, Bristol, UK) and all data was password protected. Only the first and final authors had access to the Online Surveys dashboard.

In round 3 (questionnaire 4) the panellists were given the anonymised results from the whole panel's ratings (median and range) from the previous two rounds, alongside their own personal rating for each parameter. This information was presented in a table in a Microsoft Word document (Microsoft 365) document and the final column of the table allowed them to either select a new rating for each parameter or choose to keep their rating the same. Any parameters which had already reached the consensus threshold for inclusion or exclusion from the COS were not reconsidered at this stage. The tables were created individually for each panellist and returned by email directly to the first author's password protected email account.

All results from all three rounds (four questionnaires) of the eDelphi were processed using Microsoft Excel (Microsoft 365). After all rounds were completed, all parameters had been rated by all panellists twice and a shortlist of parameters proposed for the final COS created.

The eDelphi panel:

The panel was structured to represent an international group of experts, reflecting the important stakeholders in decision making for cats with CKD. The stakeholder groups planned for inclusion were: clinical experts (first opinion vets, researcher vets, referral vets, industry representatives, veterinary nurses and clinical pathologists), journal editors, regulatory agency representatives and cat owners with experience of CKD.

The selection criteria for panellists in each stakeholder group can be seen in more detail in Table 1.

Table 1: How the stakeholder groups were selected for involvement in the eDelphi study on cats with chronic kidney disease.

Stakeholder Group	Selection criteria

Cat owners	Either currently own a cat who has been diagnosed with CKD or have owned a cat within the past two years who had been diagnosed with CKD.
First opinion vets	Vets working in first opinion veterinary practice, either small animal/ mixed or cat only practice. Not seeing cases at a referral level. Must be seeing cats with CKD.
Researcher vets	Researching cats with CKD or seeing referral patient cats with CKD.
Industry	Must be working for a company making either special diets or pharmaceuticals or nutraceuticals for the treatment and management of CKD in cats and working directly with those products. One representative per company involved.
Veterinary nurses	Working as a veterinary nurse in either first opinion or referral practice and caring for cats with CKD.
Clinical pathologists	Work must involve pathology of CKD in cats in some form.
Regulatory agencies	Working for the VMD or RCVS.
Journal editors	Currently working in an editorial role for a journal which publishes research on feline medicine and feline research.

VMD = Veterinary Medicines Directorate; RCVS = Royal College of Veterinary Surgeons

Recruitment:

The study was advertised via posts on the Facebook and Twitter accounts of the first author and the CEVM. It was also advertised on a dedicated page on the CEVM website and within veterinary specific Facebook forums via the first authors' account. In addition, feed and pharmaceutical companies making treatments or diets for cats with CKD were emailed and invited directly, either via known contacts within the company or via the companies' general enquiries email address. Journal editors from journals publishing research on feline medicine, and the Veterinary Medicines Directorate (VMD, who assure the safety, quality and efficacy of veterinary medicines in the UK) and the Royal College of Veterinary Surgeons (RCVS, who regulate the educational, professional and ethical standards of veterinary surgeons) were

invited in the same way (either known contacts or via general email addresses). Known contacts of the authors, who were working in the treatment or management of feline CKD were also invited by direct email. The study was also advertised during a PhD researchers' presentation day at the University of Nottingham. Prospective panellists registered an interest in taking part by completing a short questionnaire on Online Surveys (https://www.onlinesurveys.ac.uk, Jisc, Bristol, UK), designed to ascertain personal experience of owning cats with CKD, their qualifications, job role and which stakeholder group they belonged to.

eDelphi panel selection process:

For the stakeholder groups where the number registered as interested exceeded the number required, the panel was purposefully selected from all those registered by discussion among members of the research team. The aim was to ensure that the invited panellists would be as international as possible, with the widest possible variety in: country of origin, date and country of veterinary degree graduation, and role working with cats with CKD. The names of registered panellists were available to the whole research team at this stage only, to aid with selection of the most appropriate panellists for each group. Veterinary surgeons were selected to ensure included individuals graduated from a range of Universities across a number of years. The balance of stakeholder group proportions was decided in advance to be as close as possible to that used in the HOME group methodology study (Schmitt et al., 2011). In the HOME study, 25% of the whole panel were patients, 60% were clinical experts and 15% were a combination of journal editors and regulatory agency representatives. The only way a parameter could reach consensus for inclusion without all stakeholder groups being in agreement was if the majority of the owners and the clinical experts rated it at 8 or 9 on the Likert scale. It was thought that if this happened, the parameter would be important enough for inclusion, without needing agreement from journal editors and regulatory agencies.

Administering the questionnaires:

Personalised email links to each questionnaire were sent out using Online Surveys (https://www.onlinesurveys.ac.uk, Jisc, Bristol, UK). Each panellist was assigned a code number and letter, for example "O4" for owner number 4, so that their responses and stakeholder group could be tracked anonymously through the results. These codes were automatically captured by the online surveys site when a questionnaire was filled in. All questionnaires were otherwise filled in anonymously. Only the first author had access to the list of names and codes, and this information was password protected. If panellists failed to complete a questionnaire they were not included in subsequent rounds of questionnaires as the results of the eDelphi were cumulative. Reminder emails were sent to all panellists at regular intervals for each questionnaire, and panellists were encouraged to ask for more time to complete the questionnaires if required.

Consensus meeting

A one day in-person consensus meeting was held. This had two purposes; to address borderline parameters and to streamline the final COS.

Borderline parameters

These were defined as parameters that had been the closest to reaching the 80% consensus threshold for inclusion in the eDelphi but had not passed the threshold. Stakeholder responses to the eDelphi for the borderline parameters were separated into cat owner responses and Healthcare Professional (HCP) responses. HCPs in the context of this study were defined as all panellists who were not in the cat owner group. This was to mirror the methods used in human healthcare COSs, where patient responses are compared to HCP responses. The purpose of the consensus meeting was then to clarify and reach agreement on the ratings for parameters over which there has been the greatest disagreement in ratings between stakeholder groups in the eDelphi rounds (Thorlacius et al., 2018). The meeting was designed to ensure that both patients and HCPs fully understood the definitions of each parameter and had the opportunity to understand and appreciate each other's perspectives. This meant the final whole group ratings on each parameter reflected a shared agreement, borne out of mutual understanding.

Identifying the borderline parameters for which there was the greatest disagreement between groups was carried out using two different approaches. Firstly, by extracting the parameters with the highest percentages of the whole panel rating them as 8 or 9 (excluding those which had already reached the inclusion threshold). The second approach examined the percentages of owners and HCPs who had rated each parameter 8 or 9, and the difference between the two groups. Those where it appeared there had been the greatest disparity between the two groups ratings were targeted for discussion. For example, parameters where over 80% of HCPs had rated it as 8 or 9, but only 50% of owners had rated it as 8 or 9.

Within the consensus meeting parameters were fully discussed, defined and re-rated so that the interests and priorities of both groups could be understood by the whole panel, with the final rating fully representing the true agreement of the whole panel. Borderline parameters were shown to all panellists one by one during the meeting and were discussed. They were then re-rated anonymously and individually by all panellists. Consensus for inclusion in the final COS after discussion and re-rating was pre-defined as over 80% of the whole group of panellists rating the parameter as 8 or 9 on a Likert scale (1-9; 1 being not important, to 9 being very important to include). Consensus for exclusion from the final COS was pre-defined as over 80% of panellists as a whole group rating the parameter as 1, 2 or 3 on the Likert scale.

Streamlining the COS

In the second phase of the consensus meeting, the original COS shortlist from the eDelphi, and any parameters voted in after the additional borderline parameters had been discussed, were presented to the panellists as a list. A session of chaired discussion and voting was planned

to streamline the parameters into a more manageable list by grouping them into body systems or similar categorisations. This aimed to make the final COS as straightforward to use and understand as possible.

Recruitment and selection criteria

The aim for the consensus meeting was to include an international panel of stakeholders, aiming to represent the same stakeholder groups as in the eDelphi. The requirements for each stakeholder group (see Table 1) remained the same. All stakeholders who took part in the eDelphi and all those who had initially registered an interest in participating in the study were invited to participate in the consensus meeting. Some potential dates were circulated to check availability. If a panellist was unable to attend, they were asked if they could recommend a colleague so that the research team could directly invite them to the meeting. Where additional panellists were needed, suitable contacts who met the selection criteria and were known to the authors were invited. The aim was to achieve an equal number of owners and HCPs for the consensus meeting panel, so that discussions and ratings resulting from the meeting would be as balanced as possible.

Pre-meeting preparation

Panellists were provided with a list of the borderline parameters from the eDelphi in advance prior to the discussion. This included the anonymous ratings of owners, Healthcare Professionals (HCPs) and the whole group. They were also provided with a definition of a COS and an agenda for the day. They were asked to think in advance about their opinion on the inclusion of each of the parameters in the COS, and whether there was anything about each parameter that they did not understand. They were also asked to consider how they might streamline the list of outcomes.

Meeting logistics

The meeting was held at central location with good transport links. Travel, food and accommodation costs (where required) were paid by the research team to facilitate attendance. Both phases of the consensus meeting were attended by the same group of panellists. The meeting was chaired by an impartial chair, experienced in chairing consensus meetings for human healthcare COSs. The cat owners were invited to a separate meeting on the same day at an earlier time, to introduce themselves to each other and the chair. They were given the opportunity to ask questions and the importance of their role was explained. This was done to mirror the pre-meetings seen for patients in development of humans COSs. These are thought to help the patients to bond as a group and empower them to contribute to discussions in the main meeting.

At the start of the main meeting, everyone (panellists, chair and the study team) introduced themselves to each other. They explained their experience of owning or working with cats with CKD, the eDelphi stakeholder group they had represented, and the consensus meeting group

they represented (owner or HCP). A short presentation outlining the aims of the study, the eDelphi results, and the aims of the consensus meeting was given. The panel were also shown a video from the Core Outcome Measures in Effectiveness Trials (COMET) Initiative explaining the purpose of COSs.

When rating was carried out it was done anonymously using the online interactive presentation software Mentimeter (www.mentimeter.com). Panellists anonymously rated the parameters online when directed to do so by the chair. They either used their own tablet or smartphone device, or used one provided to them by the research team on the day. The software identified each panellist's response as an owner or HCP. After each parameter had been voted on, the results of the vote were displayed graphically on a projector screen. Throughout the meeting, the research team assisted with the presentations, note taking, photographic documentation of the day, technical support and one team member assisted a partially sighted panel member to participate in the voting process. The partially sighted panel member was provided with all documentation in Braille.

This study was carried out as part of PhD research and was approved by the ethics committee at the School of Veterinary Medicine and Science at the University of Nottingham (ethical approval number 2292 180515). Each panellist on the eDelphi specifically consented to participate during the first questionnaire. Each panellist in the consensus meeting gave their written consent to participate. All panellists were advised that their responses would be confidential and anonymous, and that participation was voluntary.

RESULTS

The flowchart in Figure 1 demonstrates the study progression from lists of outcomes found by the systematic review, to the final COS. It shows the number of parameters included and excluded at each round of the eDelphi and consensus meeting process. The number of panellists completing the work at each stage is also given.

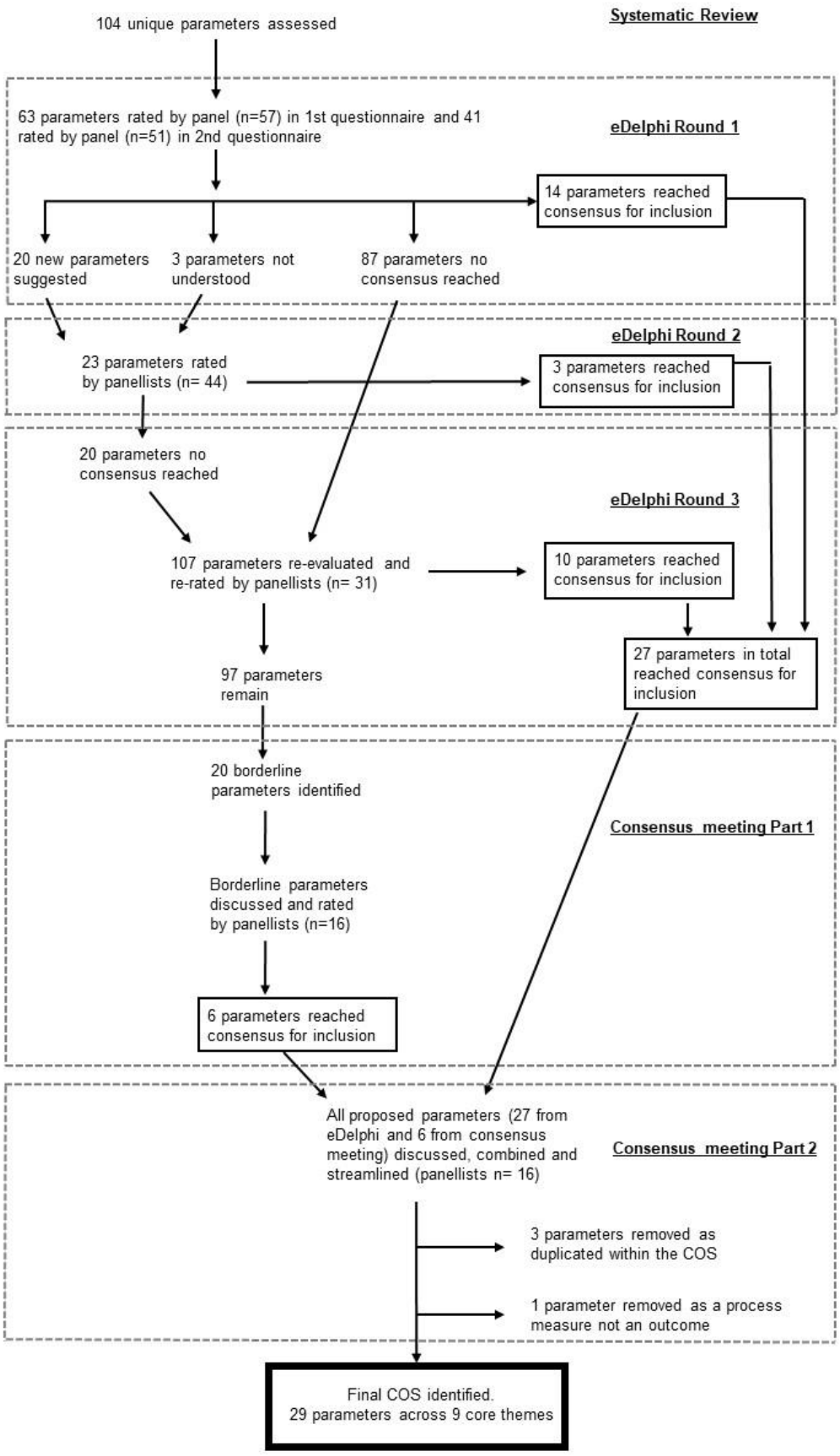
Systematic Review
104 unique parameters assessed
63 parameters rated by panel (n=57) in 1st questionnaire and 41 rated by panel (n=51) in 2nd questionnaire
eDelphi Round 1
14 parameters reached consensus for inclusion
20 new parameters suggested
3 parameters not understood
87 parameters no consensus reached
eDelphi Round 2
23 parameters rated by panellists (n= 44)
3 parameters reached consensus for inclusion
20 parameters no consensus reached
eDelphi Round 3
107 parameters re-evaluated and re-rated by panellists (n= 31)
10 parameters reached consensus for inclusion
27 parameters in total reached consensus for inclusion
97 parameters remain
20 borderline parameters identified
Consensus meeting Part 1
Borderline parameters discussed and rated by panellists (n=16)
6 parameters reached consensus for inclusion
All proposed parameters (27 from eDelphi and 6 from consensus meeting) discussed, combined and streamlined (panellists n= 16)
Consensus meeting Part 2
3 parameters removed as duplicated within the COS
1 parameter removed as a process measure not an outcome
Final COS identified.
29 parameters across 9 core themes

Figure 1: Flowchart demonstrating the overview of the research process from parameter lists extracted from research papers in a systematic review to the development of a final Core Outcome Set.

eDelphi

Two hundred and nine people registered an interest in joining the study panel via the short questionnaire. Of these, 147 were UK based, and 62 were from outside the UK, based in: Ireland, USA, Canada, Portugal, Netherlands, Spain, France, Denmark, Sweden, Switzerland, Japan, Australia and New Zealand. The relative percentage size of each stakeholder group had been pre-defined, as can be seen in the methods section. The smallest groups to register an interest were the stakeholder group "Regulatory Agencies" and "Journal Editors". For these groups combined, 11 people registered an interest in participating in the study. The methods plan was that these stakeholder groups would jointly form 15% of the final panel size. The size of the remaining stakeholder groups was adjusted accordingly, resulting in a final panel size of 73 (where 11 people = 15% of panel size). The breakdown of panel numbers can be seen in Table 2. The predefined characteristics for each group were also fulfilled (Table 1). However, full equality across all these categories was not possible due to the spectrum of applications received from prospective panellists.

Table 2. Number of panel participants in each stakeholder group selected to join the eDelphi process.

Stakeholder group (percentage of total panel size)	Further detail on stakeholders	Number of panellists
Owners (25%)	Either currently own a cat who has been diagnosed with CKD, or have owned a cat within the past two years who has been diagnosed with CKD.	18
Clinical experts (60%)	Vets working in first opinion veterinary practice	14

	Researchers or vets with additional qualifications	14
	Pharmaceutical and food industry representatives	10
	Veterinary nurses	4
	Clinical pathologists	2
Regulatory Agencies (7%)	Working for the VMD or RCVS	5
Journal Editors (8%)	Currently working in an editorial role for a journal which publishes research on feline medicine and feline research	6

For the eDelphi panellists, their ownership history of cats with CKD, and the year and country of veterinary degree qualification can be seen in Table 3. In addition to the owners, some panellists from each stakeholder group had experience of cat ownership in addition to the specific cat owner group, however, many panellists did not. The geographical origin of the eDelphi panellists is further detailed in Table 4.

Table 3: Cat ownership experience, veterinary degree qualification and location of graduation information for eDelphi panellists as part of a project creating a COS for cats with chronic kidney disease.

Stakeholder group (number of panellists)	Experience of owning a cat with CKD				Year of Graduation from Veterinary Degree					Veterinary Degree graduation location			
	Current ownership	Within previous 2 years	Prior to the previous 2 years	Never	1970-1979	1980-1989	1990-1999	2000-2009	2010-2019	UK	Europe	International	Not a veterinary graduate
Owners (18)	12	6	0	0									
Vets working in first opinion practice (14)	2	1	3	8	0	1	5	3	5	7	4	3	

Industry (10)	1	1	2	6	0	2	0	6	2	6	2	2	
Researcher vets (14)	3	5	2	4	0	2	3	5	3	8	2	3	1
Vet nurses (all either Level 3 Diploma or Uni degree) (4)	1	2	0	1									
Clinical pathologists (2)	0	0	1	1	0	0	1	0	1	0	1	1	

Regulatory agencies (5)	0	0	0	5	1	0	0	4	0	3	0	2	
Journal editors (6)	1	0	3	2	0	3	2	0	0	3	0	2	1

Table 4: Stakeholder group and country of origin of invited eDelphi panellists as part of a project creating a COS for cats with chronic kidney disease.

Stakeholder group	UK	Isle of Man	Ireland	USA	Canada	Netherlands	France	Spain	Portugal	Switzerland	Australia	Russia
Owners	9	1	1	5	1	1						
Vets working in first	10				2				1		1	

opinion practice												
Industry	5			1			1	1		2		
Researcher vets	10			2					1			1
Veterinary nurses and Clinical pathologists	5										1	
Regulatory agencies	5											
Journal editors	4			1	1							

In the first two questionnaires (round 1), the 104 parameters identified from the systematic review were presented to the panellists for rating for the first time. The first questionnaire was completed by 57/73 panellists and the second questionnaire by 54/57 panellists (Table 5. After these two questionnaires were completed, 14 parameters had reached consensus for inclusion in the COS (Table 6), and no parameters had reached consensus for exclusion from the COS.

Table 5: Number of panellists completing each round of the feline chronic kidney disease eDelphi, arranged by stakeholder group.

		eDelphi round 1		eDelphi round 2	eDelphi round 3
Stakeholder group	Invited to eDelphi panel	Completed questionnaire 1	Completed questionnaire 2	Completed questionnaire 3	Completed questionnaire 4
Owners	18	15	13	10	7
Vets working in first opinion practice	14	11	8	7	1
Industry	10	9	8	7	6
Researcher vets	14	11	11	11	11
Qualified veterinary nurses	4	1	1	1	1
Clinical pathologists	2	2	2	2	0

Regulatory agencies	5	4	4	3	2
Journal editors	6	4	4	3	3
Total	73	57	51	44	31

Table 6. Parameters which had reached consensus for inclusion in the Core Outcome Set for chronic kidney disease in cats after the first two questionnaires (round 1; questionnaire 1: n=57, questionnaire 2: n=51).

Parameter	Percentage of panellists rating the parameter 8 or 9
Urine protein: creatinine ratio	94.7
Creatinine	94.4
Phosphate	92.6
Urea	92.6
Quality of life	91.2
Urine specific gravity	89.5
End point for renal survival	86.0
Blood pressure	85.2
Biochemistry	85.1
Full clinical examination	84.2

Body condition score	84.2
IRIS stage/ stage of disease	82.5
Survival time	82.5
Packed Cell Volume (PCV)	81.5

In the third questionnaire, the 20 new parameters that had been proposed by panellists (see Supplement 1) were presented for rating, alongside the parameters which greater than 10% of panellists nominated that they did not understand (n=3 parameters). Further definitions were provided alongside the three "not understood" parameters. These three parameters were: semi quantitative urine albumin ELISA, fractional excretion of phosphorus in the urine and C-TEA clearance as a measure of effective renal plasma flow. None of these three parameters reached consensus for inclusion in the COS later in the study.

The third questionnaire was completed by 44/57 panellists (Table 5). After the third questionnaire, 3 additional parameters had reached consensus for inclusion in the COS; hydration status, pain and discomfort, symmetric dimethylarginine (SDMA). In the fourth questionnaire, the panellists were presented with their own previous ratings for each parameter, alongside the median and interquartile range of the whole group's ratings. They were then given the opportunity to re-rate the parameters or leave their rating the same. The fourth questionnaire was completed by 31/44 panellists (Table 5). After the fourth questionnaire was completed, 10 additional parameters had reached consensus for inclusion in the COS; occurrence of adverse events, overall assessment of efficacy, owner not giving the treatments to the cat, time enrolled in study, cause of death, haematocrit, progression of renal dysfunction, appetite for food, muscle condition score, and protein in urine.

Over all three rounds and four questionnaires in the eDelphi, proportionally more panellists were lost from the cat owner and first opinion vets groups than in the other stakeholder groups (Table 5). From the cat owner group, between two and three panellists failed to complete every questionnaire, so that the 4th questionnaire was completed by 7/18 panellists (39%). From the vets in first opinion practice group, between one and three panellists failed to complete every questionnaire, until the 3rd round (4th questionnaire) where six panellists did not complete the questionnaire. Out of the 14 vets in this stakeholder group, only 1 (7%) remained by the end of the eDelphi. The highest completion rates throughout the eDelphi were seen in researcher vets (79%, n=11/14) and industry (60%, n=6/10) (Table 5).

After the three rounds of eDelphi had been completed, 27 parameters were proposed for inclusion in the COS, 20 were considered borderline and none had been excluded.

Consensus Meeting

The consensus meeting was held in England in July 2019 and attended by an international group of 16 individuals, representing all eDelphi stakeholder groups except journal editors. From all invitations sent, 21 registered to attend the meeting. However, five were unable to attend on the day due to illness, travel issues or for personal reasons. The numbers of owners and HCPs who attended the meeting were well balanced (nine owners and twelve HCPs), with nearly all stakeholder groups represented. Some attendees came from further afield than the UK.

Of the 16 meeting panellists in attendance; six were cat owners, of whom four currently owned a cat with CKD and two had owned a cat with CKD in the previous two years. Two of the owners had formed part of the eDelphi panel and four were new to the process at the consensus meeting stage. Three came from the UK, one from Ireland and two from the USA. The other 10 attendees were all HCPs, of which 9 came from the UK and 1 from Canada. Five had taken part in the eDelphi process (one from industry, three vet researchers and one from regulatory agencies) and five were new to the process at the consensus meeting stage (one first opinion veterinary surgeon, two from industry, one veterinary nurse and one from regulatory agencies). Of the nine with veterinary degrees, all graduation dates were within the last 10-30 years, predominantly from UK universities, however three were from international universities.

Of the five panellists unable to attend (all from the UK), three were cat owners, two of whom had been involved in the eDelphi. There was one industry representative who was new to the study process, and one first opinion veterinary surgeon who had already been involved in the eDelphi.

Borderline parameters

Twenty borderline parameters were identified for discussion prior to the meeting and can be seen in Table 7 alongside the meeting outcome for each parameter, following group discussion and rating. Once all 20 had been discussed and rated independently by the panel, a further six parameters had reached the definition of consensus for inclusion in the COS (complete blood count, bodyweight, change in demeanour, haemoglobin, potassium, overall amount of food eaten) and five parameters had been excluded (thirst, overall history, palpable size of kidneys, drinking behaviour, erythrocyte count). Of the remaining 9/20 parameters, one (difficulty administering/ giving treatment to the cat) was discounted as it was decided by consensus to categorise it as a “process measure” rather than a true outcome. It was acknowledged that being unable to give a treatment may lead to a full or partial

treatment failure. However, it was recognised that this was not a reflection on the efficacy of the treatment alone, and more about the process of administering the treatment. Two parameters were not voted on because after group discussion, it was decided that these duplicated parameters already included in the proposed COS (phosphorus, wellbeing). The final six parameters (constipation, H inulin clearance, ocular funduscopic examination, decrease in creatinine clearance, weakness, mentation) were discussed but not voted on as it was agreed they would not add to or improve the content of the final COS.

Table 7. Borderline parameters identified by the feline chronic kidney disease eDelphi process that were discussed and rated in the consensus meeting, and the outcome of the consensus meeting process.

	Percentage of each stakeholder group who rated the parameter 8 or 9 on a Likert scale 1-9.			
Borderline parameter	Whole eDelphi Panel (n=31)	Owners in eDelphi (n=7)	Healthcare Professionals (HCPs) in eDelphi (n=24)	Consensus Meeting Results: Overall % of panellists rating the parameter 8 or 9 on a Likert scale 1-9, (n = 16)
Complete blood count	77.4	57.1	87.5	93.7
Bodyweight	77.4	71.4	83.3	100
Phosphorus	77.4	85.7	79.2	Not voted
Change in demeanour	77.4	85.7	79.2	87.5
Thirst	77.4	100	75	12.5
Wellbeing	74.2	85.7	75	Not voted

Haemoglobin	74.2	85.7	75	93.7
Overall history	74.2	85.7	70.8	12.5
Erythrocyte count	74.2	57.1	79.2	6.25
Difficulty administering/ giving treatments to cat	74.2	71.4	79.2	Not voted
Potassium	71	71.4	75	81.2
Overall amount of food eaten	71	71.4	75	87.5
Mentation	67.7	42.9	79.2	Not voted
Drinking behaviour	64.5	85.7	62.5	18.7
Ocular funduscopic examination	61.3	28.6	75	Not voted
Palpable size of kidneys	54.8	100	45.8	0
Weakness	38.7	71.4	33.3	Not voted
Constipation	32.3	71.4	16.7	Not voted
Decrease in creatinine clearance	32.3	71.4	25	Not voted
H inulin clearance	29	71.4	20.8	Not voted

Not voted = these parameters were discussed but not voted on as it was decided they would not add to the content of the final COS.

Streamlining the COS

The six parameters proposed for inclusion during the consensus meeting were discussed alongside the 27 parameters that reached inclusion as a result of the eDelphi process (33 in total). The use of flipcharts and lists created by the study team during the course of the meeting helped as a visual aid during the streamlining process. Phosphate from the eDelphi results list was replaced by phosphorus from the borderline parameters as it was felt that this was more biologically appropriate. Three parameters were then removed from the shortlist of 33 parameters as it was felt that what they represented was already addressed by other parameters within the COS list. These were: progression of renal dysfunction, time enrolled in study, urine protein. One parameter (overall assessment of efficacy) was removed from the list as it was decided to be more of a measure of the process of the study, than a true outcome. This left a final agreed shortlist of 29 parameters, which were streamlined into nine main outcome areas (Table 8). Eight of the outcome areas were also parameters to be measured. Some areas contained several parameters to measure. For example, consensus was reached that within the core parameter quality of life, the assessment of wellbeing, demeanour and voluntary appetite should also be included. Two core parameters were stand-alone parameters, these were total amount of food eaten and adverse events. No additional parameters were identified to assess as part of assessing these two core parameters.

Table 8. Final proposed Core Outcome Set for feline chronic kidney disease.

Main Outcome Area (bold italic print is itself a core parameter also)	Parameters to measure under each outcome area
Clinical examination	Body condition score
	Muscle condition score
	Bodyweight
	Blood pressure
	Hydration status
	Pain
	Demeanour/ Mentation

Total amount of food eaten	
Serum Biochemistry	Urea
	Creatinine
	Phosphorus
	Potassium
	Symmetric dimethylarginine (SDMA)
Complete Blood Count	Haemoglobin
	Haematocrit/ Packed Cell Volume
Urine tests	Urine Specific Gravity
	Urine Protein: Creatinine Ratio
Quality of Life	Wellbeing
	Demeanour
	Voluntary Appetite
Survival time	Cause of death
Progression of CKD	End point for renal survival
	International Renal Interest Society (IRIS) stage
Adverse Events	

DISCUSSION

This is the first COS to be created for the feline species. It represents the views of stakeholders from all levels of decision-making regarding cats with CKD including owners and veterinary surgeons, veterinary nurses, clinical pathologists, researchers, industry and regulatory agency representatives. Therefore, the value of this COS is not only apparent for any future treatment efficacy randomised controlled trials. It also has implications for veterinary clinical decision making as to which the most important indicators for monitoring disease progression might be and is valuable for veterinary undergraduate and postgraduate education.

The threshold definition for consensus for parameter inclusion used in this study is much higher than that used in human COS studies previously. It is also higher than the 70% threshold used in the only other existing veterinary COS, COSCAD'18 (Olivry et al., 2018). A systematic review of Delphi methodology found the most common definition of consensus used was percentage agreement, and the median threshold to define consensus was identified as 75% of participants scoring an item 1, 2, 3 or 7, 8, 9 (Diamond et al., 2014). Some examples from human COS development include a recent COS from urology, where a cut off of 75% or more of participants rating an outcome as critically important on a 9 point Likert scale, was used in developing a COS for haemodialysis therapy (Evangelidis et al, 2017). Additionally, in developing a COS for prostate cancer, effectiveness trials used a cut off of 70% of patients scoring the top two scores on a 9 point Likert scale (MacLennan et al, 2015). The higher threshold used in our study could translate to more certainty that all parameters included in our COS are very important to the stakeholder groups represented on the panel. These panellists represent decision makers at all levels of feline CKD diagnosis, treatment, and management.

Although the eDelphi and consensus meeting methodologies are well recognised for enabling the achievement of group agreement, a COS can only ever represent the views of those who have participated in its creation. It is possible that the outcomes may have been slightly different if the balance of stakeholder groups had been different or if the number of panellists had been larger. However, there is no agreed best sample size for the Delphi technique. It is recognised that more members will increase the reliability of group judgements (Murphy et al., 1998), and a minimum of 7 respondents per stakeholder group is suggested to be large enough for a consensus process (Mullen. 2003). The stakeholder groups included in COSCAD'18 (Olivry et al., 2018) were similar to those in the current study. However, the methodology in COSCAD'18 was different as no consensus meeting was included. It is hoped that the panel size used in the current eDelphi was adequate, despite the inevitable loss to follow up experienced. Although panellists were lost from all stakeholder groups, every group was still represented at all stages of this COS development, with the exception of the consensus meeting. No journal editors attended the meeting, despite a number of invitations being

distributed. Proportionally the greatest number of panellists were lost from the groups: "vets in first opinion practice", where the greatest loss of panellists occurred between eDelphi rounds 2 and 3, and "owners" where there was a gradual loss of panellists from all stages, resulting in 61% of owner panellists lost by the 3rd round of the eDelphi. However, the greatest number of parameters reached consensus for inclusion during the first two questionnaires and the greatest losses in panel members happened after these questionnaires were completed. Therefore, it is hoped that any impact of this on the overall COS results will be minimal. In addition, being prescriptive in relation to the number of participants included from each stakeholder group in the design of the study enabled opinions from a broad base to be gathered and ensured that no one stakeholder group could dominate. The panels for both the eDelphi and consensus meeting were international. However, due to the geographical range of panellists who registered for the study, the majority of panellists were from the United Kingdom and were all English speaking. It is possible that consensus on the final COS may have been different if the panels had been more geographically and linguistically diverse. Conversely, consensus methodologies are usually employed when a lack of quantitative evidence is available, or an area is contentious; they are not designed to be 'representative' but to assist decision-making by creating a structured approach to gathering expert opinion.

Many of the parameters in the COS proposed here are likely to be familiar to veterinary professionals examining and treating cats with CKD. Most are objective parameters with established methods for measurement and assessment (e.g. serum biochemistry, survival time), or should be straightforward to measure and record in clinical trials (e.g. adverse events, cause of death). The more subjective parameters (e.g. quality of life) may be more difficult to assess. However, the initial focus of the development of any COS is always to establish what to measure and then later in the process, decide how to measure (Williamson et al., 2012). The next stage of this work should focus on establishing the most appropriate assessment tools for each parameter proposed in this COS.

The methodologies used here appeared to translate well from human healthcare to the veterinary field and could be utilised to determine COSs for other veterinary diseases of importance. Further work is required to determine whether this approach works equally well for additional diseases and conditions in felines, and in a range of other veterinary species.

CONCLUSIONS

THIS IS THE FIRST COS THAT HAS EVER BEEN CREATED FOR THE FELINE SPECIES AND INCLUDES THE PERSPECTIVES OF AN INTERNATIONAL PANEL OF STAKEHOLDERS EXPERIENCED IN TREATMENT EFFICACY DECISION MAKING FOR FELINE CKD AT ALL LEVELS. THIS INCLUDES CAT OWNERS, VETERINARY SURGEONS, VETERINARY NURSES, RESEARCHERS, INDUSTRY REPRESENTATIVES, JOURNAL EDITORS AND REGULATORS. INCLUDING THIS COS IN FUTURE CLINICAL TRIALS RELATING TO CKD WILL ENSURE RESULTS WILL BE RELEVANT TO ALL STAKEHOLDERS, STRENGTHENING THE EVIDENCE BASE AVAILABLE FOR CLINICAL DECISION MAKING, AND REDUCES RESEARCH WASTE. IT WILL ALSO DIRECT CAT OWNERS AND VETERINARY PROFESSIONALS TO THE MOST IMPORTANT OUTCOMES TO MONITOR IN THESE PATIENTS IN THE VETERINARY CLINIC AND WILL BE VALUABLE FOR EDUCATIONAL INITIATIVES FOCUSED ON FELINE CKD MONITORING AND MANAGEMENT.

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9.2 Appendix 2 All parameters proposed and considered for inclusion in the Core Outcome Set

Parameters extracted from chronic kidney disease treatment efficacy systematic review (n=104):

Parameters which a cat's owner might notice at home:

- Overall history (overall signs which an owner notices before and after the cat's diagnosis)
- Appetite for food
- Overall amount of food eaten each day
- Thirst
- Drinking behaviour
- Vomiting (being sick)
- Number of bowel movements each day (number of times faeces are produced)
- Diarrhoea (runny faeces)
- Constipation
- Urination
- Halitosis (bad breath)
- Condition of coat/ fur
- Exercise tolerance (ability to carry out normal physical exercise of activities)
- Activity level (how active the cat is)
- Weakness
- Wellbeing
- Change in demeanour compared to at start of study

Parameters a vet might examine or measure during a consultation:

- Clinical signs/ full clinical exam

- Body condition score (a number which indicates the cat's weight and amount of body fat)
- Body weight
- Palpable size of kidneys (how large or small the kidneys feel when examined with the hands)
- Respiration (breathing)
- Ocular funduscopic examination (examination of the inside of the eye)
- Presence of lacerations in the mouth/ gingivitis (inflammation of the gums/ oral inflammation)
- Mucous membrane colour (colour of the gums and insides of the lips/ eyelids)
- Neurological signs (signs relating to the nerves)
- Mentation (attitude, alertness)
- Faecal phosphorus concentration (phosphorus is an electrolyte, important for metabolism)

Parameters which can be measured in the cat's urine:

- UPC (urine protein to creatinine ratio. Used to estimate the amount of protein lost in the urine)
- Urine creatinine (measures the amount of creatinine in the urine)
- Urine specific gravity (measures how concentrated the urine is)
- Urine glucose (urine sugar levels)
- Urine sediment (can include cells, crystals, parasites, sperm, bacteria)
- Level of blood in the urine
- Urine pH
- Urine leukocytes (white cells in the urine)
- Urine bilirubin (bilirubin is a product from the natural breakdown of red blood cells)

- Urine urobilinogen (formed from bilirubin)
- Semiquantitative urine albumin ELISA (used to measure a specific type of protein in the urine)
- Urine nitrites (can occur in bacterial infections)
- Urinary phosphate (a form of phosphorus in the body, important for metabolism, excreted into the urine)
- Urine ketonic bodies (a by-product of the body burning fats to make energy, for example in starvation or diabetes)
- Urine culture (to grow bacteria and look for infection)
- Urine hormone measurement (for growth hormone)
- Urine metabolism
- Urine biochemistry (measures chemicals in the urine)
- Urine sodium (an electrolyte, involved in water and blood pressure regulation)
- Urine potassium (has a role in muscle and nerve function)
- Urine phosphorus (an electrolyte, important for metabolism)
- Urine calcium (a mineral with many functions including building teeth and bones)
- Fractional excretion of phosphorus in urine (how much phosphorus is excreted in the urine compared to how much is retained in the blood)

Parameters related to the progression of chronic kidney disease and how long a cat might live for:

- Quality of life
- Progression of renal dysfunction
- IRIS stage/ stage of disease (a grading of the severity of CKD, based on blood and urine tests)
- Survival time (how long the cat lives for)

- End point for renal survival (the time at which the cat needs either intensive veterinary intervention, for example intravenous fluids or dialysis, or the cat is euthanased or dies because of CKD)
- Cause of death/ why the cat has died
- Renal histology at autopsy (the disease state of the kidney tissue after death)

Parameters related to a cat being involved in scientific studies:

- Overall assessment of efficacy (efficacy is how well the treatment works within a scientific study)
- Occurrence of adverse events (An adverse event is an unfavorable change in the cat's health, due to the treatment from the trial, either during the study or during a specified time following the study)
- Difficulty administering/ giving treatments to the cat
- Owner not giving the treatments to the cat
- Time enrolled in study (how long the cat remains in the study)

Parameters which can be measured in the cat's blood:

- Biochemistry (analysis of the blood for chemicals made by the body)
- Albumin (a protein made in the liver, roles include keeping fluid inside blood vessels)
- Globulin (proteins, made by the liver and immune system, many roles including in immunity and as enzymes)
- ALP (an enzyme found in high levels with bone or liver disorders)
- ALT (an enzyme found in liver, kidneys, heart and muscles)
- AST (an enzyme found in liver, heart and muscle)
- Chloride (an electrolyte, high levels may indicate dehydration)

- Creatinine (a waste product from muscles)
- Ionised calcium (a mineral, this is the active form)
- Phosphate (many functions, excreted or conserved by the kidneys)
- Phosphorus (an electrolyte, important for metabolism)
- Potassium (abnormal amounts can alter muscle or nerve function)
- Protein (protein in the urine comes from protein in the blood)
- Sodium (an electrolyte, involved in water and blood pressure regulation)
- Total calcium (a mineral, may be high if there is cancer or if certain drugs are used)
- Urea (end product of protein metabolism)
- Complete blood count (measures the number of different cell types in the blood)
- PCV (percentage of red blood cells to total blood volume)
- Erythrocyte count (number of red blood cells- these carry oxygen around the body)
- Haematocrit (ratio of red blood cells to total volume of blood)
- Haemoglobin (the part of the red blood cell responsible for carrying oxygen)
- White blood cell count (these cells help protect the body from disease)
- Total plasma solids (estimates the amount of protein in the blood)

More advanced tests which might be carried out to gather more information about a cat's health:

- Carbon dioxide (used as a measure of the acid-base balance)
- HC03- (bicarbonate, also used as a measure of acid-base balance)
- Aldosterone (made by the adrenal glands, regulates how the body handles salt, water and potassium)
- Plasma renin activity (important for thirst, blood pressure and urine output)

- Levels of RAA components (a hormone system, regulates blood pressure, blood flow and fluid volumes)
- T4 (thyroid hormone, controls several things including energy usage by the body)
- Plasma PTH (Parathyroid hormone- helps regulate blood calcium levels)
- 1,25 dihyroxycholecalciferol (calcitriol, regulates calcium levels)
- IGF-1 (insulin-like growth factor 1- an indirect test for growth hormone)
- FGF-23 (fibroblast growth-factor 23- reduces phosphate reabsorption)

Advanced tests which might be carried out to gather more information about a cat's health, by measuring how substances are cleared from the body:

- C-TEA clearance (C-tetraethylammonium bromide clearance, as a measure of effective renal plasma flow)
- Decrease in creatinine clearance (change in amount of creatinine excreted by the kidney)
- H-inulin clearance to represent GFR (GRF is Glomerular Filtration Rate, which estimates how much blood passes through the kidneys each minute)

Additional tests which might be carried out to gather more information about a cat's health:

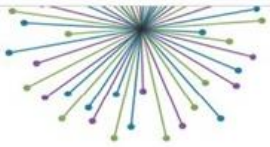
- Blood pressure
- Abdominal radiography (an x-ray of the abdomen)
- Abdominal ultrasound (an ultrasound scan of the abdomen)
- Renal biopsy (a sample of the kidney tissue) to measure the α-SMA index (α-smooth muscle actin, a protein involved in the contractile apparatus of muscle)
- Muscle potassium content from a triceps biopsy)

Parameters suggested by panellists during the first round of the eDelphi and added for rating in the third round (n=20):

- Increased vocalisation (making more noise)
- Interaction with family and other pets in the household
- Interest in life
- Nausea (feeling sick)
- Pain and discomfort
- Time spent sleeping or behaving restlessly
- Abdominal palpation- examination of the abdomen area with the hands, to feel the size and shape of some internal organs to check for abnormalities
- Thyroid palpation- examination of the thyroid gland (in the neck) with the hands, to see if it has changed in shape or size from normal.
- Hydration status- the level of hydration / dehydration can be assessed with a physical examination and with tests.
- Muscle condition score – examination visually and by hand, of the muscles around the spine, head, shoulders and pelvis, to give a severity grading.
- Cardiac auscultation and heart rate- listening to the heart rate and the heart sounds with a stethoscope, to detect changes, for example: heart murmurs
- Platelets- important for blood clotting
- Symmetric dimethylarginine assay (SDMA) – the level of SDMA increases when there is a 25% decrease in kidney filtration rate, so this is used as an early indicator of decreased kidney function.
- Vitamin B12- important in red blood cell production, nerve function and appetite
- Vitamin B9- important in red blood cell production
- Vitamin D- important in calcium absorption and bone growth
- Renal blood flow- the volume of blood delivered to the kidneys over time

- Fractional excretion of electrolytes and minerals- the amount of electrolytes and minerals leaving the body in the urine compared to the amount being retained by the kidney.
- Renal biomarkers of kidney filtration- cystatins (protein used as a marker of the kidney filtration rate) , clusterin (protein which should be filtered by the kidneys), NGAL and RBP (markers for the kidney filtration rate)
- The renal biomarker transferrin (helps understand iron and anaemia status)

9.3 Appendix 3 eDelphi Questionnaire One



Which parameters should we measure in treatment trials for cats with chronic kidney disease? Part 1

Page 1: Welcome!

In this work we hope to improve future research to help cats with chronic kidney disease (CKD). CKD can be defined as the presence of structural or functional abnormalities of one or both kidneys, that have been present for an extended period, usually three months or longer (Polzin 2011).

Why this study is important:
Research and clinical trials which test different treatments for cats with CKD can measure many different parameters. This makes it difficult for the results of research to be combined or compared. For example, imagine two medicines called A and B used to treat cats with CKD.

In the trials on treatment A the researchers measured whether the cat's appetite was improved.

In the trials on treatment B the researchers measured whether the cat's urine test results were improved.

Both A and B appeared to help the cat, but which treatment is better? Without both trials measuring the same parameters, the results from the trials cannot be easily compared. Perhaps A and B even work in similar ways, and using either A or B is better than using nothing, but as their trials measure different parameters, we cannot tell.

That is a very simple example of a real problem. Current published research on cats with chronic kidney disease measure a total of nearly 100 different parameters. We are aiming to develop a "core set" of parameters to measure for cats with CKD, in any research or clinical trial. Researchers are free to measure additional parameters in their trials, but including a core set allows trial results to be compared or combined more easily.

This study:
This is the first questionnaire in this study. There will be four questionnaires in total. Each will be open for three weeks. There will be a break between questionnaires to allow us to collate results and provide you with feedback, as each set of results will inform the next part of the study.

For further information about this work, please see here: https://www.nottingham.ac.uk/cevm/practice-based-research/small-animal/parameters-to-measure-in-feline-ckd-treatment.aspx

Your responses to the questionnaires in this study will be kept anonymous, all personal data will be removed and no individual will be identifiable. The responses will be combined with those of other participants and used to inform the next questionnaire in the study.

This study has been designed by Hannah Doit (PhD student) Dr Rachel Dean and Dr Marnie Brennan at the Centre for Evidence-based Veterinary Medicine (CEVM) at the University of Nottingham. It should take around 20 minutes to complete.

If you need more time to complete any of the questionnaires or if you have any questions about this study at any point during the process, please contact: Hannah.Doit@nottingham.ac.uk using the subject line: CKD

Your data:
The University processes your personal data (email address) in order for you to participate in this study. Details such as how to contact the University's Data Protection Officer and your rights as a data subject can be found at https://www.nottingham.ac.uk/utilities/privacy/privacy.aspx. Further detail on how your information is processed and how to find out when it will be disposed of can be found at https://www.nottingham.ac.uk/utilities/privacy/privacy-information-for-visitors-correspondents-and-prospective-applicants.aspx

Page 2: Consent

By agreeing to participate within this study, you understand that:

- Participants must be aged 18 years or over
- Your participation within this study is completely optional and you may withdraw at any time
- Your responses will remain anonymous at all times during this study and all information gathered will be treated confidentially
- Information collected during this study may be published as a written report or used at conferences at a later date, however, all information will remain anonymous
- You can ask for more information about this study by contacting: Hannah.Doit@nottingham.ac.uk

1. If you agree to take part in this research study please complete the following: * *Required*

- ○ I have read and understood the above information regarding consent and I agree to the above terms laid out for my participation in this study
- ○ Yes
- ○ No

2. I am happy for the University to process my personal data according to the privacy notice relevant for participating in the research activities of the University which can be found at https://www.nottingham.ac.uk/utilities/privacy/privacy-information-for-visitors-correspondents-and-prospective-applicants.aspx * *Required*

- ○ Yes
- ○ No

Page 3: Next step

In this questionnaire you will be presented with five groups of parameters which have previously been measured by researchers when testing treatments on cats with chronic kidney disease (CKD). They have been extracted from all the current published scientific papers on treatment for cats with CKD. The parameters are grouped together with others that are similar, to help you focus

Some definitions of scientific terms are given (in brackets). All survey participants have been provided with the same definitions. You may find that you do not recognise or you do not understand some of the parameters mentioned in the survey. Some of them represent very advanced tests or have only been recorded in one scientific paper. Please do not worry, if you do not understand what the parameter is, simply indicate it with the option provided.

What you need to do:
We need you to tell us how important it is that each parameter individually is included in the final "core set", by rating it from 1 to 9. The core set is a shortlist that we will create from this study. Everything that the participants agree is important, will be included. The core set will be recommended for inclusion in all future treatment trials for cats with CKD.

Page 4: At home

3. The following list contains parameters which a cat's owner might notice at home. Please indicate how important you think it is for each one to be included in the core set, where:
1 is not important at all
9 is very important. Please consider each individually.

Please don't select more than 1 answer(s) per row.

Please select at least 15 answer(s).

	1	2	3	4	5	6	7	8	9	I do not understand what this is	I do not understand the significance of this
Overall history (overall signs which an owner notices before and after the cat's diagnosis)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Appetite for food	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Overall amount of food eaten each day	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Thirst	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Drinking behaviour	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vomiting (being sick)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Number of bowel movements each day (number of times faeces are produced)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Diarrhoea (runny faeces)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Constipation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Urination	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Halitosis (bad breath)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Condition of coat/ fur	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Exercise tolerance (ability to carry out normal physical exercise or activities)	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐
Activity level (how active the cat is)	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐
Weakness	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐
Wellbeing	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐
Change in demeanour compared to at start of study	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐	⌐

3.a. If you think there is something important in relation to parameters an owner might notice at home, missing from this list, please write it in the box below:

Page 5: In the veterinary consultation

4. The following are parameters a vet might examine or measure during a consultation.

Please indicate how important you think it is for each one to be included in the core set, where:
1 is not important at all
9 is very important.

Please consider each individually.

Please don't select more than 1 answer(s) per row.

Please select at least 8 answer(s).

	1	2	3	4	5	6	7	8	9	I do not understand what this is	I do not understand the significance of this
Clinical signs/ full clinical exam	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Body condition score (a number which indicates the cat's weight and amount of body-fat)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Body weight	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Palpable size of kidneys (how large or small kidneys feel when examined with the hands)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Respiration (breathing)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Ocular fundoscopic examination (examination of the inside of the eye)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Presence of lacerations in the mouth/ gingivitis (inflammation of the gums) / oral	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Page 9: End of the first questionnaire

In this questionnaire we have looked at parameters from the following areas:

- Noticed by the owner at home
- Observed or measured by the vet as part of examining the cat
- Results from testing the cat's urine
- Parameters related to the progression of CKD and the length of life of the cat
- The effects of being in a clinical trial or study

Are there any additional parameters in the areas listed above, which you think are important to measure as part of the core set, which have not already been listed in this questionnaire?

The second questionnaire in this study will cover:

- Blood test results (biochemistry and haematology)
- More advanced tests

12. If yes, please describe below:

Page 10: Thank you

Thank you very much for taking the time to complete this questionnaire. Your input is very helpful to us.

If you have any questions about this work, please do contact us: Hannah.Doit@nottingham.ac.uk

We will be in touch with the second questionnaire soon.

Thank you.

www.nottingham.ac.uk/cevm

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9.4 Appendix 4 eDelphi Questionnaire 4

Study: which parameters should we measure in treatment trials for cats with Chronic Kidney Disease (CKD)?

Welcome to the next and final online stage of this study.

In this document are listed the parameters measured for cats with CKD which have not yet reached agreement to include or exclude from the final core set of parameters.

What to do in this document:

In column 1 of the table below are listed parameters which have not yet been voted into or out of the final core set by the majority of panel participants. Your previous ranking for this parameter is listed in column 2. In column 3 you will find the "median" (reflects the average opinion of all of the study participants) and in column 4 is the "interquartile range" (50% of the panel answers will sit within this range).

Now you can see the other panellist rankings alongside yours, you need to decide whether you would like to keep your original ranking or change it. Please select the ranking you would like to choose from the drop-down list available.

When you have finished, please return this document by email to: Hannah.Doit@nottingham.ac.uk using the subject line: CKD. Your answers will be anonymised before they are incorporated into the study.

Parameter	Your previous answer	Panel answer	Range on panel answer	Your answer today
Overall history (overall signs which an owner notices before and after the cat's diagnosis)		9	8-9	Choose an item.
Appetite for food		9	8-9	Choose an item.
Overall amount of food eaten each day		8	7-9	Choose an item.
Thirst		9	7-9	Choose an item.
Drinking behaviour		9	7-9	Choose an item.
Nausea (feeling sick)		9	7-9	Choose an item.
Vomiting (being sick)		8	7-9	Choose an item.
Number of bowel movements each day (number of times faeces are produced)		6	5.75-7	Choose an item.

Diarrhoea (runny faeces)		6	3.75-8	Choose an item.
Constipation		7	4-8	Choose an item.
Urination		9	6-9	Choose an item.
Halitosis (bad breath)		7	6-8	Choose an item.
Condition of coat/ fur		7	6-8.25	Choose an item.
Exercise tolerance (ability to carry out normal physical exercise or activities)		6	5-7	Choose an item.
Activity level (how active the cat is)		7	5-8	Choose an item.
Weakness		7	6-8	Choose an item.
Wellbeing		9	6-9	Choose an item.

Change in demeanour compared to at start of study		9	7-9	Choose an item.
Increased vocalisation (making more noise)		5	6-7	Choose an item.
Interaction with family and other pets in the household		7	3-8	Choose an item.
Interest in life		9	6-9	Choose an item.
Time spent sleeping or behaving restlessly		8	6-9	Choose an item.
Body weight		9	6-9	Choose an item.
Muscle condition score – examination visually and by hand, of the muscles around the spine, head, shoulders and pelvis, to give a severity grading.		9	6-9	Choose an item.
Palpable size of kidneys (how large or small kidneys feel when examined with the hands)		8	7-9	Choose an item.
Respiration (breathing)		7	6-7.25	Choose an item.

Ocular fundoscopic examination (examination of the inside of the eye)		8	6-9	Choose an item.
Presence of lacerations in the mouth/ gingivitis (inflammation of the gums) / oral inflammation		8	7-9	Choose an item.
Mucous membrane colour (colour of the gums and insides of the lips/ eyelids)		8	7-9	Choose an item.
Neurological signs (signs relating to the nerves)		7	6-8	Choose an item.
Mentation (attitude, alertness)		8.5	6-9	Choose an item.
Thyroid palpation- examination of the thyroid gland (in the neck) with the hands, to see if it has changed in shape or size from normal.		9	6-9	Choose an item.
Abdominal palpation- examination of the abdomen area with the hands, to feel the size and shape of some internal organs to check for abnormalities		9	6-9	Choose an item.
Abdominal radiography (an x-ray of the abdomen)		6	5-7	Choose an item.
Abdominal ultrasound (an ultrasound scan of the abdomen)		8	6-9	Choose an item.

Cardiac auscultation and heart rate- listening to the heart rate and the heart sounds with a stethoscope, to detect changes, for example: heart murmurs		8	6-9	Choose an item.
Progression of renal dysfunction		9	6-9	Choose an item.
Faecal phosphorus concentration (phosphorus is an electrolyte, important for metabolism)		5	6-8	Choose an item.
Renal biopsy (a sample of the kidney tissue) to measure the α-SMA index (α-smooth muscle actin, a protein involved in the contractile apparatus of muscle)		5	5-7	Choose an item.
Renal blood flow- the volume of blood delivered to the kidneys over time		7	5-8	Choose an item.
Fractional excretion of electrolytes and minerals- the amount of electrolytes and minerals leaving the body in the urine compared to the amount being retained by the kidney.		8	5.75-9	Choose an item.
Renal biomarkers of kidney filtration- cystatins (protein used as a marker of the kidney filtration rate) , clusterin (protein which should be filtered by the kidneys), NGAL and RBP (markers for the kidney filtration rate)		8	7-9	Choose an item.

The renal biomarker transferrin (helps understand iron and anaemia status)		8	7-8	Choose an item.
Muscle potassium content from a triceps biopsy)		3	4-5	Choose an item.
Overall assessment of efficacy (efficacy is how well the treatment works within a scientific study)		9	6-9	Choose an item.
Owner not giving the treatments to the cat		9	8-9	Choose an item.
Difficulty administering/ giving treatments to the cat		9	7-9	Choose an item.
Time enrolled in study (how long the cat remains in the study)		9	8-9	Choose an item.
Occurrence of adverse events (An adverse event is an unfavourable change in the cat's health, due to the treatment from the trial, either during the study or during a specified time following the study)		9	8-9	Choose an item.
Cause of death/ why the cat has died		9	8-9	Choose an item.

Renal histology at autopsy (the disease state of the kidney tissue after death)		7	6.25-9	Choose an item.
Albumin (a protein made in the liver, roles include keeping fluid inside blood vessels)		8	7-8	Choose an item.
Globulin (proteins, made by the liver and immune system, many roles including in immunity and as enzymes)		7	6-8	Choose an item.
ALP (an enzyme found in high levels with bone or liver disorders)		7	5-8	Choose an item.
ALT (an enzyme found in liver, kidneys, heart and muscles)		7	5-8	Choose an item.
AST (an enzyme found in liver, heart and muscle)		6	4.25-7	Choose an item.
Chloride (an electrolyte, high levels may indicate dehydration)		8	5-9	Choose an item.
Ionised calcium (a mineral, this is the active form)		8	7-9	Choose an item.
Phosphorus (an electrolyte, important for metabolism)		9	7-9	Choose an item.

Potassium (abnormal amounts can alter muscle or nerve function)		9	8-9	Choose an item.
Protein (protein in the urine comes from protein in the blood)		9	8-9	Choose an item.
Sodium (an electrolyte, involved in water and blood pressure regulation)		9	8-9	Choose an item.
Total calcium (a mineral, may be high if there is cancer or if certain drugs are used)		8	7-8	Choose an item.
Complete blood count (measures the number of different cell types in the blood)		9	7-9	Choose an item.
Erythrocyte count (number of red blood cells- these carry oxygen around the body)		9	7-9	Choose an item.
Haematocrit (ratio of red blood cells to total volume of blood)		9	8-9	Choose an item.
Haemoglobin (the part of the red blood cell responsible for carrying oxygen)		8.5	8-9	Choose an item.
White blood cell count (these cells help protect the body from disease)		8	7-9	Choose an item.

Total plasma solids (estimates the amount of protein in the blood)		8	7-9	Choose an item.
Carbon dioxide (used as a measure of the acid-base balance)		6	5.25-8	Choose an item.
HC03- (bicarbonate, also used as a measure of acid-base balance)		7	5-8	Choose an item.
Aldosterone (made by the adrenal glands, regulates how the body handles salt, water and potassium)		6	5-8	Choose an item.
Plasma renin activity (important for thirst, blood pressure and urine output)		6.5	5-8	Choose an item.
Levels of RAA components (a hormone system, regulates blood pressure, blood flow and fluid volumes)		6.5	5-8	Choose an item.
T4 (thyroid hormone, controls several things including energy usage by the body)		8	6-9	Choose an item.
Plasma PTH (Parathyroid hormone- helps regulate blood calcium levels)		7	6-8	Choose an item.
1,25 dihyroxycholecalciferol (calcitriol, regulates calcium levels)		7	5-8	Choose an item.

IGF-1 (insulin-like growth factor 1- an indirect test for growth hormone)		5	3-6	Choose an item.
FGF-23 (fibroblast growth-factor 23- reduces phosphate reabsorption)		6	3-8	Choose an item.
C-TEA clearance, as a measure of effective renal plasma flow (this is a test designed to measure the rate at which plasma (part of the blood) is flowing through the kidneys. This can have an impact on the filtration rate of the kidneys. Filtration of waste from the body and excess fluids is an important role of the kidneys).		7.5	5-8	Choose an item.
Decrease in creatinine clearance (change in amount of creatinine excreted by the kidney)		7	5-9	Choose an item.
H-inulin clearance to represent GFR (GRF is Glomerular Filtration Rate, which estimates how much blood passes through the kidneys each minute)		7	5-9	Choose an item.
Urine creatinine (measures the amount of creatinine in the urine)		6.5	6-9	Choose an item.
Urine glucose (urine sugar levels)		7	5-8.75	Choose an item.

Urine sediment (can include cells, crystals, parasites, sperm, bacteria)		8	6.5-9	Choose an item.
Level of blood in the urine		8	7-9	Choose an item.
Urine pH		8	7-9	Choose an item.
Urine leukocytes (white cells in the urine)		8	5-9	Choose an item.
Urine bilirubin (bilirubin is a product from the natural breakdown of red blood cells)		6	4-7	Choose an item.
Urine urobilinogen (formed from bilirubin)		6	4-7	Choose an item.
Semi quantitative urine albumin ELISA (a test to measure the amount of microalbumin in the urine. This is a very small protein which, if found in the urine, may be an indicator of damage to the filtration systems of the kidney in chronic kidney disease, but can be caused by other conditions too).		7	4-9	Choose an item.
Urine nitrites (can occur in bacterial infections)		6	4-8	Choose an item.

Urinary phosphate (a form of phosphorus in the body, important for metabolism, excreted into the urine)		7	3-8	Choose an item.
Urine ketonic bodies (a by-product of the body burning fats to make energy, for example in starvation or diabetes)		6	4-9	Choose an item.
Urine culture (to grow bacteria and look for infection)		9	5-9	Choose an item.
Urine hormone measurement (for growth hormone)		4	4.5-6	Choose an item.
Urine metabolism		5	1-6	Choose an item.
Urine biochemistry (measures chemicals in the urine)		6	2-8	Choose an item.
Urine sodium (an electrolyte, involved in water and blood pressure regulation)		5	2-8	Choose an item.
Urine potassium (has a role in muscle and nerve function)		6	2-8	Choose an item.
Urine phosphorus (an electrolyte, important for metabolism)		5	2-8	Choose an item.

Urine calcium (a mineral with many functions including building teeth and bones)		5	2-7	Choose an item.
Fractional excretion of phosphorus in urine (the amount of phosphorus that the kidneys have excreted from the body, in the urine. In CKD, when kidney function is decreased, the amount of phosphorus that the kidneys excrete is reduced, and the result can be that there is too much phosphorus in the blood. This can cause additional problems for the cat and is associated with a poorer prognosis).		8	5-9	Choose an item.

If there are any comments you would like to make or anything you would like to add, please write in the box below:

9.5 Appendix 5 Consensus Meeting Pre-Meeting Paperwork: Background and Aims of Meeting

Cats with Chronic Kidney Disease Consensus Meeting: Background and Aims

Background:

The aim of this study is to create the first Core Outcome Set (COS) for cats with Chronic Kidney Disease (CKD).

A COS is:

"an agreed minimum set of outcomes or outcome measures. It is a recommendation of 'what' should be measured and reported in all trials in a specific area" (definition from www.comet-initiative.org).

In this study, the term "parameters" has been used throughout, to describe outcomes. A parameter is anything measured and recorded in current published research when testing treatments for cats with CKD.

In current published CKD treatment research, over 100 different parameters have been measured and recorded, but there is no agreement on which are the most important. This means it can be difficult to tell which treatment is best suited to each cat, as different parameters are measured for different treatments. For example, only five out of the 20 current published studies measured whether the treatment improved the cat's quality of life.

This study aims to create a set of parameters which will be recommended to be measured in all future trials of treatments for cats with CKD, called a Core Outcome Set (COS).

The study so far:

A list of all parameters from current published research was extracted and presented to an anonymous online panel of 73 people, including: cat owners, veterinary surgeons, veterinary nurses, researchers, clinical pathologists, representatives of food and pharmaceutical companies, journal editors and regulatory agency representatives. Panellists were given a definition of a COS and asked to rate each parameter individually, from 1-9, as to how important it was to include in the final COS. They were also given the opportunity to suggest new parameters not covered by current research. Panellists were then given the results of the whole panel ratings (median and range of ratings) and their own previous rating. They were then given the opportunity to change their rating or keep it the same.

In advance of the study, a definition of consensus (agreement) for inclusion in the final COS, was for greater than 80% of the panel to rate the parameter as either 8 or 9 on the scale 1-9. Agreement for exclusion from the final COS was for greater than 80% of the panel to score the parameter either 1, 2 or 3.

Twenty-seven parameters reached the definition for inclusion in the final COS and no parameters were excluded.

Aims of the consensus meeting

Aim 1: Reassess and re-rate borderline parameters.

Often in COS development for human medicine, the ratings given to each parameter by patients and by Healthcare Professionals (HCPs) are examined separately. Both groups will have to rate the parameter highly for it to be included in the COS. In this

study, patients are represented by cat owners, and HCPs by the remainder of the panel, including veterinary surgeons, researchers, industry representatives etc. In the study so far, the ratings of all panel members have been assessed together.

However, in the consensus meeting we aim to address parameters falling just outside the definition for inclusion, called “borderline parameters”, to assess whether any of them will enhance the core set and should be included. In this document and in the meeting, the ratings of cat owners and HCPs will be presented separately so that any disagreement between the two groups can be discussed and clarified, so that the best interests of cats and HCPs are fully represented in the final COS. There will be opportunity for discussion, and then for a re-vote on the ratings. Only parameters which add to the COS as it stands, should be voted in.

Please read the list of parameters below (we will aim to cover the first 15 in the list in the meeting, but additional parameters have been added in case time allows) and think about whether you think it is important to include in the COS and whether you have any questions about the meaning of the parameter.

Parameter	% of Whole panel rating this parameter 8 or 9	% of Owners rating this parameter 8 or 9	% of HCPs rating this parameter 8 or 9	Difference in % rating this parameter 8 or 9, between owners and HCPs
Complete blood count (measures the number of different cell types in the blood)	77.4	57.1	87.5	30.4

Body weight	77.4	71.4	83.3	11.9
Phosphorus (an electrolyte, important for metabolism)	77.4	85.7	79.2	6.5
Change in demeanour compared to at start of study	77.4	85.7	79.2	6.5
Wellbeing	74.2	85.7	75.0	10.7
Thirst	77.4	100.0	75.0	25.0
Palpable size of kidneys (how large or small kidneys feel when examined with the hands)	54.8	100.0	45.8	54.2
Drinking behaviour	64.5	85.7	62.5	23.2
Erythrocyte count (number of red blood cells- these carry oxygen around the body)	74.2	57.1	79.2	22.0
Haemoglobin (the part of the	74.2	85.7	75.0	10.7

red blood cell responsible for carrying oxygen)				
Difficulty administering/ giving treatments to the cat	74.2	71.4	79.2	7.7
Potassium (abnormal amounts can alter muscle or nerve function)	71.0	71.4	75.0	3.6
Overall amount of food eaten each day	71.0	71.4	75.0	3.6
Overall history (overall signs which an owner notices before and after the cat's diagnosis)	74.2	85.7	70.8	14.9
Constipation	32.3	71.4	16.7	54.8
H-inulin clearance to represent GFR (GRF is	29.0	71.4	20.8	50.6

Glomerular Filtration Rate, which estimates how much blood passes through the kidneys each minute)				
Ocular fundoscopic examination (examination of the inside of the eye)	61.3	28.6	75.0	46.4
Decrease in creatinine clearance (change in amount of creatinine excreted by the kidney)	32.3	71.4	25.0	46.4
Weakness	38.7	71.4	33.3	38.1
Mentation (attitude, alertness)	67.7	42.9	79.2	36.3

Aim 2: Streamline the existing parameters which have been voted “in” to the core set

There are 27 parameters which greater than 80% of the total panel have already rated as 8 or 9. These are below (grouped to ease understanding). Some parameters may seem to duplicate each other, for example, a full clinical examination could be thought to include assessment of hydration status, body condition score and checking for pain and discomfort. A blood biochemistry test might include tests of creatinine, phosphate and urea.

However, these have all come through as separate parameters from the questionnaires, some because they have been extracted from the existing literature as separate parameters. Some have been suggested by participants as they felt they were missing from the published literature.

The second aim in this consensus meeting is to “streamline” the list below. The aim is to have a core set which is small enough to be useable, but also detailed enough to cover all parameters which are important. No parameters will be removed from the core set at the consensus meeting.

Where it is sensible, parameters may be combined. If you think that two parameters mean the same thing, then it may be possible to recreate one single parameter which covers both meanings. Or, parameters may be combined as sub-parameters, e.g. “blood test A, to include parameters X, Y and Z as standard”.

Please have a look at the list below and see there are any parameters you would choose to combine. We will discuss this in more detail and vote at the consensus meeting.

Examination parameters:

- Full clinical exam
- Body condition score
- Hydration status

- Blood pressure
- Pain and discomfort
- Muscle condition score – examination visually and by hand, of the muscles around the spine, head, shoulders and pelvis, to give a severity grading.
- Appetite for food

Blood test parameters:

- Biochemistry
- Creatinine
- Phosphate
- Urea
- Packed Cell Volume (PCV)
- Symmetric dimethylarginine (SDMA), (the level of SDMA increases when there is a 25% decrease in kidney filtration rate, so this is used as an early indicator of decreased kidney function
- Haematocrit (ratio of red blood cells to total volume of blood)

Urine test parameters:

- Urine specific gravity
- Urine protein to creatinine ratio
- Protein (protein in the urine comes from protein in the blood)

Life and staging parameters:

- Quality of life
- International Renal Interest Society (IRIS) stage/ stage of disease
- Survival time

- End point for renal survival (the time at which the cat needs either intensive veterinary intervention, for example, intravenous fluids or dialysis, or the can is euthanased or dies because of CKD)
- Progression of renal dysfunction
- Occurrence of adverse events (An adverse event is an unfavourable change in the cat's health, due to the treatment from the trial, either during the study or during a specified time following the study)
- Overall assessment of efficacy (efficacy is how well the treatment works within a scientific study)
- Owner not giving the treatments to the cat
- Time enrolled in study (how long the cat remains in the study)
- Cause of death/ why the cat has died

9.6 Appendix 6 Consensus Meeting Agenda

Cats with Chronic Kidney Disease

Consensus Meeting

Agenda

9th July 2019

9.00-9.20	Pre-meeting gathering for cat owner group
9.20-9.30	Refreshment break
9.30-9.45	Consensus meeting start: introductions and house- keeping
9.45-10.00	Background and what has been achieved already in this study
10.00-11.15	Session 1: Reassess and re-rate borderline parameters.
11.15-11.35	Refreshment break
11.35-12.45	Session 2: Reassess and re-rate more borderline parameters.
12.45-1.30	*Lunch*
1.30-2.45	Session 2: Reassess and re-rate more borderline parameters.
2.45-3.05	Refreshment break
3.05-4.05	Session 3: Streamlining the core outcome set
4.05-4.30	Summarise and meeting close

9.7 Appendix 7 Quality of life assessment tools for cats paper, published in The Veterinary Journal(Doit, Dean, Duz, & Brennan, 2021)

Original article

A systematic review of the quality of life assessment tools for cats in the published literature.

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Abstract

Quality of life (QoL) is an important parameter to assess in cats, as it can be pivotal to important decision-making. Research reports that owners of cats with heart disease would trade longevity for QoL, and treatment associated improvement in QoL is very important for cats with chronic kidney disease. This systematic review aimed to explore the published literature to identify the number and range of QoL assessment tools available to researchers and veterinary professionals, by discovering tools which have already been used in published studies. Medline and CAB Abstracts were searched in March 2018, using terms relevant to cats and QoL or well-being. Inclusion and exclusion criteria were applied and information on uniqueness, validation and a short description of each tool extracted.

A total of 1138 manuscripts were found, of which 96 met all criteria. Forty out of 96 manuscripts contained an assessment of QoL, using one of 32 unique tools found. Sixteen of the tools found were structured, making detailed patient assessments. Only eight of the structured tools were validated, and of these, three could be applied to healthy cats; the remainder being specific to a disease or being hospitalised. Some validated tools appeared in more than one manuscript. Overall, 12 manuscripts used a validated tool. In the 16 unstructured tools, five tools assessed QoL by assigning a single word (e.g. 'poor'). Eight tools assessed QoL on a single Likert scale (e.g. a number between one and 5=five). This work identifies the tools that are currently available for the assessment of QoL by researchers and veterinary professionals. Additionally, it demonstrates that many are not validated or lack detailed animal assessment, highlighting that further work in this important area is needed.

Keywords: Assessment tools; Cat; Quality of life; Validated; Well-being

Introduction

Quality of life (QoL) considerations are central to virtually every aspect of the welfare and humane care of animals, particularly health care (McMillan, 2000). Quality of life or the well-being of animals is a parameter regularly discussed and assessed in a range of environments (e.g. shelters, laboratory animal facilities, zoo and wildlife premises, veterinary practices, homes of owners etc.) by a number of different individuals (e.g. veterinary surgeons, pet owners, and other caregivers in these environments) including researchers developing novel treatments (Lambeth et al., 2014; Lascelles and Main, 2002; Lambeth et al., 2014; Arena et al., 2019). There is currently debate over the most suitable definition for QoL in animals and no widely accepted definition for QoL in animals exists (Gaynor and Muir, 2014). Belshaw et al. (2015) state that the "lack of a suitable definition of QoL in animals makes objective measuring of quality of life challenging". Belshaw et al. (2015) operationally define QoL as "an individual's satisfaction with its physical and psychological health, its physical and social environment and its ability to interact with that environment". In Gaynor and Muir (2014) a definition is proposed around the individual's response to their circumstances, with the following: "the subjective and dynamic evaluation by the individual of its circumstances and the extent to which these meet its expectations, which results in, or includes, an affective response to those circumstances".

Regardless of a current lack of consensus relating to the definition of QoL, assessment of QoL is an important component of veterinary surgeon and owner decision-making for many conditions. Veterinary surgeons are likely guided in their formulation and monitoring of treatment regimens by the owner's perception of their cat's QoL (Reynolds et al., 2010). In fact, QoL assessment forms a part of the decisions made at many stages of veterinary treatment, including; whether to seek veterinary advice (Hoyumpa et al., 2010), how to compare efficacy of treatments, and euthanasia decisions (McMillan, 2000). Euthanasia is commonly elected when treatment fails to maintain adequate patient QoL. If medications incur negative effects; for example, difficulty in administering medication, then treatment itself

can decrease perceived QoL (Reynolds et al., 2010). Veterinary surgeons treating dogs with osteoarthritis describe the balance between quantity and QoL when decision-making on treatments (Belshaw et al., 2016).

Work carried out by Dean (2014) looking at current treatment uncertainties for cats with chronic kidney disease (CKD) identified the top ten uncertainties for this condition. Over half of this top ten were concerned with whether treatments would "improve the life of" cats with CKD, where "improve" referred to both QoL and length of life (Dean, 2014). It is likely that these two outcomes are also important to those caring for cats with other diseases and conditions.

A structured review of the literature relating to QoL assessment is required to understand how QoL is assessed in published research, as this could be an important resource for individuals searching for established methods of QoL assessment. To the authors' knowledge there have been no previous studies identifying the number or type of QoL assessment tools for cats. Giuffrida and Kerrigan (2014) advise that reliable, validated instruments are needed to facilitate the measurement and comparison of pet QoL. Belshaw et al.. 2015 advised that the assessment of canine QoL should be done with appropriate, validated instruments and it is likely the same is true for domestic cats. Therefore, the aim of this study was to explore the published literature to identify how QoL is assessed, by determining the number and range of different assessment tools available in the literature to assess QoL or well-being in domestic cats.

Materials and methods:

For the purposes of this work, a QoL assessment tool was defined as 'any form of assessment or categorisation of a cat's QoL or well-being'. As no widely accepted definition for QoL in animals exists (Gaynor and Muir, 2014), each manuscript was not searched for a definition of quality of life. If a manuscript described that an

assessment of QoL had been carried out, it was deemed eligible for analysis for the purposes of this review.

Search methods

The OVID interface was used to search two databases: Medline (R) In-Process and Other Non-Indexed Citations (1946 to present) and CAB Abstracts (1910 to present). The search was carried out in March 2018, so results are restricted to publications appearing in the databases up until then. Search terms were adapted for cats from the review conducted by Belshaw et al. (2015). The search terms were the same for both databases and were linked with Boolean terms and the abstract, title, original title, broad terms and heading terms within publications were searched. The keywords used were: cat, cats, feline, felines, felis, quality of life, QOL, well being, wellbeing, well-being and quality-of-life. The subject headings used were: cats and quality of life.

Inclusion and exclusion criteria

The output from both databases were then exported into EndNoteX6 software (Thomson Reuters) to remove duplicates and apply inclusion and exclusion criteria, as listed in Table 1. The criteria for inclusion were as follows: (1) Written in English; (2) Full study available and published in peer reviewed literature; (3) Able to obtain through University of Nottingham library or inter-library loan request to the British Library Document Supply Centre; (4) About domestic cats either privately owned, or managed within other environments (e.g. shelters, teaching organisations) or used for research purposes; (5) Make reference to QoL or well-being within the title or abstract of the manuscript; (6) Make reference to QoL or well-being within the Materials and Methods section; (7) Study type is either randomised controlled trial, or controlled trial without randomisation, or cohort study, or case-control study, or cross sectional study or case series or case study; (8) QoL or well-being of cats is assessed within the manuscript; this may be done with a specified tool. For criteria

1-5, only the titles and abstracts of each manuscript were assessed, although whether the full manuscript was available was also checked at this stage.

Language was assessed by examining the citation information within the EndNote software. Publication type was also assessed by examining the citation information, and by searching for the journal on Ulrichsweb (https://ulrichsweb.serialssolutions.com) to see if the title was listed as “refereed”. These criteria were also assessed at the whole manuscript level if it was unclear from the above sources. The population of interest and subject criteria were assessed by reading the title and abstract. It was decided that only domestic cats would be included as it was thought that there may be variation in what constitutes good QoL between domestic and wild cats.

The criteria numbers six, seven and eight (Table 1) were then assessed at the full-text stage, including study type. The manuscripts were examined for the inclusion and exclusion criteria by assessment of the Materials and Methods section of the manuscripts. The terms “quality of life” or “well-being” and an indication of some form of assessment had to be mentioned within this section for the manuscript to meet the inclusion criteria. Reporting of the method of assessment within the manuscript was also required. For those manuscripts where the tool or form of assessment was not reported within the Materials and Methods section but was mentioned elsewhere in the manuscript, the Results section was also investigated.

All publications were assessed by HD for all inclusion and exclusion criteria. A random sample of 15% of the papers meeting the initial inclusion criteria (language, publication type, availability, population of interest and subject) were assessed independently by MB for the remaining inclusion and exclusion criteria (study type and assessment). The results of the two independent assessments were compared and any disagreements were discussed between HD and MB until agreement was reached.

Information extracted

From each manuscript remaining after application of the inclusion and exclusion criteria at the full-text stage, the following information was extracted: full reference details for the manuscript, the name of the QoL tool (if applicable), a brief description of the tool, whether the tool was unique and used for the first time or referenced elsewhere, and whether it had been validated within the study (i.e. an assessment was made as to whether the tool was truly measuring what it was designed to measure) (Belshaw et al., 2015). The tool could be applied by researchers, veterinary surgeons or cat owners or carers.

Tools were then classified by type as to the level of detail of their QoL assessment. Tools classed as "structured" were those in which more than one question or assessment was carried out and these tools attempted to go into detail regarding the cat's life or behaviour. The remaining tools either consisted of only "one word" (where QoL assessment was defined by description with one word, e.g. poor), or "single scale" (where QoL was defined by a number on a scale e.g. from 1-5), or "other" (where the QoL tool did not fit any of the previous descriptions). The validated tools were then examined in greater detail.

Results

The search results returned 1138 unique manuscripts. Figure 1 gives a summary of the number of manuscripts which were included and excluded from this review, and the number of QoL assessment tools extracted from the included manuscripts.

Of the 1138 manuscripts, 96 met the inclusion criteria 1-5 when screened at the title and abstract level, and all 96 additionally met criterion 6 when screened at whole manuscript level (Figure 1). Double assessment was carried out on 36

citations by MB and HD and resulted in initial disagreement about the inclusion of 1/36 manuscripts (97% agreement). After discussion, it was agreed that the manuscript should be excluded by both reviewers.

Manuscripts identified containing quality of life assessments

Of the 96 manuscripts included, 40 (42%) were found to contain some form of QoL tool or assessment (Figure 1). Within the 40 manuscripts containing an assessment of QoL, we found 32 unique tools or assessment methods which could be clearly identified. Twenty-nine of these appeared within a manuscript detailing their first use. An additional three unique tools appeared within the remaining 11/40 manuscripts. However, for these three, the manuscript describing their origin or first use did not appear within our search results. This made a total of 32 unique tools found. Within the remaining 8/40 manuscripts, seven referenced tools were already found within the 32 unique tools, and the final manuscript described a paper which was insufficiently described and referenced for the tool or its origin to be clearly identified. Supplemental Table 1 provides more detail on all the tools found in the 40 manuscripts where a QoL assessment was carried out, including author, title, administration of tool, how information was gathered for the tool, a brief description of the tool used, whether the tool was unique, and whether the tool was validated. The majority of tools were owner completed questionnaires, of varying complexity. Three tools clearly explained that they included a veterinary surgeon's involvement or a physical examination. Two of these tools were validated (Adamelli et al., 2004/2005; Taffin et al., 2016) and one was not validated (Fox et al., 2000). Change in QoL was assessed in 12 tools, for example, before and after treatment, or time to return to "best" QoL. Of these 12, eight tools used numbered scales e.g. rate QoL 1-10 before and after treatment, three used one word assessments e.g. QoL worse or QoL improved, one recorded the number of days e.g. to return to normal QoL.

Unique tools found across the 40 manuscripts

Out of 32 unique tools found, 16 were classed as structured and 16 were considered not structured. Structured tools were identified as those in which more than one question or assessment was carried out, and the tool went into detail regarding clinical signs and/ or life and/or behaviour. These were converted to scores, which were then summed to give overall totals. The 16 unstructured tools carried out a simple assessment of QoL as a single word, number or one or two short questions (see Figure 2). Of the 16/32 unique unstructured tools, eight tools (Brown et al., 2009; Bowles et al., 2010; Ruda and Heine, 2012; Boland et al., 2014; Hung et al., 2014; Kooij et al., 2014; Fritsch and Jewel, 2015; Matei et al., 2017) scored QoL on a Likert scale (e.g. rating of 1-3 or 5-1). In five tools (Bass et al., 2005; Lascelles et al., 2007; Pakozdy et al., 2013; Theobald et al., 2017; Guedes et al., 2018) a single word was used to describe a QoL assessment, such as "poor" or "good". In the remaining three tools, one used an owner subjective overall assessment of tumour size, eating and grooming as a proxy for QoL assessment (Sabhlok and Ayl, 2014), one looked for clinical signs and chronic diseases potentially associated with a decreased QoL from the veterinary clinical notes (Gates et al., 2017) and one asked two questions about time taken to return to best or normal QoL (Forster et al., 2010).

All 16 structured tools carried out a detailed assessment on a variety of aspects of the life and behaviour of the cats assessed and included a scoring system (titled disease or condition specific tools). Explored parameters included: physiological parameters such as breathing pattern, appetite and mobility and other more behavioural parameters including: hunting, grooming, sleeping, sunbathing, visiting favourite places, interacting with people, interacting with other cats, play behaviour and mood. There were parameters that fitted into both physiological and behavioural indicators, e.g. litter tray parameters which included different assessments depending on the tool. Litter tray parameters noted included: stool volume, diarrhoea, appropriate use of litter box and toileting habits.

Of the 16/32 tools defined as structured, 6/16 were named and of the tools considered unstructured (16/32), 2/16 were named. Some of the named tools appeared more than once in the overall search results: Karnofsky's score modified for cats appeared in 4 manuscripts: Hartmann and Kuffer, 1998; Ritz et al., 2007; Fischer et al., 2011; Taffin et al., 2016. DIAQoL-pet appeared in 2 manuscripts: Niessen et al., 2010 and Gostelow et al., 2018, and the Cats' Assessment Tool for Cardiac Health CATCH appeared in two manuscripts: Freeman et al., 2012 and Rush et al., 2015.

Validated tools

Of the 32 unique tools found, 50% were structured (16/32) and 26% were validated (8/32). Validated tools were more likely to be structured (8/8; 100%) and named (6/8; 75%). The eight validated tools which were found consisted of three tools designed to assess the QoL of healthy cats (one represented in Adamelli et al., 2004 and 2005; one in Freeman et al., 2016 and one in Tatlock et al. 2017), one tool for assessing hospitalised cats (Taffin et al., 2016), one to assess cats with chronic kidney disease (Bijsmans et al., 2016), one to assess cats with cardiac disease (Freeman et al., 2012), one tool to assess cats with diabetes (Niessen et al., 2010), and one tool to assess cats with skin disease (Noli et al., 2016) (Figure 2). All of these tools were detailed questionnaires, and 6/8 were only completed by the cat's owner. Of the remaining two tools, one included a veterinary physical examination which was coded and scored (Adamelli et al., 2004 and 2005) and the other (Karnofsky's score modified for cats, validated in Taffin et al., 2016) included a score from 0-5 given by the examining veterinary surgeon. Three of the validated tools appeared in more than one manuscript within this review. The same unnamed tool appears in Adamelli et al, (2004) and Adamelli et al, (2005), the CATCH tool (Freeman et al., 2012) appeared in two manuscripts, and the DIAQoL-pet tool (Niessen et al., 2010) appeared in three manuscripts. This made a total of 12 manuscripts where one of the eight validated tools was used. This was 30% (12/40) of all manuscripts included in this review. Supplemental Table 1 contains full details

of all 40 manuscripts. Those using a validated tool are identified by an [a] after the author names.

The number of items examined in each validated tool ranged from 17 items (CATCH tool, Freeman et al., 2012)) to 100 items (CHEW, Freeman et al., 2016) (Supplementary Table 1). In some tools these items were divided into domains, for example play, mood, energy, appetite, physique, coat (Freeman et al., 2016), and in all tools the items were scored numerically to give an overall QoL result. The number of items assessed in the tool used in both Adamelli et al, (2004) and Adamelli et al, (2005) was not stated. Nor was the number of items assessed in the tool used in Taffin et al, (2016). Most of the tools found contained an additional question to assess the assessor's impression of the QoL of the cat overall. The only stated recall periods were seven days (CHEW, Freeman et al., 2016) and the preceding 4-week period (Tatlock et al., 2017). For the other assessment tools the recall period was described as one of the following: during the study, or since the intervention, or since the previous visit, or was not stated.

Unvalidated tools

Unvalidated tools designed to assess the QoL of cats with a particular disease condition were found for degenerative joint disease (Benito et al., 2012), osteoarthritis "FMPI" (Benito et al., 2013) and cancer "HRQoL" (Lynch et al., 2011). An additional three unvalidated tools were found to assess QoL associated with chemotherapy or the presence of tumours: Tzannes et al., 2008; Sabhlok and Ayl, 2014; Williams et al., 2017. One unvalidated tool was found to assess the QoL of healthy cats: Karnofskys' score modified for cats (Hartman and Kuffer, 1998) although this was later validated (Taffin et al., 2016).

Discussion

This is the first structured literature review focused on assessment tools for QoL of cats in all circumstances, whether healthy or unwell. The only other review of QoL tools for cats that the authors are aware of is the systematic review by Giuffrida and Kerrigan (2014) looking at tools for QoL of cats (and dogs) with cancer. In this review, we aimed to understand what tools are currently available for decision makers and researchers for assessing cat QoL. Defining QoL is very complex and no universally accepted definition yet exists (Gaynor and Muir 2014). We aimed to find out whether any assessment of QoL was carried out in manuscripts which discussed QoL, whether a simple or structured tool was used, and whether that tool was validated. In human medicine, Carr and Higginson (2001) discussed how evaluation of QoL can be very specific to an individual patient. Therefore, it is possible that without an agreed definition of QoL or any validated tools, QoL may not be well assessed. Independent assessments using different tools may come to different conclusions about QoL.

We found that although QoL or well-being was mentioned in manuscripts, actual assessment of QoL with some form of tool was carried out in less than half of the manuscripts. Some papers mentioned the importance of QoL or discussed how a new treatment has the potential to improve QoL, without any actual assessment of QoL alongside this. Assessment with a validated tool was carried out in just over a quarter of manuscripts. Many tools used a Likert scale or one word to assess QoL and these very simple, unstructured tools were not validated. QoL is a very complex construct (Scott et al., 2007) so it is likely that it would not be possible to validate these over-simplified tools for QoL assessment. Assessing this important concept so simply in research studies, particularly clinical trials, may risk missing subtle differences between patients. This would reduce the useful contribution that these trials could make to the evidence-base for treatment decision-making. Quality of life assessment in cats may be more than a single construct. It may incorporate specific characteristics within different contexts, likely to have a common set of characteristics that may apply to all contexts. Scott et al. (2007) explain that QoL is a complex and subjective construct which should not be over-simplified in order to

measure it. Many papers found by the current study have over-simplified the construct by their chosen measurement methods. Even within the validated tools found, there is wide variability in the number of items assessed by each tool, and so each tool may produce a different quality of life assessment. Defining quality of life is very complex and existing publications propose several definitions, none of which has been universally accepted. The purpose of this review was not to create a new definition for quality of life, or to solve the existing problem of a lack of universally accepted definition. The authors agree that this is an important problem that needs addressing. However, the purpose of this review was to explore whether papers that discuss cat quality of life use a tool to assess it, what sort of tool they use, and whether they use a validated tool.

The validation of tools to measure QoL is important, as without validation we cannot be certain that a tool is truly measuring what it has been designed to measure (Scott et al., 2007; Belshaw et al., 2015). Assessment of the validation process used for these tools should now be carried out and if validation is found to have been conducted rigorously, users can be more reassured as to how well the validated tools measure QoL and how comparable the results gained from assessments with each tool may be. Assessment of validation should be carried out according to the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) (Prinsen et al., 2016), and the authors aim to address this in future work as it falls outside the scope of this current review. In assessing the credibility of the QoL tools the authors will also need to assess their reliability (Spofford et al., 2013). Giuffrida and Kerrigan (2014) define reliability as whether the test measures something in a reproducible manner. Spofford et al., 2013 state that using reliable tools helps to gather accurate results. The next step in this work is to look at both the validity and reliability of the QoL assessment tools, because both are important for determining how well a tool assesses what it is supposed to in a consistent way. However, we anticipate this process may be complicated by the lack of definition of QoL for animals as described by Gaynor and

Muir (2014) and Belshaw et al. (2015) which will make it difficult to fully assess the validation process, and test reliability.

As many QoL tools have not been validated, this limits what individuals involved in QoL assessments on a daily basis (e.g. veterinary surgeons, animal owners/ managers etc.) can utilise for decision-making in relation to the animals under their care, be they assessments of positive or negative QoL in healthy animals, or those suffering from a disease. For decision making in the veterinary clinic, the FMPI tool (Benito et al., 2012) is now accessible on a website for vets to use for assessing musculoskeletal pain. This may increase awareness and use of this tool, however as this tool is unvalidated for QoL assessment, the quality of assessments made using it is not known. It is hoped that this review will highlight the validated tools which do exist, to encourage future researchers and clinical practitioners to use them. It is hoped that these validated tools will provide a more thorough and appropriate QoL assessment than unvalidated tools. However, the assessment of the validation process and reliability of the tools has not yet been carried out. Therefore, users should note that further recommendations may be made after this process, and that they may not be able to rely fully on the assessments of all validated tools at this stage of the process.

There are some potential limitations to the work carried out in this review. The search strategy used only covered the databases Medline and CAB Abstracts. These databases should have good coverage of the literature relating to animals, as research has identified that CAB Abstracts covers 90% of journals relevant for veterinary medicine (Grindlay et al., 2016). However, it is possible that further searching with additional databases and hand searching the grey literature may have found more results. Since this review was carried out the authors have been made aware of an additional manuscript (Noble et al., 2018), which was likely not indexed at the time of the original search. In addition, the search terms used were very specific to QoL. The term “well-being” was included and was also helpful as

many authors seemed to use this interchangeably with QoL. The search terms used in this review were the same as used by Belshaw et al. (2015) in a review of QoL assessment tools for dogs. It is possible that using additional search terms, for example “welfare” could have returned more results, as some consider the terms “welfare” and “QoL” to be synonymous (Mullan, 2015). However, welfare can also include practical welfare measurement, which is most usually concerned with ensuring minimum standards of care are provided (Scott et al., 2007). Therefore, including this term may have made the results much broader, covering more general practical aspects of a cat’s life, and less applicable to the specific assessment of QoL, in which Scott et al. (2007) emphasise the importance of the individual’s perspective, and how the subject feels about their circumstances. In addition, the manuscripts in this review only met the inclusion criteria if they were in English. If more languages had been included in the scope of this review, it is possible that additional QoL tools may have been found.

Conclusions

Researchers appear to assess QoL in cats using a wide range of tool types, and few appear to use the small number of tools that have been validated. Researchers assessing QoL at present should aim to use the existing validated tools where appropriate, whilst being aware that future work will aim to assess the quality of the process used to validate the tools, and tool reliability. In addition, a universally agreed definition of QoL should be sought.

Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

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Table 1

Inclusion and exclusion criteria for this scoping review

Criteria No.	Criteria	Inclusion	Exclusion
Title and abstract screening			
1	Language	English	Any language other than English
2	Publication type	Full study reported Published literature	Non-peer reviewed literature (defined as Journal not stated on Ulrichsweb: https://ulrichsweb.serialssolutions.com as "refereed/ peer reviewed"). Grey literature Abstracts only available (methods and results not available on request) Book/book section/generic

3	Availability	Able to obtain through University of Nottingham library or inter-library loan request to the British Library Document Supply Centre	Cannot obtain manuscript in full
4	Population of interest	About domestic cats either privately owned, or managed within other environments (e.g. shelters, teaching organisations) or used for research purposes	Wild or big cats In vitro studies Any other species
5	Subject	Make reference to QoL or well-being within the title or abstract of the manuscript.	No reference to QoL or well-being within title and abstract
Whole manuscript screening			
6	Subject	Make reference to QoL or well-being within the materials	Does not make reference to QoL or well-being within the materials and methods section

		and methods section	
7	Study type	Randomised Controlled trials Controlled trials without randomisation Cohort studies Case-control studies Cross sectional studies Case series Case study	Narrative reviews Conference proceedings
8	Assessment	Assessment of QoL or well-being of cats within the manuscript was made, may use a specified tool to do so.	Discuss QoL without actually providing an assessment of QoL or using any tool. Manuscripts which mention QoL or well-being but do not assess it in any way.

QoL, quality of life

Supplemental Table 1

Overview of the information extracted from the 40 papers found during a scoping review of quality of life assessment tools for cats.

Author	Title	Administration of tool	How information gathered for tool	Brief description of the quality of life tool used, as it is described within the manuscript	Unique tool used for the first time? Or reference from elsewhere?	Is validation of the tool described?
Adamelli et al., 2005 [a]	Owner and cat features influence the quality of life of the cat	Owner and veterinary surgeon	Questionnaires and physical examination	Questionnaires covered “care”, for example: veterinary care and frequency of brushing and “cat behaviour”, for example: urinating outside the litter tray and time spent with owner. Each answer was coded into a number and then the sum of these numbers was	Referenced from Marinelli et al., 2001	States was previously validated by Marinelli et al., 2001

	translated into the category low or medium or high. Each aspect of the physical examination of the cat was also coded onto a numeric scale of 1-3, these aspects were then summed to give a total score. This score was then categorised as low, medium or high. QoL was calculated by adding the numeric values (from questionnaire together to give a total numeric value of QoL. Also, to assess the level of QoL, the combination of the three low, medium or high ratings was considered: an overall low QoL= three low scores or two low scores and one medium. An overall high

				QoL= three high scores or two high and one medium. All other score combinations= medium QoL.		
Adamelli et al., 2004 [a]	Factors influencing the quality of life of the cat in its relationship with owners	Owner and veterinary surgeon	Questionnaires and physical examination	Four questionnaires examined the relationship between the cat and the owners, and the influence of factors on the cat's QoL. These covered owner features (age, gender, education, marital status, job family features, place and size of swelling, social relations), cat features (age, gender, breed, neuter status, age of adoption, source, whether lives with other animals), care given to the cat and the cat's behaviour (attachment to the owner, house, soiling, behaviour towards owner and other animals). A score scale was used to codify responses and the	Referenced from Marinelli et al., 2001	States was previously validated by Marinelli et al., 2001

				sum used to represent: care given to cat, cat behaviour and physical condition. The manuscript states that some owner and some cat features were found to influence the cat's QoL. However, it is not clear from reading this manuscript in isolation how that conclusion was drawn.		
Bass et al., 2005	Retrospective study of indications for and outcome of perineal urethrostomy in cats	Owner	Questionnaire	Asked whether they considered their cat's QoL to be good, acceptable or poor, following surgery.	Unique tool, not a named tool, not referenced.	No

Benito et al., 2013	Reliability and discriminatory testing of a client-based metrology instrument, feline musculoskeletal pain index (FMPI) for the evaluation of degenerative joint disease-associated pain in cats	Owner	Questionnaire	“Feline Musculoskeletal Pain Index”: a 21-question tool with one question on overall QoL. The question was a descriptive rating scale with four descriptors: excellent, good, fair, poor.	Unique named tool used for the first time	No
Benito et al., 2012	Owner-assessed indices of quality of life in cats and the	Owner	Questionnaire	The questionnaire was modelled from Budke et al., 2008 in which owners they wrote down five activities they believe were important for the cat’s QoL. They	Referenced from Budke et al., 2008	No, in Budke et al., 2008 the tool was originally

	relationship to the presence of degenerative joint disease			were then asked to rate the importance of each activity, with the sum total of all the ratings being 100.		designed for dogs
Bijsmans et al., 2016 [a]	Psychometric validation of a general health quality of life tool for cats used to compare healthy cats and cats with chronic kidney disease	Owner	Questionnaire	"CatQoL survey" divided into four domains: general health, eating, behaviour and management, which covered 18 items in total. Each item scored according to the frequency or severity with which it impacted the cat's life (-3 to +3), along with an importance rating for each question (0 to +3). The frequency and importance ratings multiplied to give an item-weighted-impact-score (IWIS). Lowest possible IWIS was -9 and highest possible +9. An average of all the IWIS scores then taken to	Unique tool, first use	Psychometric validation is carried out and described within the paper, where two of the items are removed as a result, leading to a final 16 item tool.

				give an overall quantitative measure of the cat's QoL. An additional question allowed the owner to separately grade their cat's QoL from 0-10 (very poor-excellent). A free comments section allowed owners to add anything they wished about their cat's QoL.		
Boland et al., 2014	A survey of owners' perceptions and experiences of radioiodine treatment of feline hyperthyroidism in the UK	Owner	Questionnaire	QoL assessed on a linear analogue scale of 1-10 before and after radioiodine treatment, where 1= very poor and 10 = excellent.	Unique tool, first use	No

Bowles et al., 2010	Owner's perception of carboplatin in conjunction with other palliative treatments for cancer therapy	Owner	Questionnaire	QoL rated on a 10 point numerical system where 1= could not be worse and 10= could not be better. This was done for the following times: a) before cancer, b) after diagnosis of cancer but before treatment, c) during treatment with carboplatin.	Unique tool, first use	No
Brown et al., 2009	Gene therapy by electroporation for the treatment of chronic renal failure in companion animals	Owner	Questionnaire	Control patients not individually assessed for QoL but the veterinarians felt it was getting worse. In the treated animals the owners were asked to rate their pet's QoL as significantly increased (5); increased (4); no change (3); decreased (2) or significantly decreased (1). This was done four	Unique tool, first use	No

				times over the 60-day study period.		
Christman n et al., 2016	Effectiveness of a new dietetic weight management food to achieve weight loss in client-owned obese cats	Owner	Questionnair e	QoL described at each visit by scoring the following criteria on a Likert scale: energy level, happiness, appetite, begging behaviour, flatulence, stool volume. Scores ranged from 0-10, so for example, for happiness, a score of 0 meant sad and a score of 10, meant very happy.	Unique tool used for the first time	No
Fischer et al., 2011	Randomized, placebo-controlled study of the effect of propentofylline	See Hartmann and Kuffer (1998)	See Hartmann and Kuffer (1998)	Karnofsky's score modified for cats- see Hartman and Kuffer (1998)	Referenced from Hartmann and Kuffer (1998)	No

	on survival time and quality of life of cats with feline infectious peritonitis					
Forster et al., 2010	Owners' observations of domestic cats after limb amputation	Owner	Questionnaire	Information was collected on the owner's perception of cat's QoL. Also, the owner was asked how long the cat took to reach "best" QoL after the procedure and whether the cat returned to a "normal" QoL after the procedure. In addition, how long it took for the QoL to stop improving.	Unique tool, first use	No
Fox et al., 2000	Use of cis-bis-neodecanoato-trans-R,R-1,2-	Owner and veterinary surgeon	Questionnaire and additional	On day 10 after each treatment a "performance status questionnaire" was done,	Unique tool, first use.	No

	diaminocycloh exane platinum (II), a liposomal cisplatin analogue, in cats with oral squamous cell carcinoma		evaluation, method not described	assessing attitude and activity, appetite and weight loss. For each category it appears that owners would select the most appropriate response, e.g. for appetite: eats well without assistance/ eats well with assistance/ force-fed/ will not eat/ requires enteral nutrients. In addition, owners and clinicians evaluated the QoL and if poor, the cats were subjected to euthanasia. Method of evaluation not described.		
Freeman et al., 2012 [a]	Development and evaluation of a questionnaire for assessment of health-	Owner	Questionnaire	Cat's Assessment Tool for Cardiac Health (CATCH) A 17-item questionnaire designed to assess the degree to which the clinical signs of cardiac disease	Unique named tool used for the first time	Yes

	related quality of life in cats with cardiac disease			affected the cat's comfort or sociability, graded on a scale of 0-5 where 0= not at all and 5= very much. Responses for each of the items were summed to obtain an overall score where higher scores indicated a poorer health related QoL. Additionally, owners asked to assess overall QoL on a scale of 1-5 where 1 = excellent and 5 = very poor.		
Freeman et al., 2016 [a]	Development and initial validation of the Cat HEalth and Wellbeing	Owner	Questionnaire	Cat HEalth and Wellbeing (CHEW) questionnaire.	Unique tool, first use.	Validity and reliability evaluated

	(CHEW) Questionnaire: a generic health-related quality of life instrument for cats			Tool contained 11 domains with 100 items, over a seven day recall period, alongside two general questions determining overall HRQoL and overall health status on a five point Likert scale (to be used for validation and classification). Domains included play, mood, energy, appetite, physique and coat.		within this manuscript.
Fritsch and Jewell, 2015	Acceptance and effects of a therapeutic renal food in pet cats with chronic kidney disease	Owner	Questionnaire	Asked at each visit to rate change in QOL since previous visit, on sevenpoint scale from extreme deterioration (7) to extreme improvement (1)	Unique tool, first use	No

Gates et al., 2017	Preliminary description of aging cats and dogs presented to a New Zealand first opinion veterinary clinic at end-of-life	Researcher	Information gathered from clinical notes written by the veterinary surgeon	The presence of clinical signs potentially associated with a decreased QoL (e.g. respiratory impairment, lethargy, recumbency, poor body condition) were noted and whether the patient had chronic disease (e.g. renal failure, blindness, cardiovascular disease) potentially associated with decreased QoL was also noted.	Unique assessment, first use.	No
Giuffrida and Kerrigan, 2014	Quality of life measurement in prospective studies of cancer treatments in dogs and cats	N/A	N/A	This is a review of QoL measurement tools in prospective studies of cancer treatment in cats and dogs. The “Karnofsky’s score modified for cats” tool (Hartmann and Kuffer, 1998) found elsewhere in this search was identified in this manuscript. The identity of other tools found in this 2014 search was	Not applicable	Not applicable

				unclear from the information provided.		
Gostelow et al., 2018 [a]	Prospective evaluation of a protocol for transitioning porcine lente insulin treated diabetic cats to human recombinant protamine zinc insulin	See Niessen et al., 2010	See Niessen et al., 2010	DIAQoL-pet quality-of-life questionnaire for diabetic cats, which generates an average-weighted impact score (AWIS) to reflect pet and owner QoL (see Niessen et al., 2010, below).	Referenced from Niessen et al., 2010	States that the tool is validated
Guedes et al., 2018	Evaluation of tramadol for treatment	Owner	Questionnaire	Global quality-of-life questionnaire which asks whether the cat's life had deteriorated during the study, was the same as before the study,	Not referenced but is described as	No

	of osteoarthritis in geriatric cats			or had improved, compared with QoL before the study.	if is not unique.	
Hartmann and Kuffer, 1998	Karnofsky's score modified for cats	Owner and veterinary surgeon	Questionnaire and veterinary observations	Karnofsky's score modified for cats: Two parts. Part 1: an owner questionnaire. In this the owner compares the behaviours of the cat now to the behaviour of the cat before disease was noticed and assigned a score (0= behaviour no longer present, 1= shown only rarely, 2= shown half as often as earlier times, 3= almost as often as earlier times, 4= as often as earlier times). Each behaviour score is then multiplied by a factor (different for	Unique named tool used for the first time	No

	each behaviour) and a number of points are assigned, up to a maximum number. The maximum overall score for part 1= 50. Part 2: observations by the vet. One of six scores is chosen to represent the general condition of the patient (5= completely normal, 4 = minor changes, 3= medium changes, 2= major changes, 1= severely diseased, 0= dead). This score is multiplied by 10 to give a second score of maximum 50. Scores from part one and part two added together and then referenced to the Index of Karnofsky which indicates the QoL,

				e.g. 100% = normal, no complaints, no evidence of disease.		
Hung et al., 2014	Bovine lactoferrin and piroxicam as an adjunct treatment for lymphocytic-plasmacytic gingivitis stomatitis in cats	Owner	Questionnaire	The owner's perception of the cat's QoL was scored from 1-10 where 1=worst quality of life and 10= the best QoL.	Unique tool, first use	No
Kooij et al., 2014	Effects of an iodine-restricted food on client-owned cats with	Veterinary surgeon	Questionnaire	Scored by the veterinary surgeon from 1-5 where 1= very poor and 5 = excellent.	Unique tool, first use	No

	hyperthyroidism					
Kulendra et al., 2014[a]	Feline double pigtail ureteric stents for management of ureteric obstruction: short- and long-term follow-up of 26 cats	See Niessen et al., 2010	See Niessen et al., 2010	Assessment by questionnaire, based on DIA-QoL-pet- see Niessen et al., 2010	Referenced from Niessen et al., 2010	Yes
Lascelles et al., 2007	Evaluation of client-specific outcome measures and activity monitoring to measure pain	Owner	Questionnaire	Owner asked if QoL was worse, the same, slightly improved, moderately improved or very improved. This assessment was termed: a “Global Assessment of Quality of Life”	Unique tool, first use	No

	relief in cats with osteoarthritis					
Lynch et al., 2011	Development of a questionnaire assessing health-related quality-of-life in dogs and cats with cancer	Owner	Questionnaire	"HRQoL" questionnaire asked owners to state from 1-5 their agreement with 3 statements for 8 domains, e.g. within the domain Happiness, one of the statements reads "My pet wants to play". Owners also asked to indicate current QoL from very poor to excellent on a visual assessment scale.	Unique tool, first use	No
Matei et al., 2017	Nutritional management of overweight and obesity in dogs and cats	Not clear	Not clear	States that the QoL was assessed, and that QoL scores improved (scores are quoted in the results from -1 to +1 but it is not explained how these scores were calculated.	Unclear as not stated.	No

Niessen et al., 2010 [a]	Evaluation of a quality-of-life tool for cats with diabetes mellitus	Owner	Questionnaire	DIAQoL-pet: Twenty-nine diabetes mellitus QoL specific items. For each item, the frequency with which it impacted the owner and pet's lives and how important the item was to the owner and pet were categorised e.g.: all the time/ often/ occasionally and this was translated into a numeric value. The frequency and importance values for each item were multiplied to give a score per item and these scores were averaged across all 29 items to give a single quantitative measure of QoL. An additional two separate overview questions were included:	Unique named tool used for the first time	Yes

				"I feel my pet's quality of life is…." and "If your pet did not have diabetes, his/her quality of life would be….."		
Noli et al., 2016 [a]	Development and validation of a questionnaire to evaluate the QoL of cats with skin disease and their owners, and its use in 185 cats with skin disease	Owner	Questionnaire	The questionnaire was developed based on the "Dermatology life Quality Index" from human medicine and interviews with owners, to assess the impact of skin disease on cat, owner and families' lives and QoL. Answers were scored: 0 (not at all) to 3 (very much). Questionnaire contained 15 items, with seven questions which focussed on the QoL of the cat, covering: mood, sleep, meals, playing/exploring, habit changes, therapies and vet visits.	Unique tool, first use.	Criterion and construct validity described within the manuscript.

Pakozdy et al., 2013	Treatment and long-term follow-up of cats with suspected primary epilepsy	Owner	Questionnaire	Owner evaluated whether the cat's QoL was good/ impaired or bad, based on these definitions: Good= cat's life did not seem to be negatively influenced by the disease or treatment. Impaired= when the disease or treatment had a significant or important negative influence. Bad= when the owner considered euthanasia as result of the disease.	Unique tool, first use	No
Reynolds et al., 2010	Perceptions of quality of life and priorities of owners of cats with heart disease	Owner	Questionnaire	Owners asked about the cat's overall QoL and completed a questionnaire on the importance of 8 individual parameters on their cat's QoL. Parameters= appetite, human interaction, interaction with other pets, desire and ability to engage in play, comfort while	Unique tool, first use	No

	resting or sleeping, normal grooming activity, appropriate use of the litter box and desire to go outside. These parameters were rated from 1-10 where 1= no importance and 10 = extremely important. Owners also asked: Whether administering medication had a harmful effect on the cat's QoL (1= no effect to 10= extreme effect) About the balance between giving medications to maintain or improve QoL but at the same time potentially reduce life expectancy, what would the owners consider the ideal balance? (1= low QoL but

				long lifespan to 10= high QoL but short lifespan.		
Ritz et al., 2007	Effect of feline interferon-omega on the survival time and quality of life of cats with feline infectious peritonitis	See Hartmann and Kuffer, 1998	See Hartmann and Kuffer, 1998	Karnofsky's score modified for cats.	Referenced from Hartmann and Kuffer, 1998	No
Ruda and Heiene, 2012	Short- and long-term outcome after perineal urethrostomy in 86 cats with feline lower	Owner	Questionnaire	Overall QoL after surgery graded from 1-3.	Unique tool, first use	No

	urinary tract disease					
Rush et al., 2015 [a]	Assessment of the responsiveness of the Cats' Assessment Tool for Cardiac Health (CATCH) Questionnaire	See Freeman et al., 2012	See Freeman et al., 2012	CATCH- see Freeman et al., 2012	Referenced from Freeman et al., 2012	Yes
Sabhlok and Ayl, 2014	Palliative radiation therapy outcomes for cats with oral squamous cell carcinoma (1999-2005)	Owner	Questionnaire	Owner subjective assessments made of post-treatment QoL, based on: an observable decrease in tumour size, an improved ability to eat and return to grooming.	Unique assessment, first use.	No

Taffin et al., 2016 [a]	Evaluation of a modified Karnofsky score to assess physical and psychological well-being of cats in a hospital setting	See Hartmann and Kuffer, 1998	See Hartmann and Kuffer, 1998	Karnofsky's score (see Hartmann and Kuffer, 1998) with some aspects removed as not pertinent to hospital setting, for example: catching mice.	Referenced from Hartmann and Kuffer,1998	Yes
Tatlock et al., 2017 [a]	Development and preliminary psychometric evaluation of an owner-completed measure of	Owner	Questionnaire	A 22 -item questionnaire which covered seven domains on the topics of: interaction with surroundings and humans, gastrointestinal signs, physical activity, vocalisation, appetite, sleeping, pain, general health, toileting habits, hydration, weight loss, grooming and general	Unique tool, used for the first time	Yes, validation is described within this manuscript

	feline quality of life			happiness. Each item was rated for the preceding four week period using a five point Likert scale, from “not at all” or “strongly disagree, up to: “a great deal” or “very much” or “strongly agree”.		
Theobald et al., 2013	Clinical outcome in 19 cats with clinical and magnetic resonance imaging diagnosis of ischaemic myelopathy (2000-2011)	Owner	Questionnaire	Owner perception of QoL, no scale given. Reported as “poor” for some cases and for other cases, that the QoL negated the need for clinical re-evaluation.	Unique assessment, first use.	No

Tzannes et al., 2008	Owners 'perception of their cats' quality of life during COP chemotherapy for lymphoma	Owner	Questionnaire	Using a linear analogue scale, owners were asked to rate their cat's QoL on a scale of 1-10 (1= QoL could not be worse, 10 = QoL could not be better) pre-cancer, after diagnosis but before chemotherapy treatment, and during chemotherapy treatment. Owners also asked to rate how they thought the cat perceived their own QoL, identify aspects they considered important to their cat's QoL and describe the cat's experience of chemotherapy as "all good days", "more good days than bad days", "more bad days than good days" or "all bad days".	Unique tool, first use	No

Williams et al., 2017	Factors which influence owners when deciding to use chemotherapy in terminally ill pets	Owner	Questionnaire	QoL rated by owners on a scale from 1 (low) to 10 (high) and embedded within a questionnaire, alongside other key themes. Owners were asked to rate the potential impact of chemotherapy on 13 statements, as acceptable or unacceptable, to assess the impact of chemotherapy on QoL. For example: “My pet does not play during chemotherapy”. Other statements covered drinking, eating grooming, activity, awareness, trembling, sleeping, good days vs bad days, play behaviour, depression and diarrhoea.	Unique tool used for the first time, created based on information from Tzannes et al., 2008; Reynolds et al., 2010; Belshaw et al., 2015	Not stated.

QoL, quality of life

[a]By the authors name denotes one of the 12 manuscripts where a validated tool was used

Figure legends

Fig. 1. Flow chart to show number of manuscripts excluded according to the inclusion and exclusion criteria and number of tools extracted.

Fig. 2. Flow chart to show how many tools of each type were found.

[b] The two manuscripts by Adamelli et al were both found in the search done as part of this systematic review. They both reference the same tool, originally published in Marinelli et al., 2001. However, the manuscript by Marinelli et al, 2001 was not found in the results from this systematic review search.

(V) is used to show a tool which had been validated.

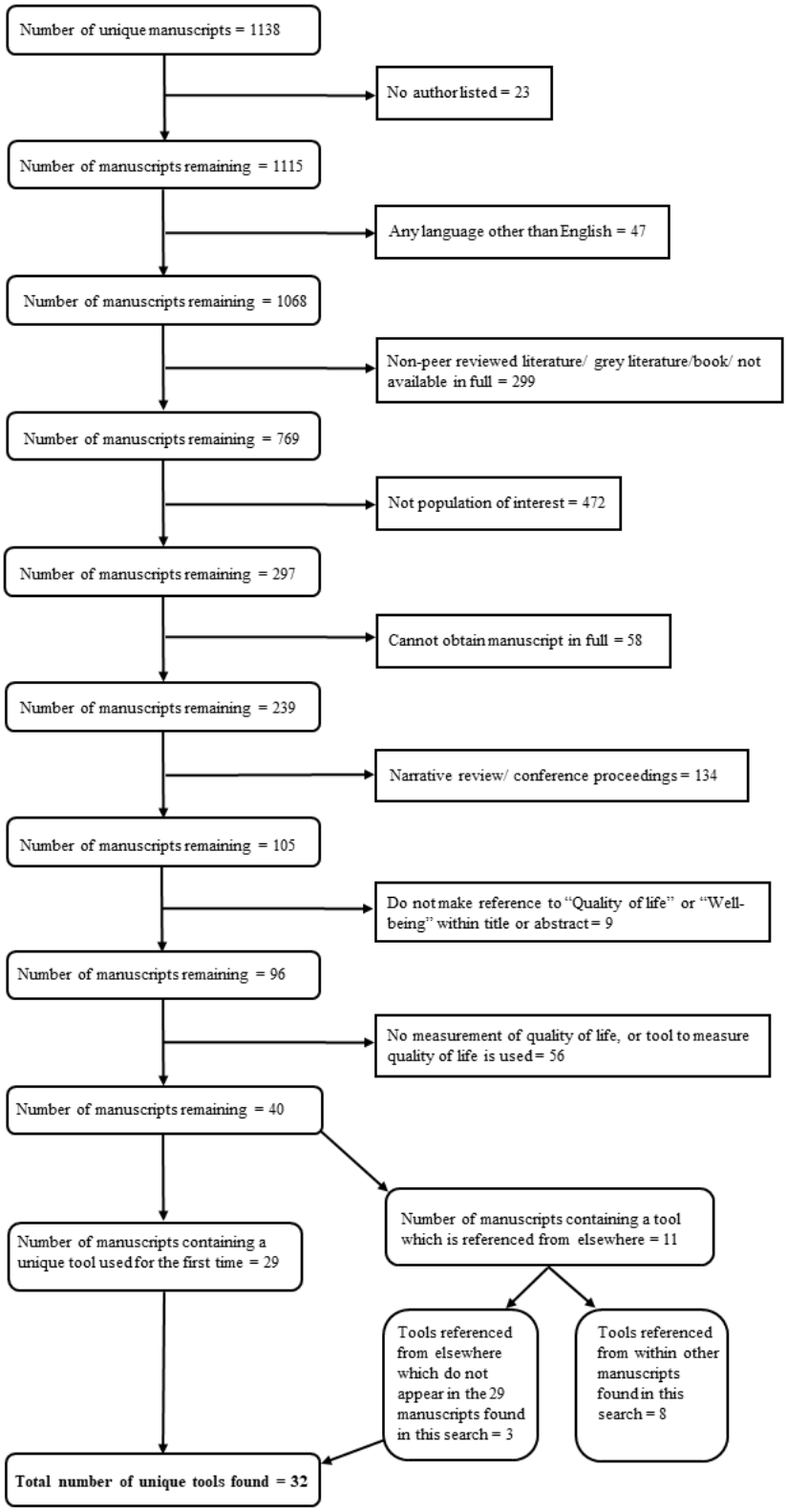

Figure 9.1 Flowchart to show inclusion and exclusion of manuscripts in the quality of life systematic review

9.8 Appendix 8 Additional information on the quality of life assessment tools extracted from each manuscript in the systematic review.

Author	Title	Brief description of the quality of life tool used, as it is described within the manuscript
Adamelli et al., 2005 [a]	Owner and cat features influence the quality of life of the cat	Questionnaires covered "care", for example: veterinary care and frequency of brushing and "cat behaviour", for example: urinating outside the litter tray and time spent with owner. Each answer was coded into a number and then the sum of these numbers was translated into the category low or medium or high. Each aspect of the physical examination of the cat was also coded onto a numeric scale of 1-3, these aspects were then summed to give a total score. This score was then categorised as low, medium or high. QoL was calculated by adding the numeric values (from questionnaire together to give a total numeric value of QoL. Also, to assess the level of QoL, the combination of the three low, medium or high ratings was considered: an overall low QoL= three low scores or two low scores and one medium. An overall high QoL= three high scores or two high and one medium. All other score combinations= medium QoL.
Adamelli et al., 2004 [a]	Factors influencing the quality of life of the cat in its	Four questionnaires examined the relationship between the cat and the owners, and the influence of factors on the cat's QoL. These covered owner features (age, gender, education, marital status, job

	relationship with owners	family features, place and size of swelling, social relations), cat features (age, gender, breed, neuter status, age of adoption, source, whether lives with other animals), care given to the cat and the cat's behaviour (attachment to the owner, house, soiling, behaviour towards owner and other animals). A score scale was used to codify responses and the sum used to represent: care given to cat, cat behaviour and physical condition. The manuscript states that some owner and some cat features were found to influence the cat's QoL. However, it is not clear from reading this manuscript in isolation how that conclusion was drawn.
Bass et al., 2005	Retrospective study of indications for and outcome of perineal urethrostomy in cats	Asked whether they considered their cat's QoL to be good, acceptable or poor, following surgery.
Benito et al., 2013	Reliability and discriminatory testing of a client-based metrology instrument, feline musculoskeletal pain index	"Feline Musculoskeletal Pain Index": a 21-question tool with one question on overall QoL. The question was a descriptive rating scale with four descriptors: excellent, good, fair, poor.

	(FMPI) for the evaluation of degenerative joint disease-associated pain in cats	
Benito et al., 2012	Owner-assessed indices of quality of life in cats and the relationship to the presence of degenerative joint disease	The questionnaire was modelled from Budke et al., 2008 in which owners they wrote down five activities they believe were important for the cat's QoL. They were then asked to rate the importance of each activity, with the sum total of all the ratings being 100.
Bijsmans et al., 2016 [a]	Psychometric validation of a general health quality of life tool for cats used to compare healthy cats and cats with chronic kidney disease	"CatQoL survey" divided into four domains: general health, eating, behaviour and management, which covered 18 items in total. Each item scored according to the frequency or severity with which it impacted the cat's life (-3 to +3), along with an importance rating for each question (0 to +3). The frequency and importance ratings multiplied to give an item-weighted-impact-score (IWIS). Lowest possible IWIS was -9 and highest possible +9. An average of all the IWIS scores then taken to give an overall quantitative measure of the cat's QoL. An additional question allowed the owner to separately grade their cat's QoL from 0-10 (very poor-

		excellent). A free comments section allowed owners to add anything they wished about their cat's QoL.
Boland et al., 2014	A survey of owners' perceptions and experiences of radioiodine treatment of feline hyperthyroidism in the UK	QoL assessed on a linear analogue scale of 1-10 before and after radioiodine treatment, where 1= very poor and 10 = excellent.
Bowles et al., 2010	Owner's perception of carboplatin in conjunction with other palliative treatments for cancer therapy	QoL rated on a 10 point numerical system where 1= could not be worse and 10= could not be better. This was done for the following times: a) before cancer, b) after diagnosis of cancer but before treatment, c) during treatment with carboplatin.
Brown et al., 2009	Gene therapy by electroporation for the treatment of chronic renal failure in companion animals	Control patients not individually assessed for QoL but the veterinarians felt it was getting worse. In the treated animals the owners were asked to rate their pet's QoL as significantly increased (5); increased (4); no change (3); decreased (2) or significantly decreased (1). This was done four times over the 60-day study period.

Christmann et al., 2016	Effectiveness of a new dietetic weight management food to achieve weight loss in client-owned obese cats	QoL described at each visit by scoring the following criteria on a Likert scale: energy level, happiness, appetite, begging behaviour, flatulence, stool volume. Scores ranged from 0-10, so for example, for happiness, a score of 0 meant sad and a score of 10, meant very happy.
(Fischer et al., 2011b)	Randomized, placebo-controlled study of the effect of propentofyllin e on survival time and quality of life of cats with feline infectious peritonitis	Karnofsky's score modified for cats- see Hartman and Kuffer (1998)
Forster et al., 2010	Owners' observations of domestic cats after limb amputation	Information was collected on the owner's perception of cat's QoL. Also, the owner was asked how long the cat took to reach "best" QoL after the procedure and whether the cat returned to a "normal" QoL after the procedure. In addition, how long it took for the QoL to stop improving.
Fox et al., 2000	Use of cis-bis-neodecanoato	On day 10 after each treatment a "performance status questionnaire" was done, assessing attitude

	-trans-R,R-1,2-diaminocyclohexane platinum (II), a liposomal cisplatin analogue, in cats with oral squamous cell carcinoma	and activity, appetite and weight loss. For each category it appears that owners would select the most appropriate response, e.g. for appetite: eats well without assistance/ eats well with assistance/ force-fed/ will not eat/ requires enteral nutrients. In addition, owners and clinicians evaluated the QoL and if poor, the cats were subjected to euthanasia. Method of evaluation not described.
Freeman et al., 2012 [a]	Development and evaluation of a questionnaire for assessment of health-related quality of life in cats with cardiac disease	Cat's Assessment Tool for Cardiac Health (CATCH) A 17-item questionnaire designed to assess the degree to which the clinical signs of cardiac disease affected the cat's comfort or sociability, graded on a scale of 0-5 where 0= not at all and 5= very much. Responses for each of the items were summed to obtain an overall score where higher scores indicated a poorer health related QoL. Additionally, owners asked to assess overall QoL on a scale of 1-5 where 1 = excellent and 5 = very poor.
Freeman et al., 2016 [a]	Development and initial validation of the Cat HEalth and Wellbeing (CHEW) Questionnaire:	Cat HEalth and Wellbeing (CHEW) questionnaire. Tool contained 11 domains with 100 items, over a seven day recall period, alongside two general questions determining overall HRQoL and overall health status on a five point Likert scale (to be used

	a generic health-related quality of life instrument for cats	for validation and classification). Domains included play, mood, energy, appetite, physique and coat.
Fritsch and Jewell, 2015	Acceptance and effects of a therapeutic renal food in pet cats with chronic kidney disease	Asked at each visit to rate change in QOL since previous visit, on sevenpoint scale from extreme deterioration (7) to extreme improvement (1)
Gates et al., 2017	Preliminary description of aging cats and dogs presented to a New Zealand first opinion veterinary clinic at end-of-life	The presence of clinical signs potentially associated with a decreased QoL (e.g. respiratory impairment, lethargy, recumbency, poor body condition) were noted and whether the patient had chronic disease (e.g. renal failure, blindness, cardiovascular disease) potentially associated with decreased QoL was also noted.
Giuffrida and Kerrigan, 2014	Quality of life measurement in prospective studies of cancer treatments in dogs and cats	This is a review of QoL measurement tools in prospective studies of cancer treatment in cats and dogs. The “Karnofsky’s score modified for cats” tool (Hartmann and Kuffer, 1998) found elsewhere in this search was identified in this manuscript. The identity of other tools found in this 2014 search was unclear from the information provided.

Gostelow et al., 2018 [a]	Prospective evaluation of a protocol for transitioning porcine lente insulin treated diabetic cats to human recombinant protamine zinc insulin	DIAQoL-pet quality-of-life questionnaire for diabetic cats, which generates an average-weighted impact score (AWIS) to reflect pet and owner QoL (see Niessen et al., 2010, below).
Guedes et al., 2018	Evaluation of tramadol for treatment of osteoarthritis in geriatric cats	Global quality-of-life questionnaire which asks whether the cat's life had deteriorated during the study, was the same as before the study, or had improved, compared with QoL before the study.
Hartmann and Kuffer, 1998	Karnofsky's score modified for cats	Karnofsky's score modified for cats: Two parts. Part 1: an owner questionnaire. In this the owner compares the behaviours of the cat now to the behaviour of the cat before disease was noticed and assigned a score (0= behaviour no longer present, 1= shown only rarely, 2= shown half as often as earlier times, 3= almost as often as earlier times, 4= as

		often as earlier times). Each behaviour score is then multiplied by a factor (different for each behaviour) and a number of points are assigned, up to a maximum number. The maximum overall score for part 1= 50. Part 2: observations by the vet. One of six scores is chosen to represent the general condition of the patient (5= completely normal, 4 = minor changes, 3= medium changes, 2= major changes, 1= severely diseased, 0= dead). This score is multiplied by 10 to give a second score of maximum 50. Scores from part one and part two added together and then referenced to the Index of Karnofsky which indicates the QoL, e.g. 100% = normal, no complaints, no evidence of disease.
Hung et al., 2014	Bovine lactoferrin and piroxicam as an adjunct treatment for lymphocytic-plasmacytic gingivitis stomatitis in cats	The owner's perception of the cat's QoL was scored from 1-10 where 1=worst quality of life and 10= the best QoL.
Kooij et al., 2014	Effects of an iodine-	Scored by the veterinary surgeon from 1-5 where 1= very poor and 5 = excellent.

	restricted food on client-owned cats with hyperthyroidism	
Kulendra et al., 2014 [a]	Feline double pigtail ureteric stents for management of ureteric obstruction: short- and long-term follow-up of 26 cats	Assessment by questionnaire, based on DIA-QoL-pet- see Niessen et al., 2010
Lascelles et al., 2007	Evaluation of client-specific outcome measures and activity monitoring to measure pain relief in cats with osteoarthritis	Owner asked if QoL was worse, the same, slightly improved, moderately improved or very improved. This assessment was termed: a "Global Assessment of Quality of Life"
Lynch et al., 2011	Development of a questionnaire assessing	"HRQoL" questionnaire asked owners to state from 1-5 their agreement with 3 statements for 8 domains, e.g. within the domain Happiness, one of the statements reads "My pet wants to play".

	health-related quality-of-life in dogs and cats with cancer	Owners also asked to indicate current QoL from very poor to excellent on a visual assessment scale.
Matei et al., 2017	Nutritional management of overweight and obesity in dogs and cats	States that the QoL was assessed, and that QoL scores improved (scores are quoted in the results from -1 to +1 but it is not explained how these scores were calculated.
Niessen et al., 2010 [a]	Evaluation of a quality-of-life tool for cats with diabetes mellitus	DIAQoL-pet: Twenty-nine diabetes mellitus QoL specific items. For each item, the frequency with which it impacted the owner and pet's lives and how important the item was to the owner and pet were categorised e.g.: all the time/ often/ occasionally and this was translated into a numeric value. The frequency and importance values for each item were multiplied to give a score per item and these scores were averaged across all 29 items to give a single quantitative measure of QoL. An additional two separate overview questions were included: "I feel my pet's quality of life is…." and "If your pet did not have diabetes, his/her quality of life would be….."
Noli et al., 2016 [a]	Development and validation of a	The questionnaire was developed based on the "Dermatology life Quality Index" from human medicine and interviews with owners, to assess the

	questionnaire to evaluate the QoL of cats with skin disease and their owners, and its use in 185 cats with skin disease	impact of skin disease on cat, owner and families' lives and QoL. Answers were scored: 0 (not at all) to 3 (very much). Questionnaire contained 15 items, with seven questions which focussed on the QoL of the cat, covering: mood, sleep, meals, playing/exploring, habit changes, therapies and vet visits.
Pakozdy et al., 2013	Treatment and long-term follow-up of cats with suspected primary epilepsy	Owner evaluated whether the cat's QoL was good/ impaired or bad, based on these definitions: Good= cat's life did not seem to be negatively influenced by the disease or treatment. Impaired= when the disease or treatment had a significant or important negative influence. Bad= when the owner considered euthanasia as result of the disease.
Reynolds et al., 2010	Perceptions of quality of life and priorities of owners of cats with heart disease	Owners asked about the cat's overall QoL and completed a questionnaire on the importance of 8 individual parameters on their cat's QoL. Parameters= appetite, human interaction, interaction with other pets, desire and ability to engage in play, comfort while resting or sleeping, normal grooming activity, appropriate use of the litter box and desire to go outside. These parameters were rated from 1-10 where 1= no importance and 10 = extremely important.

		Owners also asked: 1. Whether administering medication had a harmful effect on the cat's QoL (1= no effect to 10= extreme effect) 2. About the balance between giving medications to maintain or improve QoL but at the same time potentially reduce life expectancy, what would the owners consider the ideal balance? (1= low QoL but long lifespan to 10= high QoL but short lifespan.
Ritz et al., 2007	Effect of feline interferon-omega on the survival time and quality of life of cats with feline infectious peritonitis	Karnofsky's score modified for cats.
Ruda and Heiene, 2012	Short- and long-term outcome after perineal urethrostomy in 86 cats with feline lower urinary tract disease	Overall QoL after surgery graded from 1-3.
Rush et al., 2015 [a]	Assessment of the responsiveness of the Cats' Assessment	CATCH- see Freeman et al., 2012

	Tool for Cardiac Health (CATCH) Questionnaire	
Sabhlok and Ayl, 2014	Palliative radiation therapy outcomes for cats with oral squamous cell carcinoma (1999-2005)	Owner subjective assessments made of post-treatment QoL, based on: an observable decrease in tumour size, an improved ability to eat and return to grooming.
Taffin et al., 2016 [a]	Evaluation of a modified Karnofsky score to assess physical and psychological well-being of cats in a hospital setting	Karnofsky's score (see Hartmann and Kuffer, 1998) with some aspects removed as not pertinent to hospital setting, for example: catching mice.
Tatlock et al., 2017 [a]	Development and preliminary psychometric evaluation of an owner-completed	A 22 -item questionnaire which covered seven domains on the topics of: interaction with surroundings and humans, gastrointestinal signs, physical activity, vocalisation, appetite, sleeping, pain, general health, toileting habits, hydration, weight loss, grooming and general happiness. Each item was rated for the preceding four week period

	measure of feline quality of life	using a five point Likert scale, from “not at all” or “strongly disagree, up to: “a great deal” or “very much” or “strongly agree”.
Theobald et al., 2013	Clinical outcome in 19 cats with clinical and magnetic resonance imaging diagnosis of ischaemic myelopathy (2000-2011)	Owner perception of QoL, no scale given. Reported as “poor” for some cases and for other cases, that the QoL negated the need for clinical re-evaluation.
Tzannes et al., 2008	Owners 'perception of their cats' quality of life during COP chemotherapy for lymphoma	Using a linear analogue scale, owners were asked to rate their cat’s QoL on a scale of 1-10 (1= QoL could not be worse, 10 = QoL could not be better) pre-cancer, after diagnosis but before chemotherapy treatment, and during chemotherapy treatment. Owners also asked to rate how they thought the cat perceived their own QoL, identify aspects they considered important to their cat’s QoL and describe the cat’s experience of chemotherapy as “all good days”, “more good days than bad days”, “more bad days than good days” or “all bad days”.

Williams et al., 2017	Factors which influence owners when deciding to use chemotherapy in terminally ill pets	QoL rated by owners on a scale from 1 (low) to 10 (high) and embedded within a questionnaire, alongside other key themes. Owners were asked to rate the potential impact of chemotherapy on 13 statements, as acceptable or unacceptable, to assess the impact of chemotherapy on QoL. For example: "My pet does not play during chemotherapy". Other statements covered drinking, eating grooming, activity, awareness, trembling, sleeping, good days vs bad days, play behaviour, depression and diarrhoea.

9.9 Appendix 9 Data Sharing Agreement Between CEVM and Practice Management System

University of Nottingham
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Represented by its

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School of Veterinary Medicine and Science

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Company Number: 03481736

Unit 4, Mowat Industrial Estate,

Sandown Road,

431

Watford,

Hertfordshire, WD24 7UY

We, Medivet Group Ltd ("Medivet"), have agreed that we will deliver to the University of Nottingham's Centre for Evidence-based Veterinary Medicine (CEVM) the following veterinary practice data, for the following purpose:

PhD Research project: Methods and feasibility of conducting pragmatic clinical trials in small animal first opinion practice.

Dates of data extract: 1st January 2019- 30th June 2019 inclusive.

Researchers who will access the data: Hannah Doit (PhD Researcher)

Dr Marnie Brennan (PhD supervisor)

Dr Marco Duz (PhD supervisor)

Professor Richard Emes (PhD supervisor)

Dr Phillip Quinlan (Advanced Data Analysis Centre)

Dr David May (Database and data processing consultant)

- We will deliver data from our veterinary practices for the dates specified, to provide data for the PhD project described above, to help the CEVM build their clinical trials network and enable delivery of clinical data to enable research to fill existing gaps in knowledge in veterinary practice.

- The data will be delivered from all Medivet Group Ltd practices at no cost to the CEVM.

- The sharing of non-Personally Identifiable Information for clinical epidemiology research purposes is covered by the standard Medivet privacy policy.

- Medivet clients will be able to opt out of their data being used for any non-operational purposes, including this one. Should this occur, Medivet will supply CEVM with the Animal ID number and Practice ID number of the relevant animals. CEVM will then permanently remove those animals from the dataset.

- Only fields outlined in the Clinical Evidence Schema Rev.23 will be provided to the CEVM. Schedule 1 sets out the Clinical Evidence Schema Rev.23 as mapped to Medivet's PMS.

- Medivet will provide the data extracts for the dates stated above. Each data extract will contain the full 6 months of data, for each veterinary practice involved. The data extract will be provided to CEVM following the instructions and security standards set out in Schedule 2: Data Collection Instructions.

- The field "Entered By ID" will be delivered to the CEVM only as a reference number and will only be used to ascertain the type of interaction being

recorded in the data. No attempts will be made to identify the name of the individual entering the data.

- Before the data is used for research, every effort will be made to remove any personal data that appears in non-personal data fields. Once personal data has been redacted from these fields, the original unredacted xml file will be permanently removed by CEVM.

- The data is provided, and the PhD Research Project is undertaken in pursuit of the primary charitable objectives of the CEVM; that is the advancement of education through research and teaching. Medivet acknowledges that the results of the PhD Research Project shall belong to the CEVM (except that Medivet retains ownership of the data to the extent incorporated or included within the results), and that the CEVM may seek to publish the results of the PhD Research Project. This letter agreement shall not prevent or hinder registered students of the University of Nottingham from submitting for degrees theses based on results obtained during the course of work undertaken as part of the PhD Research Project; or from following the University of Nottingham's procedures for examinations and for admission to postgraduate degree status.

- The CEVM shall procure that in relation to any publication reporting on the results of the PhD Research Project, the publishing researcher acknowledges Medivet as the source of the data in the publication (unless otherwise instructed by Medivet) and the CEVM will state openly that they are working with the Society for Practising Veterinary Surgeons (SPVS) VetXML Consortium and Medivet Group Ltd.

- The individual practices, animals and clients involved in this research will not be publicly identified by the CEVM.

- No financial information from the practices will be delivered to the CEVM

- The data will be delivered to a secure database that only the CEVM named researchers will have access to and will be stored in line with data protection legislation.

- The data will only be accessed by the named researchers for the purposes of the PhD research described above. Any other person wishing to use the data for research must first be approved by Medivet Group Ltd and the CEVM.

- In the event of an actual or suspected data incident involving Medivet data experienced by the CEVM or any of the named researchers, In the event of an actual or suspected data incident involving Medivet data experienced by the CEVM or any of the named researchers, CEVM will inform Medivet as soon as a data breach has been identified. This will be in the form of an email to the Chief Data Officer and Data Protection Officer at Medivet (currently _____ and_____) including information on the nature and severity of the breach. The nominated contact for such a data incident is the responsible person for data protection at Medivet as set out in this agreement (below). CEVM and the University of Nottingham will provide all necessary assistance to Medivet to determine the extent and risk proposed by any such data incident.

- Medivet and CEVM will each retain a copy of the data extract provided to the CEVM for 1 month after transfer to enable any queries regarding the quality of the data to be addressed. CEVM will retain the clinical data

provided to them in the Clinical Trials database for the duration set out in this letter agreement, subject to any termination clauses.

- The data will be retained in the CEVM secure database for a period of 7 years, after which time it will be permanently removed by CEVM.

- Where data which is capable of directly or indirectly identifying an individual is provided by the Medivet Group Ltd to CEVM in line with the Clinical Evidence Schema Rev.23, this is considered personal data for the purposes of the EU General Data Protection Regulations 2016/679, the Data Protection Act 2018 (collectively the "Data Protection Law") and any superceding legislation (the data protection legislation). Each party agrees that they act as a data controller for this information, in respect of its own processing of the data in connection with this letter agreement, and shall be solely responsible and liable for its own processing of the data including (without limitation) the lawful basis for that processing and ensuring that the data is processed in compliance with the Data Protection Law and, where applicable have in place sufficient consents and notices to use this information. Where either party receives a request under GDPR in relation to this data, they notify the other party and provide assistance to ensure that any such request is dealt with in the timeframes set out in the GDPR.

- For the avoidance of doubt, Medivet Group Ltd keeps the ownership of its clinical data generated and data transferred from Medivet Group Ltd to the CEVM, and Medivet Group Ltd has the right to use such clinical data for any purposes. If the CEVM wishes to use the data containing any clinical data generated and transferred from Medivet Group Ltd to the CEVM for commercial exploitation, the CEVM shall consult with Medivet Group Ltd in good faith to determine how such commercial development and exploitation might be undertaken between them. Medivet will not delay or withhold giving such consent unreasonably.

- At the CEVM, Dr Marnie Brennan or Hannah Doit will be responsible for the protection of the data.

- At Medivet Group Ltd, the designated Data Protection Officer (currently_____) will be responsible for the protection of the data.

- This letter agreement constitutes the entire agreement between the parties. A person who is not a party to this letter agreement shall not have any rights under or in connection with it.

- The parties shall procure that in carrying out their obligations under this letter agreement, they will comply with all applicable laws, regulations and statutes, including those relating to modern slavery and anti-bribery. English law shall apply to this letter agreement, and the English courts shall have exclusive jurisdiction over any matter relating to it.

For and on behalf of Medivet Group Ltd

Signature:_____

Print Name:_____

Date:_____

For and on behalf of The University of Nottingham

Signature:_____ (

Print Name:_____

Date:_____

Schedules follow

Schedule 1: Clinical Evidence Schema Rev.23

Schedule 1 Clinical Evidence Schema Re

Schedule 2: Data Collection Instructions

- The data will be delivered to the CEVM in batches of six month's data per batch.
- The data will be uploaded to a dedicated container space on Microsoft Azure.

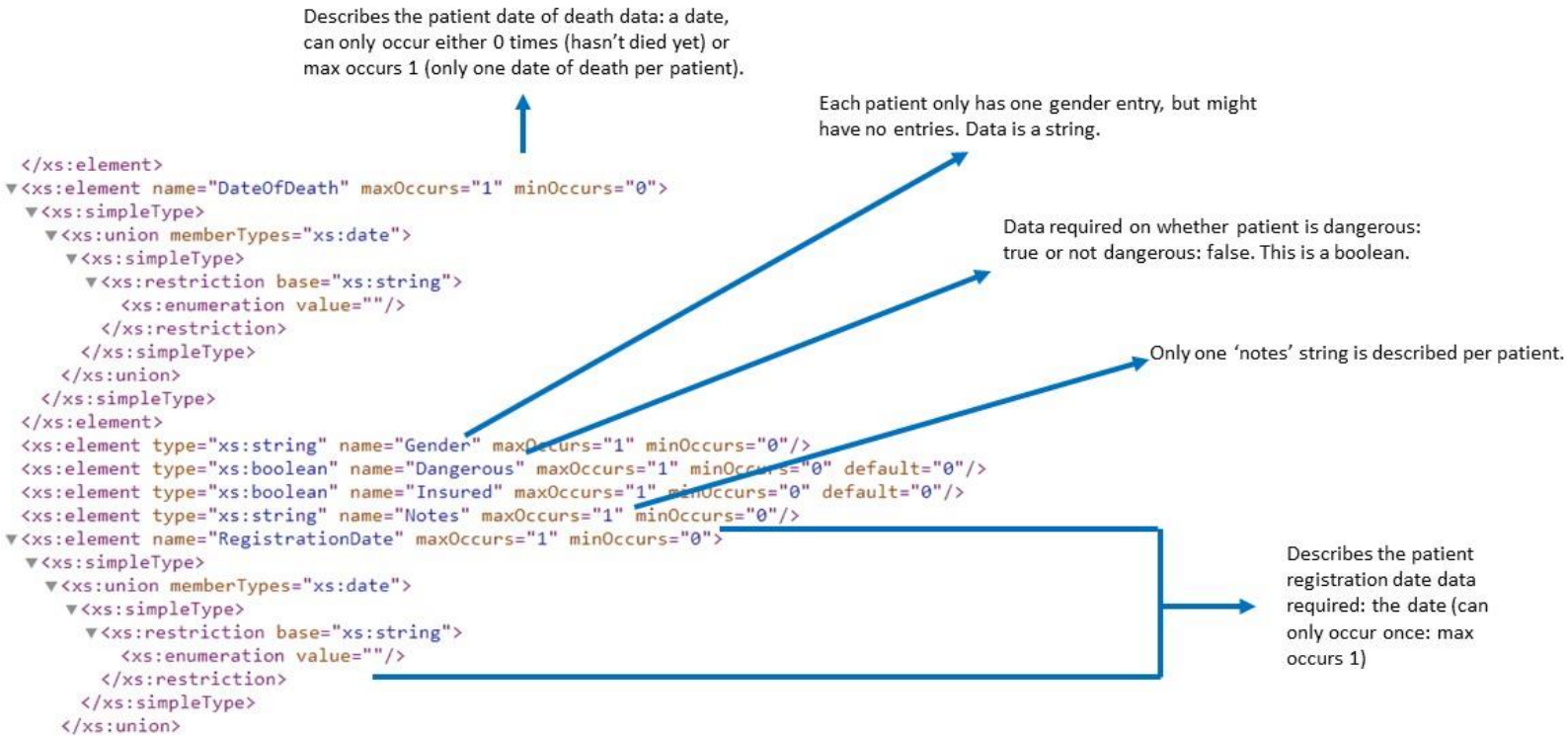
- This container will be held within a dedicated storage account created for the Medivet Freedom PMS.
- Access to upload the data is provided by use of a Connection String via the Microsoft Azure Storage Explorer App.
- Only the named researchers at CEVM as set out in the data sharing agreement, and _____ and _____ at Medivet will have access to the Connection String.
- The data transfer and storage process will both be encrypted for security.

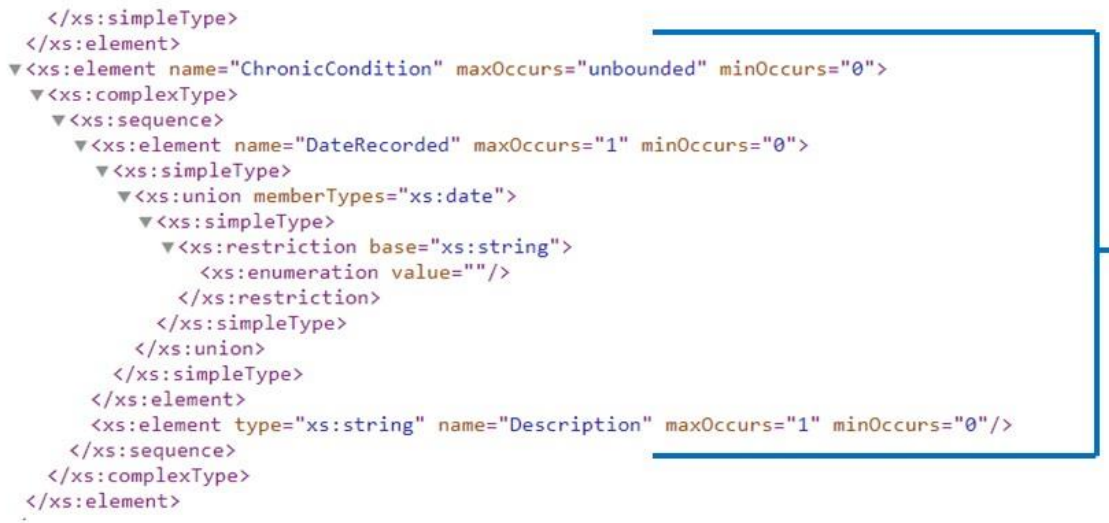
9.10 Appendix 10 Formatting Tags which were removed and replaced

Formatting tags within the free text which were not required and would cause problems with the text analysis, so were removed and replaced. The tags were created within the PMS interface and are used for text formatting.

Remove this tag if present	Replace with this
and 	“line feed”
< >	
, /a, </br>, <tr>, </tr>, <td>, </td>, , , , , , , (,)	non required
*	single space “ “
&lt, &gt, (these are rendered by browsers as arrows)	single space “ “ (these are the < and > brackets)
[finally] &	“and”
< > brackets and then the following terms which were inside the brackers (remnants of XML mark-up terms) andamp, span, style, strong, align, width, p, /p, em, /em, tr, /tr, td, /td, br, /br	non required

9.11 Appendix 11 Revised schema version 23 with explanation of features


Describes the patient date of death data: a date, can only occur either 0 times (hasn't died yet) or max occurs 1 (only one date of death per patient).
Each patient only has one gender entry, but might have no entries. Data is a string.
Data required on whether patient is dangerous: true or not dangerous: false. This is a boolean.
Only one 'notes' string is described per patient.
Describes the patient registration date data required: the date (can only occur once: max occurs 1)
</xs:element>
<xs:element name="DateOfDeath" maxOccurs="1" minOccurs="0">
<xs:simpleType>
<xs:union memberTypes="xs:date">
<xs:simpleType>
<xs:restriction base="xs:string">
<xs:enumeration value=""/>
</xs:restriction>
</xs:simpleType>
</xs:union>
</xs:simpleType>
</xs:element>
<xs:element type="xs:string" name="Gender" maxOccurs="1" minOccurs="0"/>
<xs:element type="xs:boolean" name="Dangerous" maxOccurs="1" minOccurs="0" default="0"/>
<xs:element type="xs:boolean" name="Insured" maxOccurs="1" minOccurs="0" default="0"/>
<xs:element type="xs:string" name="Notes" maxOccurs="1" minOccurs="0"/>
<xs:element name="RegistrationDate" maxOccurs="1" minOccurs="0">
<xs:simpleType>
<xs:union memberTypes="xs:date">
<xs:simpleType>
<xs:restriction base="xs:string">
<xs:enumeration value=""/>
</xs:restriction>
</xs:simpleType>
</xs:union>

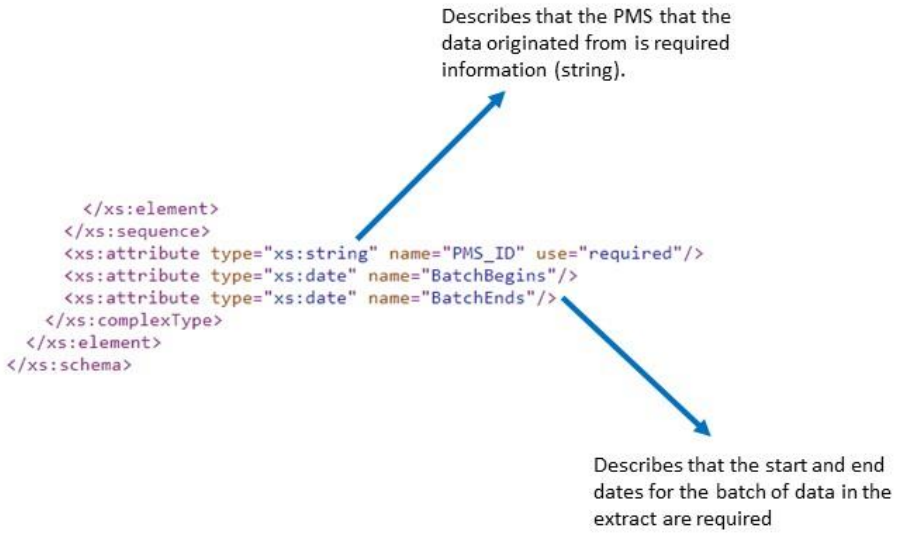

Describes the required chronic condition data: date recorded and description (string). There is no limit to the number of chronic conditions per patient (max occurs unbounded) and there is no minimum number of entries (min occurs 0).

The following nested parts of the schema describe the data required from the patient clinical history.

```
</xs:element>
<xs:element name="ClinicalHistory" maxOccurs="1" minOccurs="0">
  <xs:complexType>
    <xs:sequence>
      <xs:element name="History" maxOccurs="unbounded" minOccurs="0">
        <xs:complexType>
          <xs:sequence>
            <xs:element type="xs:dateTime" name="HistoryDateTime" maxOccurs="1" minOccurs="0"/>
            <xs:element type="xs:string" name="EnteredByID" maxOccurs="1" minOccurs="0"/>
            <xs:element type="xs:string" name="ClinicalNotes" maxOccurs="1" minOccurs="0"/>
            <xs:element type="xs:string" name="Diagnosis" maxOccurs="1" minOccurs="0"/>
            <xs:element type="xs:integer" name="DiagnosisVeNomCode" default="0" maxOccurs="1" minOccurs="0"/>
          </xs:sequence>
        </xs:complexType>
      </xs:element>
      <xs:element name="Parameters" maxOccurs="unbounded" minOccurs="0">
        <xs:complexType>
          <xs:sequence>
            <xs:element type="xs:date" name="ParametersDate" maxOccurs="1" minOccurs="0"/>
            <xs:element type="xs:decimal" name="Weight" default="0.0" maxOccurs="1" minOccurs="0"/>
            <xs:element type="xs:string" name="WeightUnit" maxOccurs="1" minOccurs="0"/>
            <xs:element type="xs:string" name="WeightNotes" maxOccurs="1" minOccurs="0"/>
            <xs:element type="xs:integer" name="BodyConditionScore" default="0" maxOccurs="1" minOccurs="0"/>
            <xs:element type="xs:integer" name="MuscleConditionScore" default="0" maxOccurs="1" minOccurs="0"/>
          </xs:sequence>
        </xs:complexType>
      </xs:element>
    </xs:sequence>
  </xs:complexType>
</xs:element>
```

Describes the required clinical history data: date and time of entry, who entered the data (string), the free text clinical notes (string), diagnosis and VeNom code (integer). There is no limit to the number of history entries per patient (max occurs unbounded) and there is no minimum number of entries (min occurs 0).

Describes the required parameters data: the date the entry was recorded, if weight- the weight number (as a decimal), units and notes (a string), or if body condition score or muscle condition score the number given (data type is an integer). All parameters read '0' by default if no entry made. There is no limit to the number of parameters entries per patient (max occurs unbounded) and there is no minimum number of entries (min occurs 0)


Describes that the PMS that the data originated from is required information (string).
</xs:element>
</xs:sequence>
<xs:attribute type="xs:string" name="PMS_ID" use="required"/>
<xs:attribute type="xs:date" name="BatchBegins"/>
<xs:attribute type="xs:date" name="BatchEnds"/>
</xs:complexType>
</xs:element>
</xs:schema>
Describes that the start and end dates for the batch of data in the extract are required

9.12 Appendix 12 Short word list

AG,ALK,ALP,ALT,ARAA,AST,B12,B9,BAR,BCS,BCS,BID,BIOP,BP,BPM,CBA,CE,CE,CKD,CKI,COB,CRF,CTEA,DLH,DSH,DUDE,DX,EDDU,EDUD,FGF23,FOL,FPL,fPL,GFR,GT,HBC,HCT,HGB,HR,IDEXX,IGF1,IRIS,IV,IVFT,K/D,L/KI,LAO,MCS,MMHG,NAD,NF,NGAL,NSAID,NVMB,PARR,PCR,PCV,PO,PR,PTH,PTS,QID,R2HPTH,RBC,RBCs,RBP,RC,RCW,RF,RR,RTA,SDMA,SG,SID,SIN,STO,T4,TID,TLI,TLI/FOL/COB,TPR,TT4,UPC,UPCR,USG,WNL

9.14 Appendix 13 Long word list

Abdomen,Abdominal,Absorp,Accurate,Acid,acute,Administer,Adult,Adverse,Albumin,Aldosterone,Alert,Amlodipine,Amodip,Appetite,Appropriate,Appropriate,Assay,Associat,Autopsy,Azotae,Beaphar,Behaviour,Benazepril,Benign,Bile,Bilirubin,Biochem,Biomarkers,Biop,Bleed,Blood,Blood,Bodyweight,Calcium,Canine,Carbon,Cardiac,Castrate,Cataract,Cell,Chest,Chlori,Cholesterol,Chromatin,Chronic,Clearance,Clinic,Clot,Clusterin,Coat,Cobalamin,Complete,Condition,Constipation,Count,Creased,Creatinine,Crine,CTEA,Culture,Cystatin,Damage,Date,Death,Decreas,Defaecat,Dehydrated,Demeanour,Diagnosis,Diarrhoea,Diet,Dihydroxycholecalciferol,Dimethylarginine,Dioxide,Discomfort,Disease,Dose,Drink,Drip,drop,Drug,Dysfunction,Eating,EDDU,EDUD,Efficacy,Electrolyte,ELISA,Emaciated,Endocrin,Erythrocyte,Eukanuba,Euthanasia,Exam,excret,Excretion,Exercise,Failure,Failure,fast,Feed,Feline,Filtration,Fluid,Folate,folate,Food,Fortekor,Function,Fur,g/d,g/l,Gamma,Gingivitis,Globulin,Glucose,Gold,Gravity,Group,Guideline,Haem,Halitosis,Heart,hepatic,Hgb,High,Hills,Histology,Hormone,Hospital,hour,Hydration,Hyper,Hyper,IGF1,Increas,indicat,Interpret,intestin,Inulin,Ionised,Ipakitine,IRIS,Istin,IVFT,Kaminox,Ketonic,Kidney,l/l,Laboratory,leuco,Leukocytes,level,Life,like,limit,lipase,little,Liver,Low,Loxicom,Lung,lymph,Male,Medicine,Meds,Meloxicam,Membrane,Mentation,Metabolism,Metacam,Mineralisain,Mirtazipine,MMHG,Mucous,Murmur,Muscle,Nausea,Negative,Nephrocalcinosis,Nerve,Neurological,Neuter,NGAL,Nitrites,normal,NSAID,Nutri,Ocular,often,ophil,organic,Overnight,Owner,Pain,palp,Palpable,Palpation,Pancrea,pancrea,Patholog,Patient,Pedigree,Phosphatase,Phosphate,Phosphorus,Phosphorus,Phosphorus,pipette,Plasma,Platelet,Please,Positive,Potass,Prescription,Pressure,Prinovox,Profile,Prognosis,Progression,Pronefra,Proplan,Protein,Pyelonephritis,Quality,R2HPTH,Radiograph,Range,Ratio,recommend,reduc,Reference,relate,Renal,Renate,Renin,Report,Requested,Restricted,result,retin,s/e,Sampl,Score,Screen,SDMA,Secondary,Sediment,Semintra,serum,sgot,sgpt,significan,Skin,small,Sodium,Spay,spec,stable,Stage,status,submi,sufficien,Supplement,Support,support,Supportive,Survival,suspect,Symmetric,Symptomatic,tablet,teeth,Telmisartan,Tempt,Tent,Test,Thirst,Thyroid,Time,Tissue,Total,Total,Transferrin,Treat,Treatment,troph,Tubule,Ultrasound,Unis,unit,UPCR,uraemic,Urea,Urin,urobilinogen,value,Vitamin,volume,voluntary,Vomiting,Weakness,weigh,Well being,White

9.15 Appendix 14 Syntax corrections made to XML files

Syntax corrections made to the XML files where tags were incorrectly named, incorrect data types were used, and data formatting was incompatible with the schema and database.

- Where a date of death was entered as “yes” or “no” it was changed to “NULL”
- Where insurance entries were yes/no these were changed to 1 or 0 (Boolean format)
- Some data elements were missing and had been incorrectly written in the .xml files, e.g. <RegistrationDate /> which was changed to <RegistrationDate></RegistrationDate> which is the correct syntax to show the element opening and then closing with no data provided inbetween.
- Some elements were mislabelled and had to be changed so they conformed to the schema, e.g. <ChronicConditionDescription> became <Description>
- Empty chronic conditions fields were filled with the term “non recorded”
- Multiple, undated chronic condition entries for an individual animal were compiled into one chronic condition entry
- Where the ChronicCondition or ParametersDate field date was not filled in, the registration date for the patient was used instead
- Where the RegistrationDate was empty, it was filled with “0000-00-00”
- The weight entry formatting was corrected to 000.00 format
- Additional data fields for ChronicCondition and HistoryDateTime from feline_history which were too long were trimmed to more appropriate character lengths
- Where there were duplicate 'HistoryDateTime' entries for a patient (due to rapid PMS uploading) then the value of the last second was dithered to create unique times

9.16 Appendix 15 Script for how many cats are registered at more than one practice

```
# How many cats are registered at more than one practice? v 28th Sept

USE rev23_282;

# Basic statistics: How many entries in the feline_overview table, and
how many are distinct cats (not duplicated across practices)
SELECT COUNT(animalid) 'Number of entries in feline_overview' FROM
feline_overview;
SELECT COUNT(DISTINCT animalid) 'Number of distinct cats' FROM
feline_overview;
SELECT (COUNT(animalid) - COUNT(DISTINCT animalid))/COUNT(animalid) *
100 'Percentage registered more than once' FROM feline_overview ;

# Count how many times each animalid occurs (ie how many practices the
cat has registered with).
# The animalid countis called number_of_practices
CREATE TEMPORARY TABLE temp1
SELECT COUNT(animalid) AS 'number_of_practices', animalid FROM
feline_overview
GROUP BY animalid ORDER BY COUNT(animalid) DESC;

# Show a few examples from temp1
SELECT * FROM temp1 LIMIT 10;

# Count how many examples of multiple registrations exist
# NB The sum of the products of number_of_practices * instances =
number of entries in feline_overview
CREATE TEMPORARY TABLE temp2
SELECT COUNT(number_of_practices) AS 'instances', number_of_practices
FROM temp1 GROUP BY number_of_practices ORDER BY
COUNT(number_of_practices
);

# Show the statistics
SELECT instances,number_of_practices FROM temp2;
```

9.17 Appendix 16 Most common cat breeds recorded

```
# Count the number of each breed in feline_overview
# v 3rd Nov 2020 using cats table

use rev23_282;

CREATE TEMPORARY TABLE cat_count
SELECT COUNT(breed) AS 'breed_total', breed FROM cats GROUP BY breed
ORDER BY COUNT(breed);

SELECT * FROM cat_count ORDER BY breed_total DESC LIMIT 30;
```

9.18 Appendix 17 Gender and neuter status of all cats which die during the study

```
# Find the ages of cats when CKD was first mentioned v 3rd Oct

Use rev23_282;
SELECT COUNT(animalid) INTO @studycats FROM cats WHERE dateofbirth >
'1988-07-01';
SELECT @studycats 'Number of cats in study with real ages';
SELECT COUNT(animalid) INTO @ckdcats FROM ckd INNER JOIN cats USING
(animalid) WHERE dateofbirth > '1988-07-01';
SELECT @ckdcats 'Number of ckd cats in study with real ages';

#-----------------------------------------------------------------------
--------

# Find all the cats that died during the study (NB 'cats' table does
not contain cats that were dead before the study)
CREATE TEMPORARY TABLE cat_died
SELECT * FROM cats
WHERE dateofdeath IS NOT NULL
AND dateofdeath < '2019-07-01'
;
SELECT COUNT(animalid) INTO @deadmale FROM cat_died WHERE gender =
'Male';
SELECT @deadmale 'Number & % of Males',
TRUNCATE(@deadmale/@studycats*100,1);

SELECT COUNT(animalid) INTO @deadfemale FROM cat_died WHERE gender =
'Female';
SELECT @deadfemale 'Number & % of Females',
TRUNCATE(@deadfemale/@studycats*100,1);

SELECT COUNT(animalid) INTO @deadmaleneut FROM cat_died WHERE gender =
'Male - Neutered';
SELECT @deadmaleneut 'Number & % of Neutered Males',
TRUNCATE(@deadmaleneut/@studycats*100,1);

SELECT COUNT(animalid) INTO @deadfemaleneut FROM cat_died WHERE gender
= 'Female - Neutered';
SELECT @deadfemaleneut 'Number & % of Neutered Females',
TRUNCATE(@deadfemaleneut/@studycats*100,1);


# Find all the ckds that died during the study
CREATE TEMPORARY TABLE ckd_died
SELECT animalid, historydatetime, dateofbirth, dateofdeath FROM ckd
INNER JOIN cats USING (animalid)
WHERE dateofdeath IS NOT NULL
AND dateofdeath < '2019-07-01'
;
SELECT COUNT(animalid) INTO @deadckd FROM ckd_died;
SELECT @deadckd 'Number & % of ckd that died',
TRUNCATE(@deadckd/@ckdcats*100,1);
```

```
# Find all not-ckd cats that died during study
CREATE TEMPORARY TABLE notckd_died
SELECT * FROM cat_died
WHERE cat_died.animalid NOT IN (SELECT ckd_died.animalid FROM ckd_died)
;
SELECT COUNT(animalid) INTO @deadnotckd FROM notckd_died;
SELECT @deadnotckd 'Number & % of not-ckd cats that died',
TRUNCATE(@deadnotckd/@studycats*100,1);

#----------------------------------------OUTPUTS----------------------
------------

SELECT 'Age at death for male cats';
CREATE TEMPORARY TABLE catstat
SELECT animalid, TRUNCATE(DATEDIFF(dateofdeath,dateofbirth)/365,0) As
'Lifespan' FROM cat_died
WHERE gender = 'Male'
;
SELECT TRUNCATE(Count(animalid)/@deadmale*100,1), Lifespan FROM catstat
GROUP BY Lifespan ORDER BY Lifespan ASC;
DROP TABLE catstat;

SELECT 'Age at death for female cats';
CREATE TEMPORARY TABLE catstat
SELECT animalid, TRUNCATE(DATEDIFF(dateofdeath,dateofbirth)/365,0) As
'Lifespan' FROM cat_died
WHERE gender = 'Female'
;
SELECT TRUNCATE(Count(animalid)/@deadfemale*100,1), Lifespan FROM
catstat GROUP BY Lifespan ORDER BY Lifespan ASC;
DROP TABLE catstat;

SELECT 'Age at death for male neutered cats';
CREATE TEMPORARY TABLE catstat
SELECT animalid, TRUNCATE(DATEDIFF(dateofdeath,dateofbirth)/365,0) As
'Lifespan' FROM cat_died
WHERE gender = 'Male - Neutered'
;
SELECT TRUNCATE(Count(animalid)/@deadmaleneut*100,1), Lifespan FROM
catstat GROUP BY Lifespan ORDER BY Lifespan ASC;
DROP TABLE catstat;

SELECT 'Age at death for female neuteredcats';
CREATE TEMPORARY TABLE catstat
SELECT animalid, TRUNCATE(DATEDIFF(dateofdeath,dateofbirth)/365,0) As
'Lifespan' FROM cat_died
WHERE gender = 'Female - Neutered'
;
SELECT TRUNCATE(Count(animalid)/@deadfemaleneut*100,1), Lifespan FROM
catstat GROUP BY Lifespan ORDER BY Lifespan ASC;
DROP TABLE catstat;



#SELECT 'Age at death for ckd cats';
#CREATE TEMPORARY TABLE ckdstat
```

```
#SELECT animalid, TRUNCATE(DATEDIFF(dateofdeath,dateofbirth)/365,0) As
'Lifespan' FROM ckd_died
#;
#SELECT TRUNCATE(Count(animalid)/@deadckd*100,1), Lifespan FROM ckdstat
GROUP BY Lifespan ORDER BY Lifespan ASC;


#SELECT 'Age at death for not-ckd cats';
#CREATE TEMPORARY TABLE notckdstat
#SELECT animalid, TRUNCATE(DATEDIFF(dateofdeath,dateofbirth)/365,0) As
'Lifespan' FROM notckd_died
#;
#SELECT TRUNCATE(Count(animalid)/@deadnotckd*100,1), Lifespan FROM
notckdstat GROUP BY Lifespan ORDER BY Lifespan ASC;
```

9.19 Appendix 18 The CKD script, reports the number of cats with chronic kidney disease in the dataset

```
# Extract distinct cats with CKD (template) 23rd March 2021
# Create tables 'cats' and 'ckd' which are used in place of
feline_overview
# Exclude cats with unreal dateofbirth & exclude cats that die before
the study & include only one record per animal
# Exclude cats with AKI or pre-renal or pre renal or acute kidney


Use rev23_282;
DROP TABLE IF EXISTS cats;
DROP TABLE IF EXISTS ckd;
DROP TABLE IF EXISTS ckd2;
DROP TABLE IF EXISTS aki;

CREATE TABLE cats
SELECT * FROM feline_overview
WHERE (dateofdeath > '2018-12-31' OR dateofdeath IS NULL)
AND dateofbirth > '1988-07-01'
GROUP BY animalid
;
CREATE INDEX anid ON cats(animalid);

# Report how many distinct cats are on the database
SELECT COUNT(animalid) 'Number of distinct cats' FROM cats;

# Select all the records that have kidney terms in the clinical notes
(in date order)
CREATE TEMPORARY TABLE temp_ckd
SELECT cats.animalid, feline_history.historydatetime FROM
feline_history
INNER JOIN cats USING (animalid)
WHERE (feline_history.ClinicalNotes LIKE '% CKD%')

# 23.3.21 do not include cats with capilliary refill in CRF notes
OR (feline_history.clinicalnotes LIKE '% CRF%' AND clinicalnotes NOT
LIKE '% CRF__s%')
OR (feline_history.ClinicalNotes LIKE '% CKF%')

OR (feline_history.ClinicalNotes LIKE '%kidney dx%')
OR (feline_history.ClinicalNotes LIKE '%kidney dz%')
OR (feline_history.ClinicalNotes LIKE '%kidney dis%')
OR (feline_history.ClinicalNotes LIKE '%kidney deteriorat%')
OR (feline_history.ClinicalNotes LIKE '%kidney fail%')
OR (feline_history.ClinicalNotes LIKE '%kidney ins%')
OR (feline_history.ClinicalNotes LIKE '%kidney failure%')

OR (feline_history.ClinicalNotes LIKE '%kideny dx%')
OR (feline_history.ClinicalNotes LIKE '%kideny dz%')
OR (feline_history.ClinicalNotes LIKE '%kideny dis%')
OR (feline_history.ClinicalNotes LIKE '%kideny deteriorat%')
OR (feline_history.ClinicalNotes LIKE '%kideny fail%')
OR (feline_history.ClinicalNotes LIKE '%kideny ins%')
OR (feline_history.ClinicalNotes LIKE '%kideny failure%')
```

```
OR (feline_history.ClinicalNotes LIKE '%kiddney dx%')
OR (feline_history.ClinicalNotes LIKE '%kiddney dz%')
OR (feline_history.ClinicalNotes LIKE '%kiddney dis%')
OR (feline_history.ClinicalNotes LIKE '%kiddney deteriorat%')
OR (feline_history.ClinicalNotes LIKE '%kiddney fail%')
OR (feline_history.ClinicalNotes LIKE '%kiddney ins%')
OR (feline_history.ClinicalNotes LIKE '%kiddney failure%')

OR (feline_history.ClinicalNotes LIKE '%kidnay dx%')
OR (feline_history.ClinicalNotes LIKE '%kidnay dz%')
OR (feline_history.ClinicalNotes LIKE '%kidnay dis%')
OR (feline_history.ClinicalNotes LIKE '%kidnay deteriorat%')
OR (feline_history.ClinicalNotes LIKE '%kidnay fail%')
OR (feline_history.ClinicalNotes LIKE '%kidnay ins%')
OR (feline_history.ClinicalNotes LIKE '%kidnay failure%')

OR (feline_history.ClinicalNotes LIKE '%kidny dx%')
OR (feline_history.ClinicalNotes LIKE '%kidny dz%')
OR (feline_history.ClinicalNotes LIKE '%kidny dis%')
OR (feline_history.ClinicalNotes LIKE '%kidny deteriorat%')
OR (feline_history.ClinicalNotes LIKE '%kidny fail%')
OR (feline_history.ClinicalNotes LIKE '%kidny ins%')
OR (feline_history.ClinicalNotes LIKE '%kidny failure%')

OR (feline_history.ClinicalNotes LIKE '%kidnies dx%')
OR (feline_history.ClinicalNotes LIKE '%kidnies dz%')
OR (feline_history.ClinicalNotes LIKE '%kidnies dis%')
OR (feline_history.ClinicalNotes LIKE '%kidnies deteriorat%')
OR (feline_history.ClinicalNotes LIKE '%kidnies fail%')
OR (feline_history.ClinicalNotes LIKE '%kidnies ins%')
OR (feline_history.ClinicalNotes LIKE '%kidnies failure%')

OR (feline_history.ClinicalNotes LIKE '%kidey dx%')
OR (feline_history.ClinicalNotes LIKE '%kidey dz%')
OR (feline_history.ClinicalNotes LIKE '%kidey dis%')
OR (feline_history.ClinicalNotes LIKE '%kidey deteriorat%')
OR (feline_history.ClinicalNotes LIKE '%kidey fail%')
OR (feline_history.ClinicalNotes LIKE '%kidey ins%')
OR (feline_history.ClinicalNotes LIKE '%kidey failure%')

OR (feline_history.ClinicalNotes LIKE '%renal dx%')
OR (feline_history.ClinicalNotes LIKE '%renal dz%')
OR (feline_history.ClinicalNotes LIKE '%renal dis%')
OR (feline_history.ClinicalNotes LIKE '%renal deteriorat%')
OR (feline_history.ClinicalNotes LIKE '%renal fail%')
OR (feline_history.ClinicalNotes LIKE '%renal ins%')
OR (feline_history.ClinicalNotes LIKE '%renal failure%')

ORDER BY historydatetime ASC
;

# Select animalid and earliest ClinicalNotes record
CREATE TEMPORARY TABLE ckd2
SELECT * FROM temp_ckd
GROUP BY animalid
```

```
;
CREATE INDEX anid ON ckd2(animalid);

# Report how many cats have CKD
SELECT COUNT(animalid) 'CKD cats maybe with AKI' FROM ckd2;

# ------------------------------------------------------------------
-----------------

# Select all the records that have acute terms in the clinical notes
(in date order)
CREATE TEMPORARY TABLE temp_aki
SELECT cats.animalid, feline_history.historydatetime FROM
feline_history
INNER JOIN cats USING (animalid)
WHERE (feline_history.ClinicalNotes LIKE BINARY '%AKI%')
OR (feline_history.ClinicalNotes LIKE BINARY '%ARF%')
OR (feline_history.ClinicalNotes LIKE '%pre_renal%')
OR (feline_history.ClinicalNotes LIKE '%post_renal%')
OR (feline_history.ClinicalNotes LIKE '%acute kidney%')
OR (feline_history.ClinicalNotes LIKE '%acute kiddney%')
OR (feline_history.ClinicalNotes LIKE '%acute kideny%')
OR (feline_history.ClinicalNotes LIKE '%acute kidey%')
OR (feline_history.ClinicalNotes LIKE '%acute kidnay%')
OR (feline_history.ClinicalNotes LIKE '%acute kidnies%')
OR (feline_history.ClinicalNotes LIKE '%acute kidny%')
OR (feline_history.ClinicalNotes LIKE '%acute renal%')
ORDER BY historydatetime ASC
;

# Select animalid and earliest ClinicalNotes record
CREATE TEMPORARY TABLE aki
SELECT * FROM temp_aki
GROUP BY animalid
;
CREATE INDEX anid ON aki(animalid);

# Report how many cats have AKI
SELECT COUNT(animalid) 'AKI cats' FROM aki;

CREATE TABLE ckd
SELECT * FROM ckd2
WHERE ckd2.animalid NOT IN (SELECT animalid FROM aki)
;
CREATE INDEX anid ON ckd(animalid);

#Report on CKD animals not having AKI
SELECT COUNT(animalid) 'CKD cats' FROM ckd;
```

9.20 Appendix 19 All breeds of cats with CKD, sorted by frequency

```
# Count the percentage of each breed that have kidney disease v 30th
Sept
# Use the stub tables 'cats' and 'ckd'

Use rev23_282;
SELECT COUNT(animalid)'Number of cats in study' FROM cats;
SELECT COUNT(animalid)'Number of CKD cats' FROM ckd;

# ------------------------------------------------------------------------
----------------

# Count the breeds in the cats table
CREATE TEMPORARY TABLE temp1
SELECT COUNT(breed) AS 'Number_this_breed', breed FROM cats
GROUP BY breed
;

# Count the breeds in the ckd table
CREATE TEMPORARY TABLE temp2
SELECT COUNT(breed) AS 'Number_with_CKD', breed FROM cats
INNER JOIN ckd USING(animalid)
GROUP BY breed
;

# Show statistics:
SELECT breed, Number_with_CKD, Number_this_breed, (Number_with_CKD /
Number_this_breed)*100
FROM temp1 INNER JOIN temp2 USING (breed)
WHERE Number_this_breed > 200
ORDER BY (Number_with_CKD / Number_this_breed)*100 DESC
;
```

9.21 Appendix 20 Age at death for cats with and without CKD

```
# Find the ages of cats when CKD was first mentioned v 3rd Oct

Use rev23_282;
SELECT COUNT(animalid) INTO @studycats FROM cats WHERE dateofbirth >
'1988-07-01';
SELECT @studycats 'Number of cats in study with real ages';
SELECT COUNT(animalid) INTO @ckdcats FROM ckd INNER JOIN cats USING
(animalid) WHERE dateofbirth > '1988-07-01';
SELECT @ckdcats 'Number of ckd cats in study with real ages';

#-------------------------------------------------------------------
--------

# Find all the cats that died during the study (NB 'cats' table does
not contain cats that were dead before the study)
CREATE TEMPORARY TABLE cat_died
SELECT * FROM cats
WHERE dateofdeath IS NOT NULL
AND dateofdeath < '2019-07-01'
;
SELECT COUNT(animalid) INTO @deadcat FROM cat_died;
SELECT @deadcat 'Number & percent of cats that died',
TRUNCATE(@deadcat/@studycats*100,1)
;

# Find all the ckds that died during the study
CREATE TEMPORARY TABLE ckd_died
SELECT animalid, historydatetime, dateofbirth, dateofdeath FROM ckd
INNER JOIN cats USING (animalid)
WHERE dateofdeath IS NOT NULL
AND dateofdeath < '2019-07-01'
;
SELECT COUNT(animalid) INTO @deadckd FROM ckd_died;
SELECT @deadckd 'Number & % of ckd that died',
TRUNCATE(@deadckd/@ckdcats*100,1);


# Find all not-ckd cats that died during study
CREATE TEMPORARY TABLE notckd_died
SELECT * FROM cat_died
WHERE cat_died.animalid NOT IN (SELECT ckd_died.animalid FROM ckd_died)
;
SELECT COUNT(animalid) INTO @deadnotckd FROM notckd_died;
SELECT @deadnotckd 'Number & % of not-ckd cats that died',
TRUNCATE(@deadnotckd/@studycats*100,1);

#----------------------------------------OUTPUTS---------------------
------------

SELECT 'Age at death for all cats';
CREATE TEMPORARY TABLE catstat
SELECT animalid, TRUNCATE(DATEDIFF(dateofdeath,dateofbirth)/365,0) As
'Lifespan' FROM cat_died
;
```

```
SELECT TRUNCATE(Count(animalid)/@deadcat*100,1), Lifespan FROM catstat
GROUP BY Lifespan ORDER BY Lifespan ASC;


SELECT 'Age at death for ckd cats';
CREATE TEMPORARY TABLE ckdstat
SELECT animalid, TRUNCATE(DATEDIFF(dateofdeath,dateofbirth)/365,0) As
'Lifespan' FROM ckd_died
;
SELECT TRUNCATE(Count(animalid)/@deadckd*100,1), Lifespan FROM ckdstat
GROUP BY Lifespan ORDER BY Lifespan ASC;


SELECT 'Age at death for not-ckd cats';
CREATE TEMPORARY TABLE notckdstat
SELECT animalid, TRUNCATE(DATEDIFF(dateofdeath,dateofbirth)/365,0) As
'Lifespan' FROM notckd_died
;
SELECT TRUNCATE(Count(animalid)/@deadnotckd*100,1), Lifespan FROM
notckdstat GROUP BY Lifespan ORDER BY Lifespan ASC;
```

9.22 Appendix 21a Age at diagnosis- numbers

```
# Find the ages of cats when CKD was first mentioned v 9th June 2021

Use rev23_282;
SELECT COUNT(animalid) INTO @studycats FROM cats WHERE dateofbirth >
'1988-07-01';
SELECT @studycats 'Number of cats in study with real ages';
SELECT COUNT(animalid) INTO @ckdcats FROM ckd INNER JOIN cats USING
(animalid) WHERE dateofbirth > '1988-07-01';
SELECT @ckdcats 'Number of ckd cats in study with real ages';

#-------------------------------------------------------------------
--------

# animalid and first mentioned date and pull the DOB out of feline
overview
# then do the date diff in a second temp table.
# then the stats of %
# Find all the ckds and when they were diagnosed during the study

CREATE TEMPORARY TABLE ckd_diagnosed
SELECT animalid, historydatetime, DateOfBirth FROM ckd
INNER JOIN cats USING (animalid)
WHERE dateofbirth IS NOT NULL
;

SELECT 'Age at diagnosis for ckd cats';
CREATE TEMPORARY TABLE ckddiagnosisdate
SELECT animalid, TRUNCATE(DATEDIFF(historydatetime,dateofbirth)/365,0)
As 'BirthToDiagnosis' FROM ckd_diagnosed
;

SELECT Count(animalid), BirthToDiagnosis FROM ckddiagnosisdate GROUP BY
BirthToDiagnosis ORDER BY BirthToDiagnosis ASC;
```

9.23 Appendix 21b Age at diagnosis- percentages

```
# Find the ages of cats when CKD was first mentioned v 9th June 2021

Use rev23_282;
SELECT COUNT(animalid) INTO @studycats FROM cats WHERE dateofbirth >
'1988-07-01';
SELECT @studycats 'Number of cats in study with real ages';
SELECT COUNT(animalid) INTO @ckdcats FROM ckd INNER JOIN cats USING
(animalid) WHERE dateofbirth > '1988-07-01';
SELECT @ckdcats 'Number of ckd cats in study with real ages';

#-----------------------------------------------------------------------
--------

# animalid and first mentioned date and pull the DOB out of feline
overview
# then do the date diff in a second temp table.
# then the stats of %
# Find all the ckds and when they were diagnosed during the study

CREATE TEMPORARY TABLE ckd_diagnosed
SELECT animalid, historydatetime, DateOfBirth FROM ckd
INNER JOIN cats USING (animalid)
WHERE dateofbirth IS NOT NULL
;

SELECT 'Age at diagnosis for ckd cats';
CREATE TEMPORARY TABLE ckddiagnosisdate
SELECT animalid, TRUNCATE(DATEDIFF(historydatetime,dateofbirth)/365,0)
As 'BirthToDiagnosis' FROM ckd_diagnosed
;

SELECT TRUNCATE(Count(animalid)/@ckdcats*100,1), BirthToDiagnosis FROM
ckddiagnosisdate GROUP BY BirthToDiagnosis ORDER BY BirthToDiagnosis
ASC;
```

9.24 Appendix 22 Age in years when death recorded

```
# Find % of each age that die 5th Oct 2020

Use rev23_282;
SELECT COUNT(animalid) INTO @studycats FROM cats WHERE dateofbirth >
'1988-07-01';
SELECT @studycats 'Number of cats in study with real ages';
SELECT COUNT(animalid) INTO @ckdcats FROM ckd INNER JOIN cats USING
(animalid) WHERE dateofbirth > '1988-07-01';
SELECT @ckdcats 'Number of ckd cats in study with real ages';

#-----------------------------------------------------------------------
--------

# Find all the cats that died during the study NB 'cats' table does not
contain cats that were dead before the study
CREATE TEMPORARY TABLE cat_died
SELECT * FROM cats
WHERE dateofdeath IS NOT NULL
AND dateofdeath < '2019-07-01'
AND dateofbirth > '1988-07-01'
;
SELECT COUNT(animalid) INTO @deadcat FROM cat_died;
SELECT @deadcat 'Number & % of cats that died',
TRUNCATE(@deadcat/@studycats*100,1)

;
# Find all the ckds that died during the study NB 'ckd' table does not
contain cats that were dead before the study
CREATE TEMPORARY TABLE ckd_died
SELECT animalid, historydatetime, dateofbirth, dateofdeath FROM ckd
INNER JOIN cats USING (animalid)
WHERE dateofdeath IS NOT NULL
AND dateofdeath < '2019-07-01'
AND dateofbirth > '1988-07-01'
;
SELECT COUNT(animalid) INTO @deadckd FROM ckd_died;
SELECT @deadckd 'Number & % of ckd that died',
TRUNCATE(@deadckd/@ckdcats*100,1);

#---------------------------------------OUTPUTS---------------------
------------

CREATE TEMPORARY TABLE allstat
SELECT animalid, TRUNCATE(DATEDIFF('2019-03-31',dateofbirth)/365,0) As
'age_mid_study' FROM cats;

CREATE TEMPORARY TABLE age
SELECT COUNT(animalid) AS 'number_of_cats', age_mid_study FROM allstat
GROUP BY age_mid_study ORDER BY age_mid_study ASC;

CREATE TEMPORARY TABLE ckdstat
SELECT animalid, TRUNCATE(DATEDIFF('2019-03-31',dateofbirth)/365,0) As
'ckd_age_mid_study' FROM ckd
INNER JOIN cats USING (animalid);
```

```
CREATE TEMPORARY TABLE ckdage
SELECT COUNT(animalid) AS 'ckd_number_of_cats', ckd_age_mid_study FROM
ckdstat GROUP BY ckd_age_mid_study ORDER BY ckd_age_mid_study ASC;


CREATE TEMPORARY TABLE diedstat
SELECT animalid, TRUNCATE(DATEDIFF(dateofdeath,dateofbirth)/365,0) As
'Lifespan' FROM cat_died;

CREATE TEMPORARY TABLE diedage
SELECT COUNT(animalid) AS 'number_that_died', Lifespan FROM diedstat
GROUP BY Lifespan ORDER BY Lifespan ASC;


CREATE TEMPORARY TABLE diedckdstat
SELECT animalid, TRUNCATE(DATEDIFF(dateofdeath,dateofbirth)/365,0) As
'ckd_Lifespan' FROM ckd_died;

CREATE TEMPORARY TABLE ckddiedage
SELECT COUNT(animalid) AS 'number_of_ckd_that_died', ckd_Lifespan FROM
diedckdstat GROUP BY ckd_Lifespan ORDER BY ckd_Lifespan ASC;


SELECT age_mid_study, number_that_died,number_of_cats,
TRUNCATE(number_that_died/number_of_cats*100,1) FROM diedage
INNER JOIN age WHERE (diedage.Lifespan = age.age_mid_study)
GROUP BY age_mid_study
ORDER BY age_mid_study ASC
;

SELECT ckd_age_mid_study, number_of_ckd_that_died,ckd_number_of_cats,
TRUNCATE(number_of_ckd_that_died/ckd_number_of_cats*100,1) FROM
ckddiedage
INNER JOIN ckdage WHERE (ckddiedage.ckd_Lifespan =
ckdage.ckd_age_mid_study)
GROUP BY ckd_age_mid_study
ORDER BY ckd_age_mid_study ASC
;
```

9.25 Appendix 23a Age distribution ongoing CKD and diagnosis

```
# Find the ages of all cats at the beginning of the study and that are
seen at least 3 times with their diagnosis
# Comparing CKD and cancer cats
# Oct 9th 2020
# Note: cats in the 'cats' and 'ckd' tables are alive at the beginning
of the study and have real ages

Use rev23_282;

SELECT COUNT(animalid) INTO @studycats FROM cats;
SELECT @studycats 'Number of cats in study with real ages';
SELECT COUNT(animalid) INTO @ckdcats FROM ckd INNER JOIN cats USING
(animalid);
SELECT @ckdcats 'Number of ckd cats in study with real ages';

#-------------------------------------------------------------------------
--------

# Select ages of all cats alive (with real dob) at the beginning of the
study
CREATE TEMPORARY TABLE age_table
SELECT animalid, TRUNCATE(DATEDIFF('2019-01-01',dateofbirth)/365,0) As
'cat_age', gender FROM cats
WHERE dateofbirth < '2019-01-01'
;

SELECT COUNT(animalid) 'Number of all cats alive at the beginning of
the study' FROM age_table;

CREATE TEMPORARY TABLE cancer_table
SELECT * FROM age_table
INNER JOIN feline_history USING (animalid)
WHERE (feline_history.ClinicalNotes LIKE '%cancer%')
OR (feline_history.ClinicalNotes LIKE '%tumour%')
OR (feline_history.ClinicalNotes LIKE '%sarcoma%')
OR (feline_history.ClinicalNotes LIKE '%neoplas%')
OR (feline_history.ClinicalNotes LIKE '%metasta%')
;

# This creates unique animalid and date combinations! It's the DISTINCT
that does it...
CREATE TEMPORARY TABLE cancer_table_2
SELECT DISTINCT animalid, cat_age, gender,
CONVERT(feline_history.historydatetime,DATE) As 'history_date' FROM
cancer_table
INNER JOIN feline_history USING (animalid)
;

CREATE TEMPORARY TABLE cancer_table_3
SELECT animalid ,cat_age FROM cancer_table_2 GROUP BY animalid HAVING
COUNT(animalid) > 2 ORDER BY animalid ASC;

SELECT 'Cancer cats seen at least 3 times';
```

```
SELECT cat_age , COUNT(*) FROM cancer_table_3 GROUP BY cat_age ORDER BY
cat_age ASC;
DROP TABLE age_table;
DROP TABLE cancer_table;
DROP TABLE cancer_table_2;
DROP TABLE cancer_table_3;

#-----------------------------------------------------------------------
-----------------------------------

# Select ages of all ckd cats alive (with real dob) at the beginning of
the study
CREATE TEMPORARY TABLE ckd_age_table
SELECT animalid, TRUNCATE(DATEDIFF('2019-01-01',dateofbirth)/365,0) As
'ckd_age', gender FROM ckd
INNER JOIN cats USING (animalid)
WHERE dateofbirth < '2019-01-01'
;

SELECT Count(animalid) 'Number of ckd cats alive at beginning of study'
FROM ckd_age_table;

# This creates unique animalid and date combinations! It's the DISTINCT
that does it...
CREATE TEMPORARY TABLE ckd_age_table_2
SELECT DISTINCT animalid, ckd_age, gender,
CONVERT(historydatetime,DATE) As 'history_date' FROM ckd_age_table
INNER JOIN feline_history USING (animalid)
;

CREATE TEMPORARY TABLE ckd_age_table_3
SELECT animalid ,ckd_age FROM ckd_age_table_2 GROUP BY animalid HAVING
COUNT(animalid) > 2 ORDER BY animalid ASC;

SELECT 'CKD cats seen at least 3 times';
SELECT ckd_age , COUNT(*) FROM ckd_age_table_3 GROUP BY ckd_age ORDER
BY ckd_age ASC;
DROP TABLE ckd_age_table;
DROP TABLE ckd_age_table_2;
DROP TABLE ckd_age_table_3;
```

9.26 Appendix 23b Age distribution ongoing CKD and death

```
# Find the ages of all cats at the beginning of the study and that are
seen at least 3 times with their diagnosis
# Comparing CKD and cancer cats
# Oct 9th 2020
# Note: cats in the 'cats' and 'ckd' tables are alive at the beginning
of the study and have real ages

Use rev23_282;

SELECT COUNT(animalid) INTO @studycats FROM cats;
SELECT @studycats 'Number of cats in study with real ages';
SELECT COUNT(animalid) INTO @ckdcats FROM ckd INNER JOIN cats USING
(animalid);
SELECT @ckdcats 'Number of ckd cats in study with real ages';

#-------------------------------------------------------------------------
--------

# Select ages of all cats alive (with real dob) at the beginning of the
study
CREATE TEMPORARY TABLE age_table
SELECT animalid, TRUNCATE(DATEDIFF('2019-01-01',dateofbirth)/365,0) As
'cat_age', gender FROM cats
WHERE dateofbirth < '2019-01-01'
;

SELECT COUNT(animalid) 'Number of all cats alive at the beginning of
the study' FROM age_table;

CREATE TEMPORARY TABLE cancer_table
SELECT * FROM age_table
INNER JOIN feline_history USING (animalid)
WHERE (feline_history.ClinicalNotes LIKE '%cancer%')
OR (feline_history.ClinicalNotes LIKE '%tumour%')
OR (feline_history.ClinicalNotes LIKE '%sarcoma%')
OR (feline_history.ClinicalNotes LIKE '%neoplas%')
OR (feline_history.ClinicalNotes LIKE '%metasta%')
;

# This creates unique animalid and date combinations! It's the DISTINCT
that does it...
CREATE TEMPORARY TABLE cancer_table_2
SELECT DISTINCT animalid, cat_age, gender,
CONVERT(feline_history.historydatetime,DATE) As 'history_date' FROM
cancer_table
INNER JOIN feline_history USING (animalid)
;

CREATE TEMPORARY TABLE cancer_table_3
SELECT animalid ,cat_age FROM cancer_table_2 GROUP BY animalid HAVING
COUNT(animalid) > 2 ORDER BY animalid ASC;

SELECT 'Cancer cats age at death after ongoing';
SELECT cat_age , COUNT(*) FROM cancer_table_3
```

```
INNER JOIN cats USING (animalid)
WHERE dateofdeath < '2019-06-30'
GROUP BY cat_age ORDER BY cat_age ASC
;
DROP TABLE age_table;
DROP TABLE cancer_table;
DROP TABLE cancer_table_2;
DROP TABLE cancer_table_3;

#-------------------------------------------------------------------------
-----------------------------------

# Select ages of all ckd cats alive (with real dob) at the beginning of
the study
CREATE TEMPORARY TABLE ckd_age_table
SELECT animalid, TRUNCATE(DATEDIFF('2019-01-01',dateofbirth)/365,0) As
'ckd_age', gender FROM ckd
INNER JOIN cats USING (animalid)
WHERE dateofbirth < '2019-01-01'
;

SELECT Count(animalid) 'Number of ckd cats alive at beginning of study'
FROM ckd_age_table;

# This creates unique animalid and date combinations! It's the DISTINCT
that does it...
CREATE TEMPORARY TABLE ckd_age_table_2
SELECT DISTINCT animalid, ckd_age, gender,
CONVERT(historydatetime,DATE) As 'history_date' FROM ckd_age_table
INNER JOIN feline_history USING (animalid)
;

CREATE TEMPORARY TABLE ckd_age_table_3
SELECT animalid ,ckd_age FROM ckd_age_table_2 GROUP BY animalid HAVING
COUNT(animalid) > 2 ORDER BY animalid ASC;

SELECT 'CKD cats seen at least 3 times, age at death';
SELECT ckd_age , COUNT(*) FROM ckd_age_table_3
INNER JOIN cats USING (animalid)
WHERE dateofdeath < '2019-6-30'
GROUP BY ckd_age ORDER BY ckd_age ASC
;
DROP TABLE ckd_age_table;
DROP TABLE ckd_age_table_2;
DROP TABLE ckd_age_table_3;
```

9.27 Appendix 24 Survival at 60 days

```
# Drug survival 1st October

Use rev23_282;
SELECT COUNT(animalid)'Number of cats in study' FROM cats;
SELECT COUNT(animalid)'Number of CKD cats' FROM ckd;
#-----------------------------------------------------------------------
-------------------

# List the animals first seen in months 3 - 4 of the trial
CREATE TEMPORARY TABLE two
SELECT animalid,CONVERT(historydatetime,DATE) AS 'first_seen' FROM ckd
#WHERE CONVERT(historydatetime,DATE) > '2019-02-28'
#AND CONVERT(historydatetime,DATE) < '2019-05-01'
WHERE CONVERT(historydatetime,DATE) > '2019-05-01'
AND CONVERT(historydatetime,DATE) < '2019-06-30'
;

#---------- DRUG etc CONDITION GOES HERE--------------
SELECT '-Both-';
CREATE TEMPORARY TABLE two_intervention
SELECT * FROM two
INNER JOIN feline_history USING (animalid)
WHERE feline_history.ClinicalNotes LIKE '% %'
#OR feline_history.ClinicalNotes LIKE '%t4%'
#OR feline_history.ClinicalNotes LIKE '% thyroid%'
#OR feline_history.ClinicalNotes LIKE '%iv fluids%'
GROUP BY animalid
;
SELECT COUNT(animalid) INTO @seen FROM two_intervention;
SELECT @seen 'Number seen in months 2 - 4';
#-------------------------------------------------

# Of these, list the ones that survived 60 days or more
CREATE TEMPORARY TABLE survived
SELECT animalid, dateofdeath, first_seen FROM two_intervention
INNER JOIN cats USING (animalid)
WHERE (DATEDIFF(dateofdeath,first_seen) > 60)
OR (dateofdeath IS NULL)
;
SELECT COUNT(animalid) INTO @survived FROM survived;
SELECT @survived 'Survived 60+ days after first consult';
SELECT TRUNCATE((@survived/@seen)*100,0) 'Percent survived';
```

9.28 Appendix 25 Frequency of weighing, all cats

```
# FREQUENCY OF WEIGHING v 8th October

USE rev23_282;

SELECT (COUNT(animalid) - COUNT(DISTINCT animalid))/COUNT(animalid) *
100 'Percentage weighed more than once' FROM feline_parameters ;

CREATE TEMPORARY TABLE temp3
SELECT DISTINCT animalid, parametersdate FROM feline_parameters;

# Count how many times each animalid occurs.
# The animalid countis called number_of_weighings
CREATE TEMPORARY TABLE temp1
SELECT COUNT(animalid) AS 'number_of_weighings', animalid FROM temp3
GROUP BY animalid ORDER BY COUNT(animalid) DESC
;

SELECT * FROM temp1 ORDER BY number_of_weighings DESC LIMIT 20;

# Count how many examples of multiple weighings exist

CREATE TEMPORARY TABLE temp2
SELECT COUNT(number_of_weighings) AS 'distinct_cats',
number_of_weighings FROM temp1
GROUP BY number_of_weighings
ORDER BY COUNT(number_of_weighings)
;

# Show the statistics
;
SELECT SUM(distinct_cats) AS 'Sum_of_cats' FROM temp2
;

SELECT distinct_cats,number_of_weighings FROM temp2
ORDER BY number_of_weighings ASC
;
```

9.29 Appendix 25b Frequency of weighing for cats with CKD

```
# FREQUENCY OF WEIGHING v 26th March CKD cats only

USE rev23_282;

# Hold the total number of CKD cats for later
SELECT COUNT(animalid) INTO @ckd_cats FROM ckd;

# Show the percentage weighed more than once
SELECT TRUNCATE((COUNT(animalid) - COUNT(DISTINCT
animalid))/COUNT(animalid) * 100,1) 'Percentage weighed more than once'
FROM feline_parameters
INNER JOIN ckd USING (animalid)
;

# Count how many times each animalid occurs.
# The animalid countis called number_of_weighings

CREATE TEMPORARY TABLE temp3
SELECT DISTINCT animalid, parametersdate FROM feline_parameters
INNER JOIN ckd USING (animalid)
;

CREATE TEMPORARY TABLE temp1
SELECT COUNT(parametersdate) AS 'number_of_weighings', animalid FROM
temp3
GROUP BY animalid
ORDER BY number_of_weighings DESC
;

SELECT * FROM temp1 WHERE number_of_weighings > 9;

# Count how many examples of multiple weighings exist
CREATE TEMPORARY TABLE temp2
SELECT COUNT(number_of_weighings) AS 'distinct_cats',
number_of_weighings FROM temp1
GROUP BY number_of_weighings
ORDER BY COUNT(number_of_weighings)
;

# Show the statistics

SELECT SUM(distinct_cats) INTO @Sum_of_weighed_cats FROM temp2;

# Show how many were weighed altogether
SELECT @Sum_of_weighed_cats;

# Show percentage not weighed
SELECT TRUNCATE(((@ckd_cats-@Sum_of_weighed_cats)/@ckd_cats)*100,1)
'Percentage not weighed';
;

SELECT distinct_cats,number_of_weighings FROM temp2
ORDER BY number_of_weighings ASC
;
```

9.30 Appendix 26a Percentage weight change cats who died

```
# Input animalid manually (this script works for one animal)
# 25th March 2021
Use Rev23_282;

SELECT '119041413' INTO @animalid;

# Find the average weight
SELECT AVG(Weight) INTO @AverageWeight FROM feline_parameters where
animalid = @animalid;

# Find the results;
CREATE TEMPORARY TABLE temp2
SELECT DISTINCT animalid, DateOfDeath, ParametersDate, Weight,
TRUNCATE((Weight/@AverageWeight*100),0) AS 'percentage',
DATEDIFF(ParametersDate,DateOfDeath) AS 'days' FROM ckd
INNER JOIN feline_parameters USING (animalid)
INNER JOIN cats USING (animalid)
WHERE animalid=@animalid
ORDER BY Parametersdate ASC
;

# Show the results
SELECT * FROM temp2;
```

9.31 Appendix 26b Percentage weight change, cats who lived

```
# Manual input of animalid required (this script works per animal)
# 25th March 2021

Use Rev23_282;

SELECT '151602178' INTO @animalid;

# Find the average weight
SELECT AVG(Weight) INTO @AverageWeight FROM feline_parameters where
animalid = @animalid;

# Find the last day of weighing
CREATE TEMPORARY TABLE maxweight
SELECT DISTINCT animalid, ParametersDate FROM feline_parameters WHERE
animalid = @animalid ORDER BY ParametersDate DESC LIMIT 1
;
SELECT ParametersDate INTO @LastParametersDate FROM maxweight;

# Show the results so far
SELECT @animalid, @LastParametersDate, @AverageWeight;


# Find the weight percentages and days before last weighing
# NB Truncate function rounds down, eg 100.9% is shown as 100%
CREATE TEMPORARY TABLE temp2
SELECT DISTINCT animalid, DateOfDeath, ParametersDate, Weight,
TRUNCATE((Weight/@AverageWeight*100),0) AS 'percentage',
DATEDIFF(ParametersDate,@LastParametersDate) AS 'days' FROM ckd
INNER JOIN feline_parameters USING (animalid)
INNER JOIN cats USING (animalid)
WHERE animalid=@animalid
ORDER BY Parametersdate ASC
;

# Show the results
SELECT * FROM temp2;
```

9.32 Appendix 26c Most regularly weighed cats

```
# Find the cats with CKD that have been weighed regularly v 16th Oct
modified 26.1.21 removing comment that CKD only mentioned after March
# Using table 'ckd' excludes cats with unreal dateofbirth & exclude
cats that die before the study & includes only one record per animal
# 'lived' contains those animals from the 'ckd' table that did NOT die

Use rev23_282;

# CKD cats that died during study
CREATE TEMPORARY TABLE died
SELECT DISTINCT animalid, CONVERT(historydatetime,DATE) AS
'first_mentioned', dateofdeath FROM ckd
INNER JOIN cats USING (animalid)
WHERE dateofdeath < '2019-06-30'
;

CREATE TEMPORARY TABLE lived
SELECT DISTINCT animalid, CONVERT(historydatetime,DATE) AS
'first_mentioned' FROM ckd
WHERE animalid NOT IN (SELECT animalid FROM died)
;


SELECT COUNT(*) FROM ckd INTO @all;
SELECT COUNT(*) FROM died INTO @died;
SELECT COUNT(*) FROM lived INTO @lived;

SELECT 'Number of CKD cats in study', @all;
SELECT 'Number of CKD cats that died during the study', @died;
SELECT 'Number of CKD cats that did NOT die', @lived;

#----------------------------FOR THOSE THAT DIED-----------------------
-----------

CREATE TEMPORARY TABLE temp1
SELECT DISTINCT animalid, first_mentioned, parametersdate FROM
feline_parameters
INNER JOIN died USING (animalid)
;

CREATE TEMPORARY TABLE temp2
SELECT COUNT(parametersdate) As 'weighings_died', animalid,
first_mentioned FROM temp1
GROUP BY animalid
;

SELECT AVG(weighings_died) FROM temp2
# WHERE weighings_died > 1
;

SELECT animalid, weighings_died, first_mentioned FROM temp2 WHERE
weighings_died > 9 ORDER BY weighings_died DESC;

#--------------------------FOR THOSE THAT DID NOT DIE------------------
-------------
```

```
CREATE TEMPORARY TABLE temp3
SELECT DISTINCT animalid, first_mentioned, parametersdate FROM
feline_parameters
INNER JOIN lived USING (animalid)
;

CREATE TEMPORARY TABLE temp4
SELECT COUNT(parametersdate) As 'weighings_lived', animalid,
first_mentioned FROM temp3
GROUP BY animalid
;

SELECT AVG(weighings_lived) from temp4
# WHERE weighings_lived > 1
;

SELECT animalid, weighings_lived, first_mentioned
 FROM temp4 WHERE weighings_lived > 9 ORDER BY weighings_lived DESC;
```

9.33 Appendix 27 Blood pressure measurements extraction

```
# Nov 6th 2020
# July 30th 2021

# Find cats that have CKD and had mmHg mentions in their clinical
notes.
# Of these, find those mentioned most often.
# then show their clinical notes for the dates when mmHg mentioned.

Use rev23_282;

SELECT COUNT(animalid) INTO @studycats FROM cats;
SELECT @studycats 'Number of cats in study with real ages';
SELECT COUNT(animalid) INTO @ckdcats FROM ckd INNER JOIN cats USING
(animalid);
SELECT @ckdcats 'Number of ckd cats in study with real ages';

# ------------------------------------------------------------------
----------

CREATE TEMPORARY TABLE bptemp
SELECT DISTINCT ckd.animalid,
CONVERT(feline_history.historydatetime,DATE) As 'historydate' FROM ckd
INNER JOIN feline_history USING (animalid)
WHERE feline_history.clinicalnotes LIKE '%mmHg%'
;

SELECT 'Number of distinct CKD animals that have BP measurements';
SELECT COUNT(DISTINCT animalid) FROM bptemp;

CREATE TEMPORARY TABLE bp
SELECT animalid, COUNT(historydate) AS 'Number' FROM bptemp
GROUP BY animalid
;

SELECT 'Number of different days that BP measurements were taken';
SELECT * FROM bp WHERE Number > 3 ORDER BY Number DESC;

CREATE TEMPORARY TABLE bptemphistory
SELECT animalid FROM bp WHERE Number > 3 ORDER BY Number DESC;

SELECT * FROM bptemphistory;

CREATE TEMPORARY TABLE allhistories
SELECT DISTINCT animalid, historydatetime, clinicalnotes FROM
feline_history WHERE feline_history.clinicalnotes LIKE '%mmHg%'
;

SELECT * FROM allhistories INNER JOIN bptemphistory ON
bptemphistory.animalid = allhistories.animalid
;
```