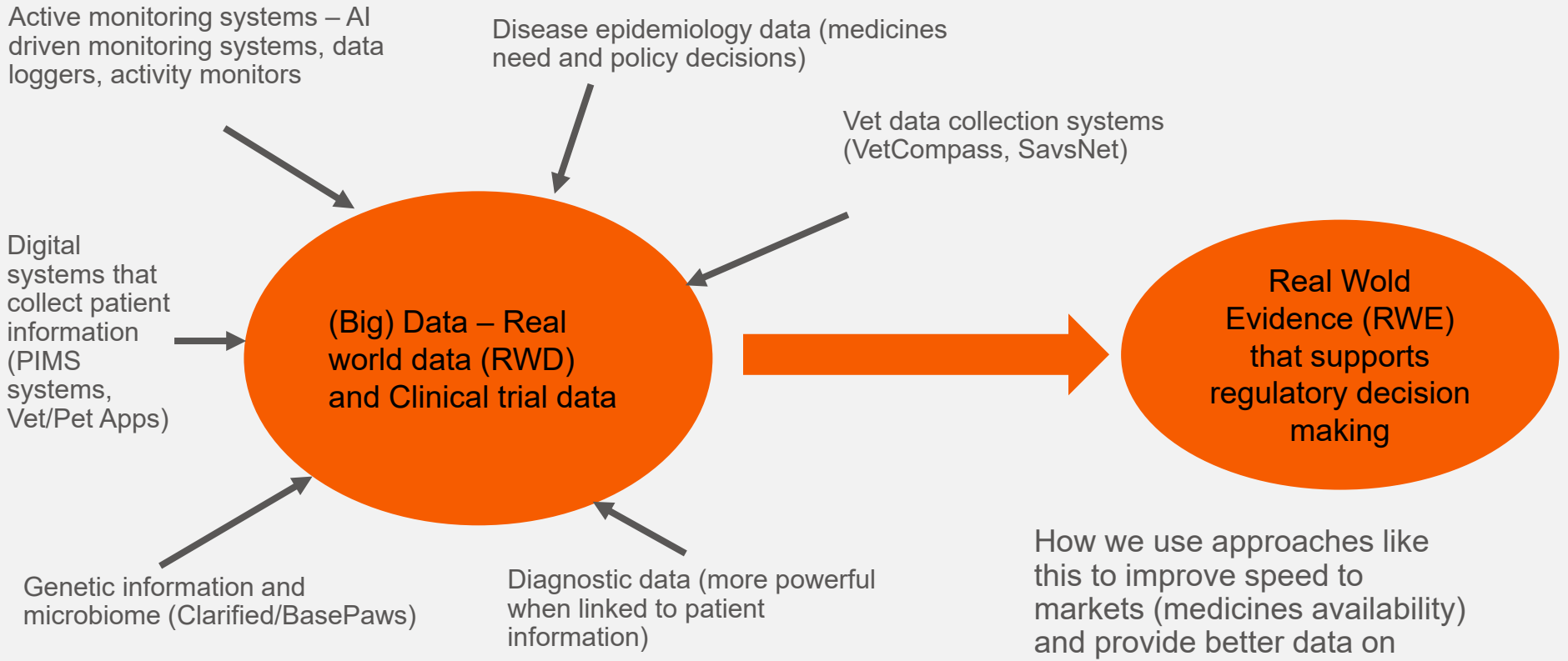
Big data to support innovation and regulatory decision making

3rd Veterinary Big Data Stakeholder forum|
23rd Nov 2023

Dr Catrina Stirling
Director Regulatory Affairs

zoetis

The big picture on the use of data in medicines development



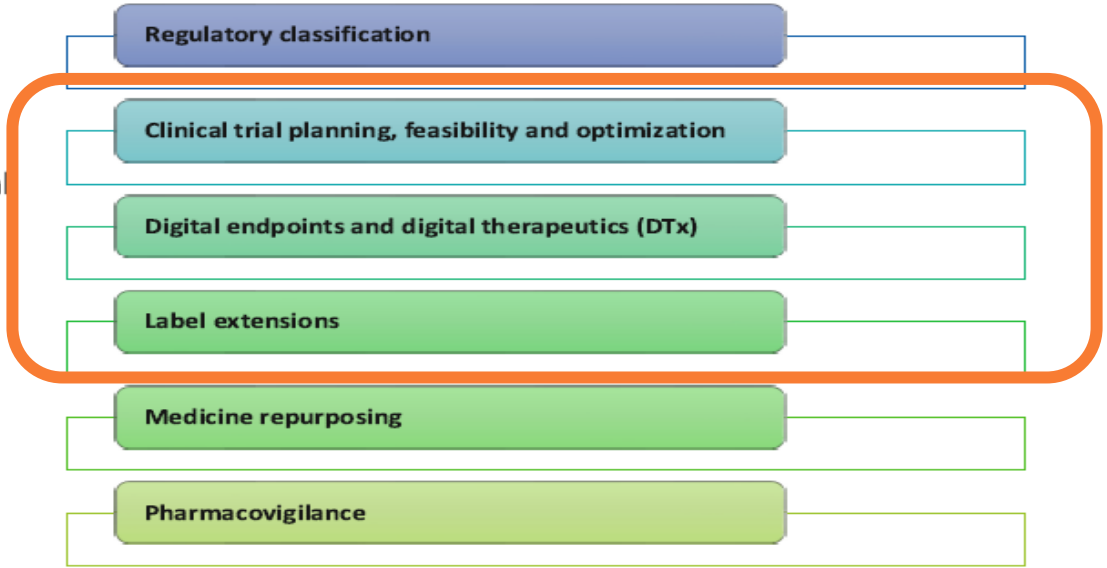
How we use approaches like this to improve speed to markets (medicines availability) and provide better data on which to make decisions is key to supporting innovation

Classified as internal/staff & contractors by the European Medicines Agency

The power of data in medicines development and registration

1. Regulatory Uses of RWE

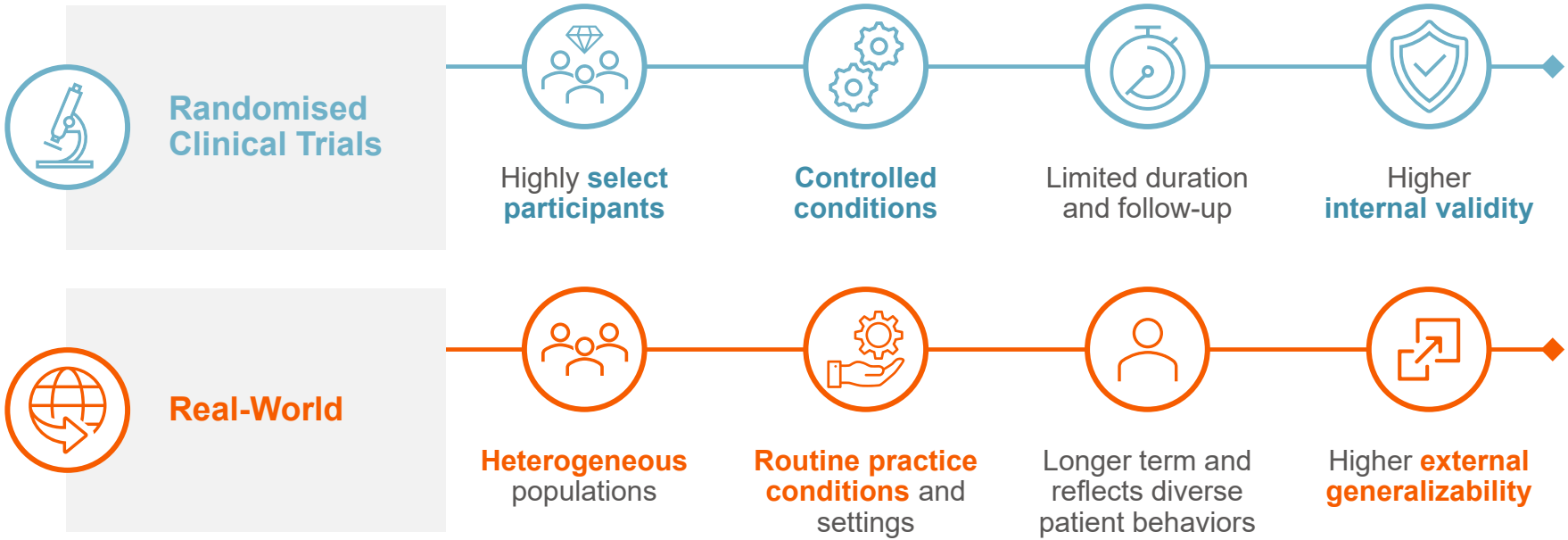
- RWD can be used throughout the lifecycle for a variety of use cases, including orphan designations, clinical trial planning or pharmacovigilance
- Within marketing approval decisions, RWE can be particularly relevant for label extensions, as well as for repurposed medicines



https://www.ema.europa.eu/en/documents/presentation/presentation-session-2-stakeholder-perspective-use-cases-pharmaceutical-industry-medicines-europe-k_en.pdf

Classified as public by the European Medicines Agency

To Meet Evidence Requirements, We Can Use Complementary Data Streams



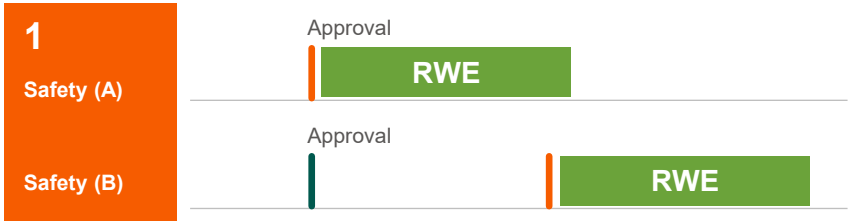
RCT=randomized controlled trial; RWE=real-world evidence

Classified as internal/staff & contractors by the European Medicines Agency

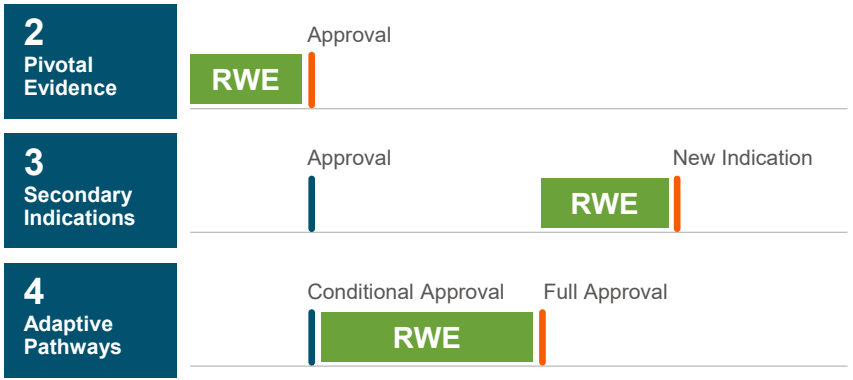
Role for Fit for Purpose RWE Incrementally Evolving Beyond Traditional Use Cases

1. **Long-term Safety (and Effectiveness)**
   - Comparator for single arm extension trial or registry
2. **New Approval**
   - To compare disease trajectory to interventional single arm trial of new medication when traditional RCT is not operationally feasible
     - Rare disease or subtype (oncology)
     - Identify eligible patients exposed to an approved alternative or no treatment
     - Well defined indication, outcomes, and predictable clinical course can be identified and measured in existing RWD
3. **Secondary Indications**
   - Effectiveness of new therapy for expanded population (e.g., pediatrics) or new indication (e.g., oncology)
4. **Confirmatory Evidence with Accelerated Approval**
   - In the scenario where RCT is not feasible (rare disease or subtype, or unethical) or to supplement for relevant outcomes

More Traditional Work By Epidemiologists In Industry



Opportunity to Complement Clinical Trial Data with Filing



Franklin J et al. Evaluating the use of non-randomized real-world analyses for regulatory decision-making. *Clin Pharm Ther*. 2019,105(4). Doi:10.100/cpt 1351

Classified as internal/staff & contractors by the European Medicines Agency

Its not one or the other

- RWD leading RWE is complementary to RCT data (and other standard regulatory data)
- Clinical trial data remains key, but RWE can complement it, enhance our understanding of RCT data and in some cases be the only option to fully substantiate efficacy
- It is critical both enable its use but also establish its value that we
  - Understand data sources and validity
  - Trust in data and its relevance
  - Understand and use both structured and unstructured data sources
  - Policy and governance of data (ownership, GDPR etc)
- Talking to regulators early and often is important to enable both use and regulatory acceptance

Classified as internal/staff & contractors by the European Medicines Agency

zoetis

Use of RWD and RWE in Human Medicine is increasing but the power of this in Vet Med is yet to be fully explored

Recent publications suggest in some cases up to 100% of new submissions to FDA and EMA for Human Medicines used RWE/RWD in some way to support the regulatory decision-making process

Classified as internal/staff & contractors by the European Medicines Agency

zoetis

What is happening in Human Health?

Using real world data in regulatory decision making is a reality

real-world-evidence-framework-support-eu-regulatory-decision-making-report-experience-gained_en.pdf (europa.eu)

Ways to use RWD - Using AI to mine data – workshop this week (20-21st Nov)

Joint Heads of Medicines Agencies (HMA)/European Medicines Agency (EMA) AI workshop – Smart regulation in a rapidly evolving world | European Medicines Agency (europa.eu)

All of these examples and use cases can translate to use in Veterinary medicine

Classified as internal/staff & contractors by the European Medicines Agency

zoetis

RWE to support product benefits

Using RWE to understand broader product benefits

- We are used to understanding medicines effect at the individual animal level
- Reg 2019/6 opens the door to exploring benefits at the herd and population level – change from therapeutic benefit to benefit wording and this is also considered within Regulatory Science strategy

- Examples of using RWE to show the impact of a medicine on reducing antimicrobial use

Classified as internal/staff & contractors by the European Medicines Agency

zoetis

DIMINISHED ANTIMICROBIAL DRUG USE IN DOGS WITH ALLERGIC DERMATITIS TREATED WITH OCLACITINIB

Graphical Abstract

AUTHORS: Kennedy Mwacalimba, Andrew Hillier, Michele Rosenbaum, Christopher Brennan and Deborah Amodie

Year of the Publication: 2023

Background

Dogs with allergic dermatitis often suffer from concurrent skin and ear infections.

Objective

Primary Objective: Quantify systemic and topical antimicrobial transactions in dogs with allergic dermatitis after oclacitinib or glucocorticoid treatment compared to those without pruritus therapy when there is a concurrent diagnosis of pyoderma.

Secondary Objective: Dogs on oclacitinib use fewer antimicrobials and concomitant therapies over time and have improved quality of life and Treatment Satisfaction.

Methodology

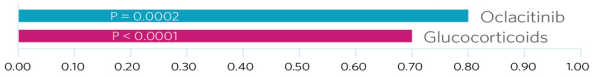
Retrospective case-control study using data from 1,134 U.S. hospitals & 47,856 canine patients.

A prospective study with 58 client-owned dogs.

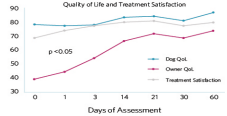
- Odds ratios were calculated to assess antimicrobial transactions.
- Linear Mixed Model Approach was used to analyze Quality of Life and dermatitis severity ($\alpha = 0.05$)
- Parametric Bootstrapping provided statistical insights.

Primary Results:

Reduced Odds of additional Antimicrobial Drugs Usage for Oclacitinib (n=5,132) and Glucocorticoid (n = 7,024) Treatments Compared to Controls (n = 12,997)

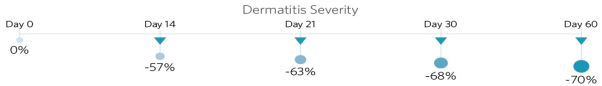


Oclacitinib showed a statistically significant improvement in Quality of Life & Treatment Satisfaction scores over time

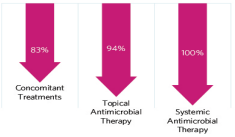


Secondary Results:

Veterinarian assessment showed a 70% reduction in dermatitis severity over time ($p < 0.05$).



Reduction in Concomitant Treatments, Topical Antimicrobial Therapy, & Systemic Antimicrobial Therapy over eight weeks



Discussion

Dogs receiving oclacitinib showed no increase in antimicrobial therapy transactions compared to glucocorticoid recipients at the initial pyoderma diagnosis. Having a pruritus therapy at the index pyoderma visit reduced the odds of subsequent antimicrobial transactions. In addition to reducing concomitant therapy usage, oclacitinib improved owner and pet QoL, suggesting a paradigm shift in treatment success that could reshape allergic pruritus therapy recommendations. The study provides empirical evidence of oclacitinib's reduction in antibacterial therapy, supporting its therapeutic value and antimicrobial stewardship.

Mwacalimba K, Hillier A, Rosenbaum M, Brennan C and Amodie D (2023) Diminished antimicrobial drug use in dogs with allergic dermatitis treated with oclacitinib. Front. Vet. Sci. 10:1207582. https://doi.org/10.3389/fvets.2023.1207582

THE EFFECTS OF OCLACITINIB TREATMENT ON ANTIMICROBIAL USAGE IN ALLERGIC DOGS IN PRIMARY PRACTICE: AN AUSTRALIA-WIDE CASE-CONTROL STUDY

Graphical Abstract

AUTHORS:
Hester Rynhoud, Catriona Croton, Grace Henry, Erika Meler, Justine S. Gibson and Ricardo J. Soares Magalhaes

Year of the Publication: 2022

Background

Canine allergic dermatitis Prevalence is a common veterinary diagnosis

Multivariable logistic regression models were developed and adjusted for the presence of concurrent skin or ear infections

Objective was to measure oclacitinib's impact on antimicrobial and therapy usage

Antimicrobial & Therapy Usage

Dataset drawn from VetCompass Australia database

Methodology

Retrospective case-controlled review conducted for analysis

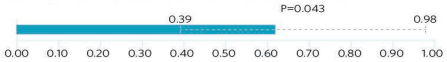
Analysis included canine patients diagnosed with allergic dermatitis from 2008 to 2018 Over 700,000 Observations

2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018

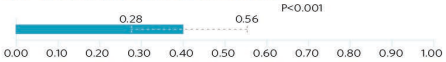
Results

Reduction in Antimicrobial Prescriptionoclacitinib-treated cases had fewer antimicrobial courses.

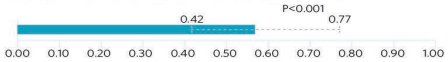
The odds of usage of Cefovecin was lower for Oclacitinib vs controls



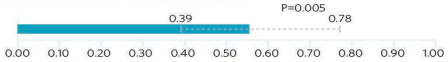
The odds of usage of Neomycin was lower for Oclacitinib vs controls



The odds of usage of Chlorhexidine was lower for Oclacitinib vs controls



The odds of usage of AMC was lower for Oclacitinib vs controls



Conclusion

This study demonstrates a potential sparing effect of oclacitinib on the prescription of antimicrobials for the treatment of allergic skin diseases in dogs. This information may assist in the planning of treatment for canine allergic dermatitis, with consideration for antimicrobial stewardship.

Rynhoud, H., Croton, C., Henry, G. et al. The effects of oclacitinib treatment on antimicrobial usage in allergic dogs in primary practice: an Australia wide case-control study. BMC Vet Res 18, 151 (2022). https://doi.org/10.1186/s12917-022-03255-y

Digital data capture - devices

What can digital data capture give us

- Major advances in technology allow more advanced and objective ways to measure collet data in both clinical trial and real-world settings

  - Advanced herd monitoring systems in the livestock industry measuring feed in-take, methane emissions, milk yield and other parameters – benefits in precision farming but also in data capture to evaluate medicines

  - Activity monitoring devices where algorithms can be trained using machine learning and AI to recognise itch for example but also simple activity increase of decrease to assess pain
    - Onsior Regulatory example – activity monitors measuring impact on pain
    - Whistle Alert paper – activity monitors measuring itch

Classified as internal/staff & contractors by the European Medicines Agency

zoetis

Onsior Regulatory example – claim extension

Onsior, Robenacoxib (europa.eu) (EPAR for Variation assessment)

- Used activity monitors as an objective measure of how much pain an animal was on for a claim extension

- Use justified based on publications –
  - Lascelles et al., 2007b: 'Both an AM and a CSOM system can detect behaviour associated with pain relief in cats that are arthritic. Objective activity data might allow subjective assessment systems to be validated for use in clinical studies.';
  - Lascelles, 2008: 'Acceleration-based activity monitors may allow for objective measurement of improved mobility following analgesic treatment for conditions such as osteoarthritis.'.
  - Other studies that have used accelerometers as an important objective outcome measure for assessing the efficacy of new treatments in cats with degenerative joint disease or osteoarthritis (Lascelles et al., 2007b; 2010; Benito et al., 2013a; Guillot et al., 2013; Gruen et al., 2015; 2016).
- The CVMP concluded that, for the purposes of the current submission, sufficient validation of the activity monitors has been provided.

Classified as internal/staff & contractors by the European Medicines Agency

Response of pet owners to WhistleFit® activity monitor digital alerts of increased pruritic activity in their dogs: A retrospective observational study

Aletha Carson[1]*, Cassie Kresnye[1], Taranpreet Rai[2], Kevin Wells[2], Andrea Wright[3], Andrew Hillier[3]
[1]Pet Insight Project, Kinship, Inc., Portland, OR, United States
[2]The Veterinary Health Innovation Engine, School of Veterinary Medicine, University of Surrey, Guildford GU2 7AL, United Kingdom
[3]Zoetis, Parsippany, NJ, United States

Keywords: dog, pruritus alert, scratching, licking, wearable activity monitor, dermatology, pet owner, deep learning computer algorithm

Front. Vet. Sci. 10:1123266. doi: 10.3389/fvets.2023.1123266

Classified as internal/staff & contractors by the European Medicines Agency

Whistle™

Whistle's line of devices do everything from activity monitoring to tracking vital health insights, including time spent scratching and licking—allowing users a daily snapshot of their pet's health and the empowerment that comes from early awareness.

kinship

PET INSIGHT PROJECT

Banfield PET HOSPITAL

In collaboration with Banfield Pet Hospitals and Whistle Labs, the Pet Insight Project (PI) was launched in 2018 to conduct one of the largest digital health study in pet care. PI is a team of data scientists, technologists, and vets, using AI to link changes in behaviors with changes in health.

Real-World Validation paper

- Collar position independence– result of large data set trained on many examples. Allows **accuracy in home environments** outside of the lab “two finger tight”
- Study objective
- To validate behavior classification models for commercially available Whistle FIT® canine activity monitor
- Validation was based on large-scale activity data obtained over 2-3 yrs from dogs in experimental and clinical settings from the Pet Insight project

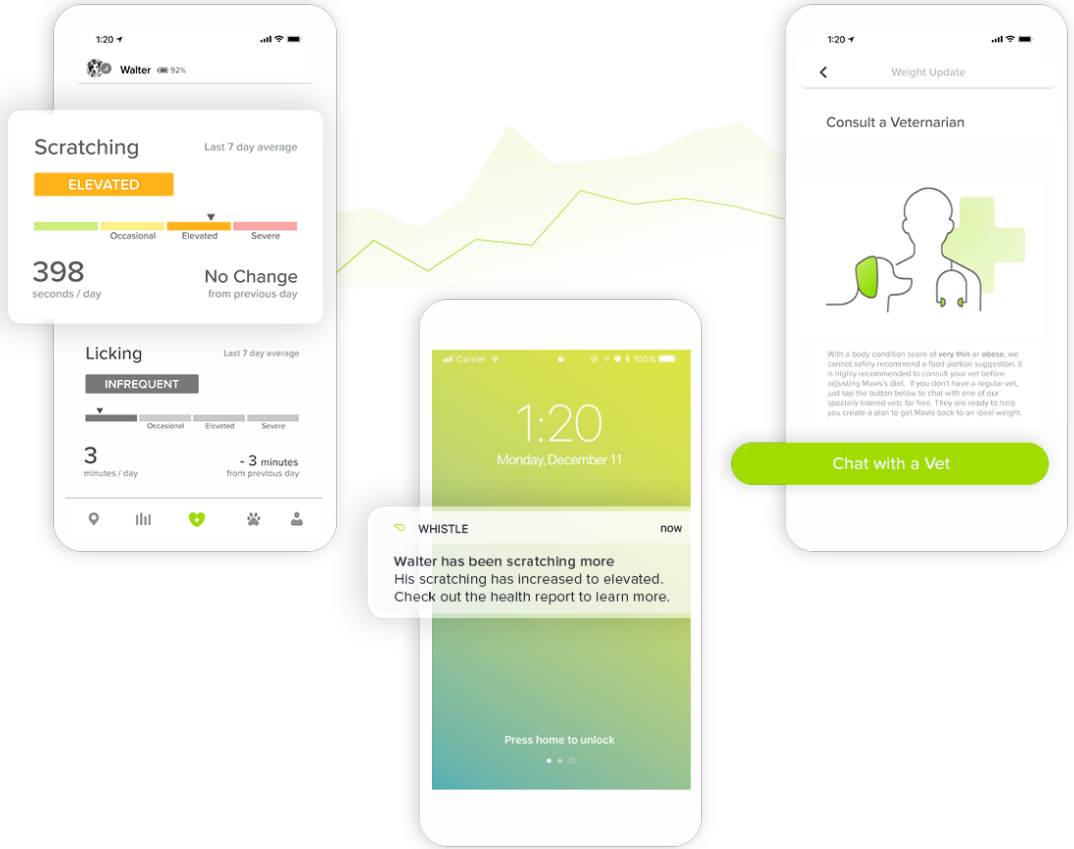
Chambers, R.D.; Yoder, N.C.; Carson, A.B.; Junge, C.; Allen, D.E.; Prescott, L.M.; Bradley, S.; Wymore, G.; Lloyd, K.; Lyle, S. Deep Learning Classification of Canine Behavior Using a Single Collar-Mounted Accelerometer: Real-World Validation. *Animals* **2021**, *11*, 1549. https://doi.org/10.3390/ani11061549

Classified as internal/staff & contractors by the European Medicines Agency

The value of objective data

Owners' perception of how much their dog scratches is very subjective

Devices can monitor in the background and provide just in time alerts when a dog's behavioral data is trending in a concerning direction.



Classified as internal/staff & contractors by the European Medicines Agency

Is Whistle Fit as good as pVAS (traditional measure)?

Comparison of scratching severity between owner-completed pruritus Visual Analog Scale and Whistle canine collar

A. CARSON*, A. WRIGHT†, R. HOLLAND‡, N. CERNICCHIARO§, C. KRESNYE and S. LYLE¶

As scratching severity increased, as measured by the Whistle canine collar, pVAS scores significantly ($P < 0.01$) increased.

https://onlinelibrary.wiley.com/doi/10.1111/vde.13021

Classified as internal/staff & contractors by the European Medicines Agency

PVAS modeled against scratching quartiles and Whistle Bucket scores

Pet owners can tell it is bad or not bad. But they have very little accuracy in the middle– this is the critical time for early detection and intervention.

Also useful in measuring efficacy of therapeutics

Table 2. Unconditional associations between scratching categories (in quartiles, and in "bucket" scores, modeled separately) with PVAS scores obtained from the first questionnaire.

Variable, units	n	PVAS scores Q1 Mean score[1]	PVAS scores Q1 Mean score 95% CI	PVAS scores Q1 *P*-value[2]	AIC BIC
Scratching (in quartiles Q1)				<0.001	-120.02
1 - 1-56 s	89	29.4[a]	25.4-33.7		-100.62
2 - 57-97 s	56	28.2[a]	23.4-33.6		
3 - 98-170 s	123	50.6[b]	46.5-54.6		
4 - 171-2,271 s	90	52.8[b]	48.1-57.5		
Scratching (in "bucket" scores Q1)				<0.001	-74.49
0 - Infrequent (0-52 s)	86	30.4[a]	26.1-35.1		-55.09
1 - Occasional (53-199 s)	132	42.2[b]	38.3-46.3		
2 - Elevated (120-299 s)	115	48.9[b]	44.5-53.3		
3 - Severe (>= 300 s)	25	52.8[b]	43.4-62.0		

n = number of observations, CI = Confidence Interval, AIC-BIC = Akaike Information and Bayesian Information Criteria.
[1] Significant ($P < 0.05$) differences in PVAS scores between scratching categories are depicted by different letter superscripts (*P*-values adjusted using the Tukey-Kramer method).
[2] Overall significance of variable (Wald test).

Classified as internal/staff & contractors by the European Medicines Agency

Summary

- The results of this study suggest that transmitting alerts to a dog owner's smartphone app by the Whistle system may help dog owners to recognize pruritic behaviors in their dogs, prompt changes in dog owner behavior, and increase the likelihood of a veterinary visit in response to receiving the alert.
- Pet owners appear to be highly motivated to manage their dogs' pruritus and will seek veterinary treatment when alerted to increases in their dogs' pruritic behaviors, particularly in dogs without a history of pruritus.

Are dogs better off (does it work)?

33rd EUROPEAN VETERINARY DERMATOLOGY CONGRESS ORGANIZED BY ESVD-ECVD PORTO - PORTUGAL 29 SEPTEMBER - 1 OCTOBER 2022

frontiers

1.9x
Increase in vet visits for new allergy patients

6x
Medications prescribed to Whistle users

16x
Topicals prescribed to Whistle users

3.9x
Increase in vet prescribed nutrition purchases

Revealed that **40.8% of dogs were predisposed but undiagnosed until the pet parent received a Whistle alert.**

Classified as internal/staff & contractors by the European Medicines Agency

Utilising data to support 3Rs

How can data help advance the 3Rs

The concept of virtual control groups in toxicology studies (similar to an external control arm in an RCT)

- Sharing legacy data from *in vivo* toxicity studies offers the opportunity to analyse the variability of control groups
- Historical animal control group data collected in a repository could be used to construct virtual control groups (VCGs) for toxicity studies.
- The use of VCGs has the potential to reduce animal use by 25% by replacing control group animals with existing randomized data sets.
- Prerequisites for such an approach are the **availability of large and well-structured control data sets** as well as thorough statistical evaluations.

Steger-Hartmann et al 2020 ALTEX 37(3), 343-349 Introducing the Concept of Virtual Control Groups into Preclinical Toxicology Animal Testing

Classified as internal/staff & contractors by the European Medicines Agency

zoetis

Conclusions

Big Potential in Big data

- Data sources and use of data in Vet Med can be varied and variable but all of it has the power to enhance and improve regulator decision making and accelerate innovation in medicines

- Benefits exist for innovation in both new types of medicines but also in how we understand and enhance existing medicines

- Experiences in and guidance from Human Heath give us a place to start but needs to be balanced to the Vet Context

- RWE and Data can potentially become a more powerful approach to support Veterinary medicines given the breadth and complexity of both our patient populations and contexts of use

Classified as internal/staff & contractors by the European Medicines Agency

zoetis

Classified as internal/staff & contractors by the European Medicines Agency