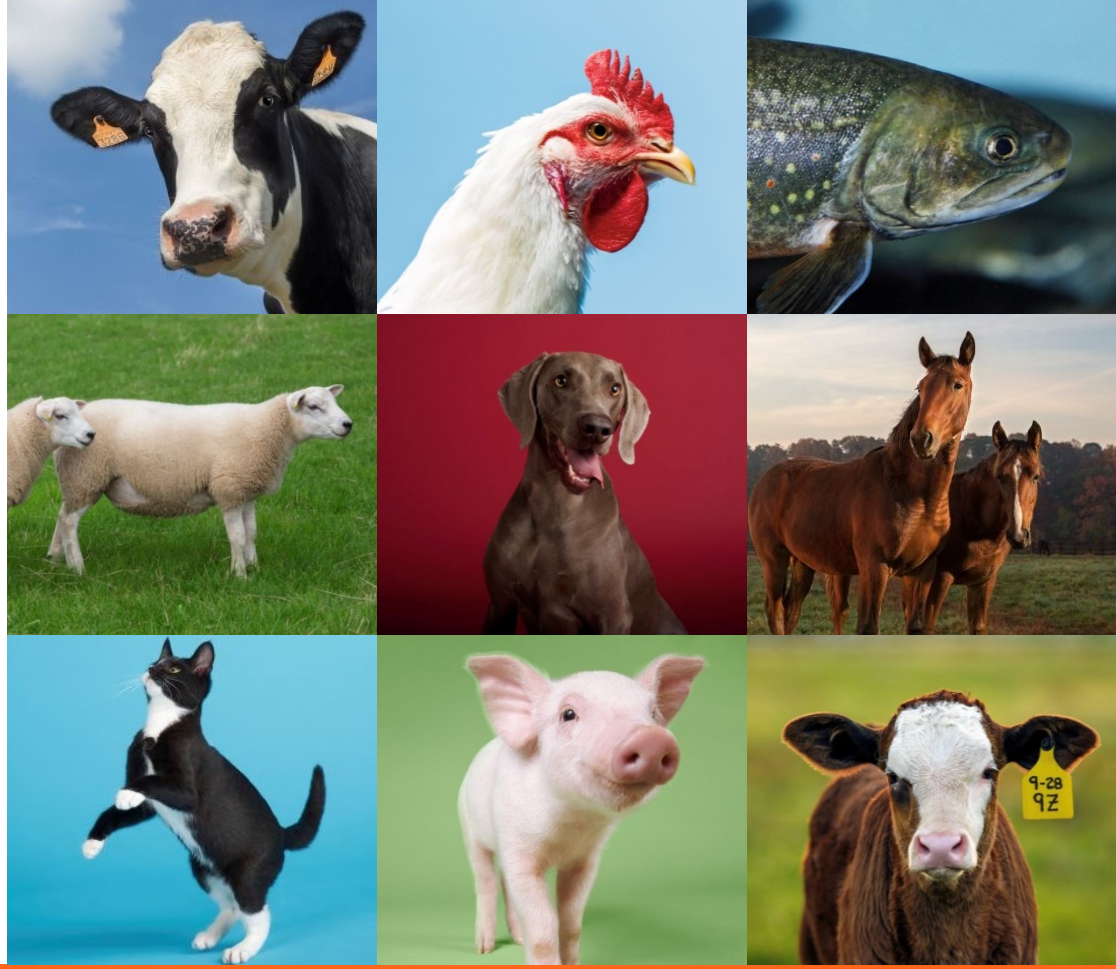
RWE Examples of Big data & biodevices to support efficacy and effectiveness

Dr Catrina Stirling
Dr Andrea Wright



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How are we using Big Data right now – and the possible future

- In Outcomes Research (OR) to support product in the field
- In R&D to assess potential to use Apps, biosensors or other digital technology to collect data in clinical trials
- Exploring QoL for Companion animals to support product benefits
- Using herd data tracking software to assessment impact of medicines on herd heath and performance
- Technology has the potential to support products in a regulatory context
  - Additional/non-conventional endpoints
  - Objective data collection from biosensors
  - Data collection on Antimicrobial use
  - Impact of products on animal health at a herd/population level
  - Broader benefit/risk assessment

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Veterinary Big Data and RWE is here

Retrospective Analysis of Heartworm (Dirofilia immitis) Prevention Medication Compliance and Economic Value in Dogs in Veterinary Practices in Australia[1]

Kennedy Mwacalimba1*, Andrea Wright1, Konstantinos Giannakakis2, Richard L'Estrange3 and Tinh-Son Nguyen3
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CalfTracker

Recent submission paper to the Journal of Dairy Science looking at the use of calf tracker results for monitoring calf weights

The records comprised 5,139,337 rows of data, from 1,951,652 individual invoices

The dataset analyzed contained records between June 5, 2014, and February 28, 2020, from 28 veterinary practices servicing 139 farms with 19,642 calves up to 20 weeks of age, from which there were 59,590 weight recordings

RESEARCH ARTICLE

Automatic early warning of tail biting in pigs: 3D cameras can detect lowered tail posture before an outbreak

Richard B. D'Eath[1]*, Mhairi Jack[1], Agnieszka Futro[1], Darren Talbot[2], Qiming Zhu[3], David Barclay[3], Emma M. Baxter[1]

1 SRUC, Edinburgh, United Kingdom, 2 Royal (Dick) School of Veterinary Studies, University of Edinburgh, Easter Bush, Midlothian, United Kingdom, 3 Innovent Technology Ltd, Turriff, Aberdeenshire, United Kingdom

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vHive
VETERINARY HEALTH INNOVATION ENGINE

ZOETIS CENTRE FOR DIGITAL INNOVATION

UNIVERSITY OF SURREY

1. https://www.frontiersin.org/articles/10.3389/fvets.2020.602907/full

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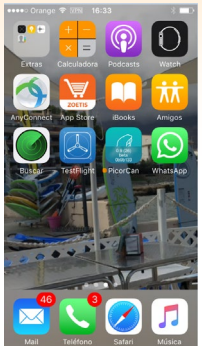
Using APPs to collect data

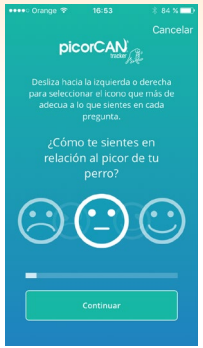
Emotional

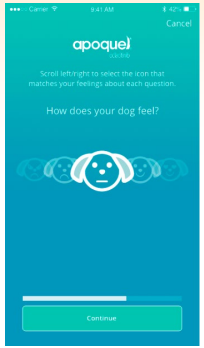
Technical

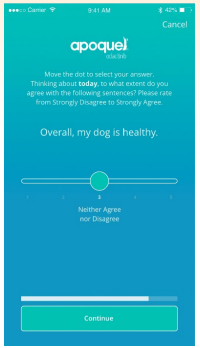
QOL

Dog picture









Vet dashboard

CONCLUSIONS

- **A mobile app is accepted by dog owners for monitoring pruritus, QoI and response to oclacitinib**
- **Using a mobile app has the potential to enhance communication between veterinarians and dog owners**

Preliminary results from a mobile app monitoring canine pruritus and quality of life in dogs prescribed oclacitinib
publication May 15, 2018 Veterinary Dermatology Abstracts of the North American Veterinary Dermatology Forum May 1–5th 2018, Maui, Hawaii, USA
First published: 15 May 2018 https://doi.org/10.1111/vde.12546

QUALITY OF LIFE ASSESSMENT

SUPPORTING PRODUCT BENEFIT/RISK ASSESSMENT

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WHY ASSESS QUALITY OF LIFE IN OWNERS AND COMPANION ANIMALS?

- A 'central part of veterinary practice'[1]
- Treatment success can be further defined by owners' perception of pet's improvement in QoL[2]
- Tracking QoL can enhance vet-owner communication and inform effective treatment decision making

"It caused us to focus on particular therapeutic options, and gave us another level of engagement with our clients."

"made us more focused on outcomes"

Can QoL measures be used in a regulatory context?

1. Yeates, J., & Main, D. (2009). Assessment of companion animal quality of life in veterinary practice and research. Journal of Small Animal Practice, 50(6), 274-281.
2. Levine, J. M., Budke, C. M., Levine, G. J., Kerwin, S. C., Hettlich, B. F., & Slater, M. R. (2008). Owner-perceived, weighted quality-of-life assessments in dogs with spinal cord injuries. Journal of the American *Veterinary Medical Association*, *233*(6), 931-935.

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STUDY CONCLUSIONS

- For both outcomes, QOL of dogs and of owners of dogs that received oclacitinib, only pruritus score and study day were significant predictors in both uni- and multi-variable models.

- Neither dose, age, weight, sex nor diagnosis were significantly associated with these outcomes.

Association of administration of oclacitinib with improvement of quality of life of acutely pruritic dogs and their owners in seven days
publication May 15, 2018 Veterinary DermatologyAbstracts of the North American Veterinary Dermatology Forum May 1–5th 2018, Maui, Hawaii, USA
First published: 15 May 2018 https://doi.org/10.1111/vde.12546

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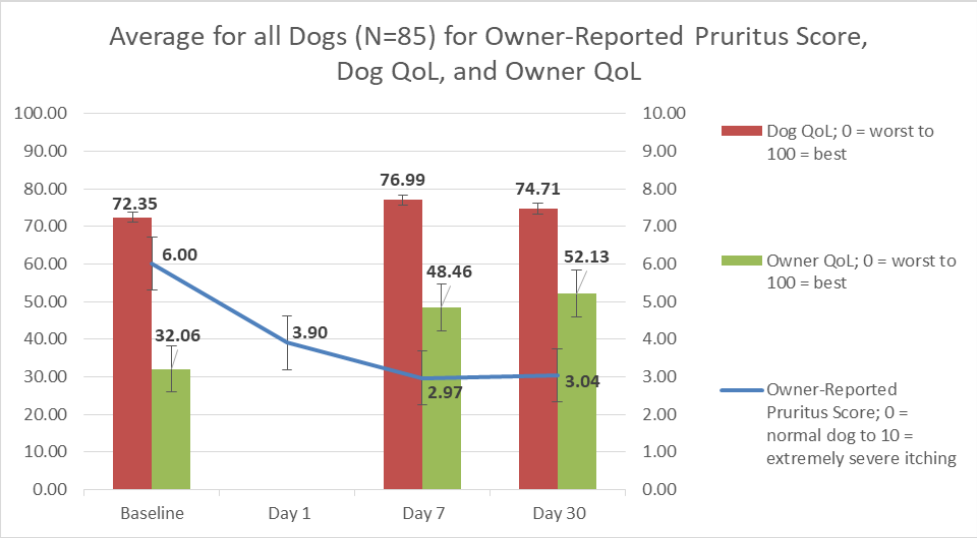
Progress report from an early experience program involving atopic dogs treated with lokivetmab reaching 30 days post injection using a mobile application monitoring pruritus and dog and owner quality of life (QoL)

- **AIMS:** Lokivetmab (CYTOPOINT®) is a novel, caninized monoclonal antibody that targets interleukin (IL)-31, a key pruritus-inducing cytokine in canine atopic dermatitis (AD). The subcutaneous injection is administered monthly by a veterinarian. This study sought to evaluate the changes in both pruritus and QoL for the dog and owner through the use of a mobile application based on a previously validated QoL tool, the Canine Dermatitis Qualify of Life Questionnaire (CDQoLQ).



How could data like this be used in a regulatory context?

Points to consider

- demonstrating and supporting product efficacy and benefit/risk balance – in addition to pivotal clinical data

- Regulatory expectations for validation of a QoL tool?

- Use post approval to support expanded claims/on-going benefit risk?
  - Considerations in a Pharmacovigilance context?

- How would this be reflected on an SPC?
  - Supporting the indication but not described?
  - Indication for QoL improvement?

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CORRELATING DIGITAL TOOLS TO CURRENT APPROACH FOR EFFICACY DATA COLLECTION

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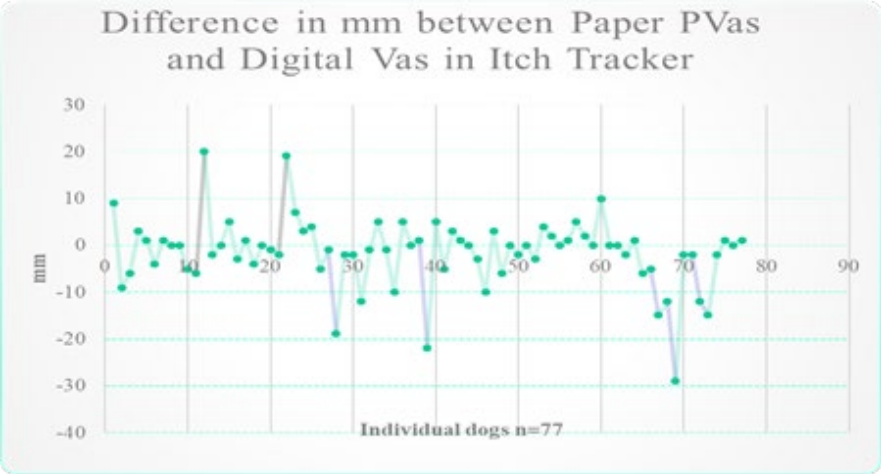
IS A DIGITAL PVAS EQUIVALENT TO A PAPER PVAS TO MEASURE ITCH IN DOGS SUFFERING FROM ATOPIC DERMATITIS?

Results

- Mean average from the app PVAS was -1.5 mm below paper PVAS mean. This difference was much smaller than the allowable 10mm.
- Only 13% of all the scores fell out of range of the estimated 10 mm difference with 17% equal , 48% below and 35% above the estimated 10 mm difference.



CONCLUSIONS

The app-based PVAS was shown to be equivalent to the paper-based PVAS and can be used by owners to track pruritus at home.

In the original paper version 20 mm is the difference between the six categories so using a digital PVAS when scaled correctly may assist veterinarians and dog owners track response to pruritus therapy in between visits to the veterinary clinic.

- Special Issue: Abstracts from the 9th World Congress of Veterinary Dermatology, October 2020 – April 2021, Sydney, Australia https://doi.org/10.1111/vde.12907

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Proving clinical efficacy in a controlled environment for registration is very different to OR monitoring efficacy in the real world

Regulatory context questions

- Data validation, App validation expectations to use the App to collect efficacy data in a pivotal trial?
- GCP considerations – how do you audit big data/digital data collection?
- Validation of the digital tool – expectations?
- Are there differences if used for primary vs secondary variable?
- Could an app like this be used to support decision on dosing interval on individual basis?

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BIOSENSORS AND ACTIVITY MONITORS FOR DATA COLLECTION

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Biosensors/Activity Monitors

Griffies et al. BMC Veterinary Research (2018) 14:124
https://doi.org/10.1186/s12917-018-1428-x

BMC Veterinary Research

RESEARCH ARTICLE Open Access

Wearable sensor shown to specifically quantify pruritic behaviors in dogs

Joel D. Griffies[1*], Jason Zutty[2], Marcel Sarzen[3] and Stuart Soorholtz[3]

sensors

MDPI

Article

Use of Accelerometer Activity Monitors to Detect Changes in Pruritic Behaviors: Interim Clinical Data on 6 Dogs

- **Deep learning classification of canine behavior using a single collar-mounted accelerometer: Real-world validation**
- Robert D. Chambers,
- Nathanael C. Yoder, Aletha B. Carson, Christian Junge, David E. Allen, Laura M. Prescott, Sophie Bradley, Garrett Wymore, Kevin Lloyd, Scott Lyle
- **doi:** https://doi.org/10.1101/2020.12.14.422660

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Comparison of scratching severity by owner completed PVAS to Whistle canine collar

- Monitoring severity of pruritus is a challenge for dog owners but important in communicating with veterinarians and evaluating response to therapy.
- Pruritus visual analogue scoring (PVAS) is effective but requires pet owner recording.
- This study compares scratching severity recorded using Whistle canine activity monitors* (Mars Petcare, McLean, VA);
- The association between Whistle scratching categories with PVAS scores was modelled using a logistic regression model with a beta distribution and logit link.
- As scratching severity increased as measured by the Whistle canine collar, PVAS scores significantly ($P < 0.01$) increased.
- **Whistle provides a practical tool to objectively evaluate pruritus severity**.

This works well to support veterinary care and treatment plans but could you use in a formal registration context ?

Submitted to ESVD 2021 Abstract and Publication in Progress

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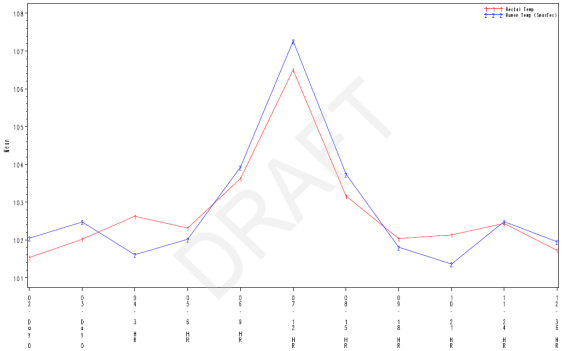
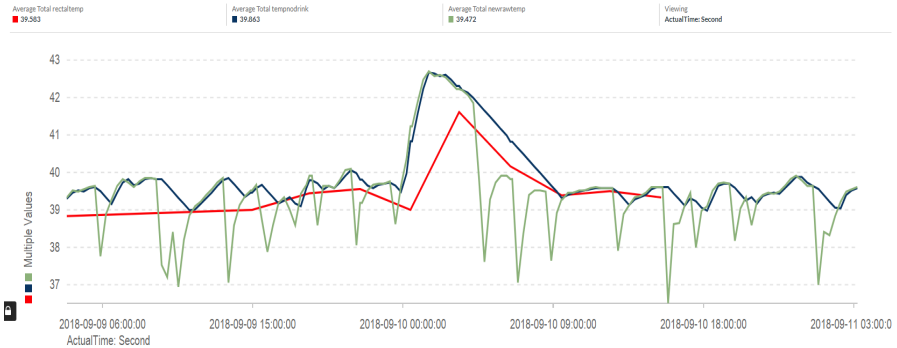
OBSERVATION OF A POSITIVE CORRELATION BETWEEN RECTAL TEMPERATURES AND BIOSENSOR



Positive correlation when comparing specific timepoints of rectal temps vs sensor (Pearson coefficient of >0.81)



However, rectal temps can miss key curve events during challenge

Assessing clinical signs in an E.coli challenge model

Rumen temperature provides a better indication of physiological state than rectal temperature alone

- More consistent peaks of temperature
- Provides additional information about drinking behavior

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Sounds great – BUT…….

How would this work in a Regulatory context ?

- Expectations for validation of a biosensor?
- Correlation to traditional/gold standard method?
- GLP/GCP considerations for data collection and validation and auditing
- Use for traditional end points eg Temperature monitoring - a first step?
- Use for non-traditional endpoints – a bigger challenge?

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Summary - Use of large data sets ("big data") & regulatory questions

Use/value	Data type	Questions
Regulated label* claim target or diagnostic to support traditional outcomes (e.g., use of sensor for temperature evaluations)	Omics, diagnostics, biomarkers, devices metrics & sensor data	• What are the requirements if there is a gold standard? • Data access and requirements if algorithms are used? • Regulatory GLP/GCP expectations for data validation/collection and storage
Novel outcomes to support **regulated** label claims*		• Is it possible to reference human health examples and paths (HRQL)? • What are the data and submission expectations?
Novel outcomes including monitoring devices to support customer use of licensed products or therapeutic plan		• Not intended for additional label claim • There should be greater flexibility of use • Product use/therapeutic plan# - new prescription or product use without veterinary recommendation • Considerations for long term use to support posology on label?
Non-regulated space: (not used as pivotal data to support regulatory approval*, consumer, research use devices) (Outcomes research)		• Greater flexibility of use • Regulation specific to device in terms of machine vs diagnostic/therapeutic use (non-registered device does not equal not-certified)

*Regulated label claims/approvals refers to oversight by EMA, USDA-CVB & FDA-CVM
#Must meet basic criteria, cannot be false and misleading

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A few last overall industry thoughts

Basic principles and concepts established by the human health industry, which would be very similar for animal health:

- **Vision for data-driven medicines regulation is supported (”innovate to turn data into decisions on medicines that create a healthier world”).**
- **Evolution of Precision medicine**
- **Global Harmonisation is important**
- **A collaborative approach is needed to address the challenges, including developing best practice guidance to ensure quality in the context of different data sources and use cases.**
- **We recognising the value of RWD as a complement to clinical trials.**
- **Health digitalisation requires digital and health education (in a continuous and federated form of learning).**
- **Industry needs to be regarded/involved as a true partner**

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QUESTIONS?

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