Construction of a conceptual framework for assessment of health-related quality of life in calves with respiratory disease

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Abstract

Bovine respiratory disease (**BRD**) is one of the most prevalent diseases affecting beef and dairy calves worldwide, with implications for lifetime productivity, antimicrobial use, and animal welfare. Our objective was to construct a conceptual framework for assessment of health-related quality of life (**HRQL**) in calves with respiratory disease, based on indicators suitable for direct pen-side visual observation. HRQL measures aim to evaluate the subjective experience of the animal rather than any related pathology. A conceptual framework graphically represents the concepts to be measured and the potential relationships between them. A multistage, mixed method approach involving diverse data sources, collection methods and stakeholders, was applied to promote comprehensiveness, understanding and validity of findings. A scoping review was conducted to identify, characterise and collate evidence of behavioural indicators of BRD studies. The indicators identified were mapped against the principal attributes of five prominent

animal welfare assessment frameworks to appraise their correspondence with different characterisations of the dimensions of welfare. Forty-two semi-structured, individual, qualitative interviews with a purposeful sample of experienced veterinarians and stockpersons from UK, US and Canada, elicited in-depth descriptions of the visual observations of HRQL they make in diagnosing and assessing the response to treatment of calves with BRD. Verbatim interview transcripts were examined using inductive thematic analysis. Respondents provided insights and understanding of indicators of HRQL in BRD such as interaction with feed source, hair coat condition, specific characteristics of eye appearance, eye contact, rumen fill and stretching (pandiculation). In an on-farm pilot study to assess the value of potential HRQL behavioural indicators, there was a moderate positive correlation between behaviour and clinical scores (r_S = 0.59) across the 5 days preceding veterinary treatment for BRD. Interestingly the behaviours evaluated were observed a median of 1.0 (interquartile range, **IQR**: 1.0 – 3.5) days before clinical indicators used in the scoring system. The proposed conceptual framework for assessment of HRQL features 23 putative indicators of HRQL distributed across two interrelated domains – clinical signs and behavioural expressions of emotional wellbeing. It has potential applications to inform the development of new HRQL measures such as structured questionnaires and automated sensor technologies.

Keywords

subjective experience, welfare, bovine, qualitative, measurement

Implications

The conceptual framework constructed in this study integrates clinical and behavioural indicators to advance understanding of HRQL in BRD. It includes several putative behavioural indicators of HRQL in BRD that could complement existing pen side scoring systems. The framework can guide the development of valid and reliable instruments to operationalise measurement of HRQL in BRD and inform welfare assessments. These have potential to complement BRD diagnosis, treatment decisions and evaluation of treatment outcomes, and thereby enhance cattle health, welfare and lifetime productivity, and advance antimicrobial stewardship through improved disease management.

Introduction

Bovine respiratory disease (**BRD**) is one of the most prevalent diseases affecting beef and dairy calves, with implications for lifetime productivity, antimicrobial use, and animal welfare. Prevalence in dairy herds from birth to weaning and in beef feedlots is around 20% (USDA, 2013; Dubrovsky *et al*., 2019). BRD is the cause of around a quarter and over half of all mortalities respectively in preweaned and weaned dairy calves destined to be heifer replacements (USDA, 2018), and around half of all mortalities in beef feedlots (Peel, 2020). BRD in dairy calves has been associated with increased age at first calving (Van der Fels-Klerx *et al*., 2002; Stanton *et al*., 2012), decreased calving ease and survival to first calving (Stanton *et al*., 2012), reductions in lactation yield (Schaffer *et al*., 2016) and reduced longevity in the dairy herd (Bach, 2011). BRD in beef cattle has been associated with reduced daily liveweight gain and carcass value at slaughter (Blakebrough-Hall *et al*., 2020).

Various approaches to diagnosis and monitoring BRD have been proposed including systematic scoring of clinical signs (McGuirk and Peek, 2014), continuous automated monitoring of behaviour and feeding (Cramer *et al*., 2020), medical imaging of lung lesions, including thoracic ultrasonography (Cramer and Ollivett., 2019), evaluation of blood markers of respiratory disease, and necropsy (Blakebrough-Hall *et al*., 2020). A clinical respiratory scoring system for young dairy calves has been developed at the University of Wisconsin using observations of rectal temperature, nasal discharge, cough, eye discharge, and ear position (McGuirk and Peek, 2014) and by the University of California based on ocular discharge, nasal discharge, ear droop or head tilt, cough, breathing quality, and rectal temperature (Love *et al*., 2014).

The primary purpose of clinical scoring systems is to identify calves that require veterinary treatments. By contrast, health-related quality of life (HRQL) assessments aim to assess, in the context of an altered health state and associated health interventions, the evaluation by the individual of its circumstances (internal and external), and the affective (emotional) response to those circumstances (Wiseman-Orr *et al*., 2006). In other words, they aim to reflect the experience for the patient and aim to provide a more holistic assessment of the impact of the condition and its treatment. Since animals are unable to directly report subjective experience, debate is ongoing concerning the definition and assessment of animal welfare and quality of life (**QL**) (Fraser *et al.*, 1997; Broom, 2007). Other authors have discussed the relationship between behaviour and QL (Wemelsfelder, 2007). Conceptual frameworks, such as Five Freedoms (FAWC, 1993); Five Domains Model (Mellor,

2016) and Welfare Quality® Assessment (Welfare Quality, 2009), have been proposed as systematic approaches for assessment of animal welfare and QL.

HRQL assessments are widely used in human medicine. The Food and Drug Administration (**FDA**) patient-reported outcome (**PRO**) guidance (FDA, 2009) outlines methods for the development and validation of human PROs and HRQL measures that can be used to support claims in medical product labelling. Generic and disease-specific HRQL measures have been developed for dogs (Belshaw *et al*., 2015; Vøls *et al*., 2016; Giuffrida *et al*., 2018; Davies *et al*., 2019), cats (Tatlock *et al*., 2017; Noble *et al*., 2019) and a measure for pigs (Wiseman-Orr *et al*., 2011), but to date no instrument purporting to measure HRQL has been described for cattle.

The objective of this study was to construct a conceptual framework for assessment of HRQL in calves with respiratory disease, based on indicators suitable for direct pen-side visual observation. Direct observation of animal behaviour has been suggested as a critical component of quality of life assessments, which can guide management decisions (Wemelsfelder, 2007). Other authors have used conceptual frameworks to inform the development and comprehensiveness of companion animal QL measures (Tatlock *et al*., 2017). Since HRQL assessments are intended to be used directly by animal carers to promote welfare enhancement, it is also important to involve animal carers in their development (Wiseman-Orr *et al*., 2011). The approach adopted here, therefore, uses both qualitative and quantitative methods, with reliance on multiple sources of information (Patrick *et al*., 2011; Cheng and Clark, 2017). By reviewing the literature for behavioural indicators of BRD, mapping indicators against the principle attributes of five prominent animal welfare

assessment frameworks and by consulting key informants, this study aims to identify and pilot test pen-side observations reflecting the animal's experience (as determined by it's behavioural expressions) of BRD that are suitable for inclusion within a HRQL conceptual framework.

Material and methods

A multistage, mixed method approach involving diverse data sources, collection methods and stakeholders was applied to promote comprehensiveness, understanding and validity of findings (Fig. 1). Information from the scoping review, mapping and concept elicitation interviews served to support the selection and development of appropriate indicators. Behavioural indicators were evaluated on-farm to assess their suitability for inclusion in the proposed conceptual framework.

Scoping review

A scoping review, an approach to evidence synthesis particularly suited to identifying and mapping key characteristics of a concept (Munn *et al*., 2018), was conducted to identify, characterise and collate evidence of behavioural indicators of BRD reported in behaviour research and clinical studies evaluating the effectiveness of antimicrobial treatments. The Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (**PRISMA-ScR**) checklist was used to guide the conduct and reporting of the review (Tricco *et al*., 2018). A review protocol was established in advance. The research question and eligibility criteria were formulated according to the Population – Concept – Context framework recommended for scoping reviews (Peters *et al*., 2020). The review aimed to address the following research question: What is the evidence for behavioural and

148 emotional indicators of respiratory disease in beef or dairy calves in any production
149 system? The following characteristics of records were predefined eligibility criteria:

150 • Population: beef or dairy calves; domestic cattle, *Bos taurus;* any breed or
151 sex.
152 • Concept: behavioural or emotional indicators of respiratory disease; indicator
153 explicitly characterised.
154 • Context: natural infection or artificial challenge, any production system, pre- or
155 post-intervention (if any), experimental or commercial settings.
156 • Types of evidence source: original research report, written in English
157 language, published in a peer-reviewed journal, full text accessible through
158 institutional access or by contacting the authors using the ResearchGate
159 platform.

160 An electronic search of CAB Abstracts (1971 – 2019) was performed in August 2019
161 via the EBSCOhost platform. CAB Abstracts bibliographic database was selected
162 based on its extensive coverage of veterinary journals (Grindlay *et al.,* 2012). Search
163 terms were combined with Boolean operators into the following search string:
164 (respiratory disease OR BRD OR pneumonia) AND (calf OR calves OR heifer OR
165 bull) AND (behaviour OR emotion OR emotional OR cognitive). Clinical studies
166 included in a meta-analysis to evaluate the effectiveness of antimicrobial treatments
167 in BRD (Abell *et al*., 2017) provided an additional source of records for analysis. A
168 comprehensive data charting table, purpose-built for this review and refined
169 iteratively during its conduct, was used to extract relevant information from included
170 sources of evidence. A single reviewer (EB) performed the initial search, applied
171 eligibility criteria and extracted the data. Eligibility and extracted data were verified
172 independently by a second reviewer (DM). Any disagreements were resolved by

discussion. Consistent with published guidance for scoping reviews (Tricco *et al*., 2018; Sargeant and O'Connor, 2020), the approach was to chart the data to collate a comprehensive categorised list of reported behaviours of calves with respiratory disease, rather than to extract and compile study results and critically appraise methodological quality and risk of bias.

Mapping to established animal welfare assessment frameworks

The indicators identified from the scoping review were categorised into the key attributes of five established animal welfare assessment frameworks to appraise their correspondence with different characterisations of the dimensions of welfare: Five Freedoms (FAWC, 1993); A Good Life in terms of the Five Freedoms (FAWC, 2009); Five Domains Model (Mellor, 2016); Three Orientations (Mellor, 2016); Welfare Quality® Assessment (Welfare Quality, 2009).

Concept elicitation interviews

Key informants are considered vital to the construction of measurement conceptual frameworks because they will ultimately become the users of any instruments subsequently derived and should have expert knowledge of the observations relevant to assessment of the health condition concerned (Wiseman-Orr *et al*., 2011; Patrick *et al*., 2011). A purposeful and diverse sample of 42 experienced veterinarians and stockpersons from the UK, US and CA was selected as key informants based on their working relationship with beef or dairy calves across a range of different production systems. Calves were defined as any animal <10 months to reflect differences in weaning age across production systems. Potentially eligible interview participants were identified through a combination of professional

198 connections, social media invitation and chain referral. Interviews were used to elicit
199 in-depth descriptions of the QL-related visual observations they make in diagnosing
200 and assessing the response to treatment of calves with BRD. Critical incident
201 technique methodology (Golding *et al*., 2019) was applied to develop a semi-
202 structured interview topic guide in which participants were asked to consider recent
203 scenarios in which they had diagnosed and treated calves with respiratory infection.
204 Audio-recorded, individual interviews were conducted by one author (EB) by
205 telephone (UK, Canada) or face-to-face (US). The interview style adopted was
206 consistent with that proposed by Brédart *et al*. (2014) for exploratory interviews to
207 elicit in depth reports of participants' experiences. The recruitment process continued
208 until it was estimated that conceptual saturation had been reached because no new
209 relevant information was emerging.

210

211 *Interview data analysis*

212 Verbatim interview transcripts were imported into NVivo for Windows (version 12)
213 (QSR International Pty Ltd., Melbourne, Australia) (Hoover and Koerber, 2011).
214 Transcripts were analysed using inductive thematic coding which involved iteratively
215 reading and rereading the data, grouping extracts into common themes, and naming
216 concepts. This ensured that the data generated were grounded in, or emergent from,
217 the narratives of the interview participants. Conceptual saturation was confirmed
218 during analysis by the non-emergence of new codes or themes (Braun and Clarke,
219 2006). Relevant interview excerpts were selected to represent the perceptions of
220 participants relevant to the themes and explanations being constructed. Differences
221 from behaviours identified in the scoping review were discerned and highlighted.
222 Following the Golding *et al*. (2019) methodology, one person was mainly responsible

for the analysis, but team members participated in evaluating each concept in relation to its study excerpts, and the final rechecking of the analysis.

Pilot study

A pilot study was conducted to examine the construct validity of multiple putative behavioural indicators as a composite index to assess in principle whether behavioural indicators could measure HRQL. Construct validity appraises the ability of the indicators to measure the concept they are intended to measure (a construct) (Patrick *et al*., 2007), in this case HRQL. HRQL is not measurable directly (a latent variable) and in the current absence of an agreed standard for its estimation, we postulated that if the behavioural observations identified in the draft conceptual framework were suitable indicators of HRQL in BRD there would be a moderate correlation between the total number of behavioural indicators observed and clinical signs of BRD. This hypothesis was tested on-farm in a prospective observational cohort study involving 76 mixed sex, 8 – 10 weeks old, loose-housed beef x dairy crossbred calves at a single UK facility. Calves were housed in a single shed divided into two pens, each with 38 calves and ~5.5 m^2 floor area per calf. Calves were fed commercial milk replacer twice daily from multi-teat feeders and had *ad libitum* access to starter feed. One researcher (BC) recorded a behaviour score based on 18 behavioural indicators (Supplementary Table S1) and a clinical respiratory score (**CRS**) based on the Wisconsin calf clinical respiratory scoring system (McGuirk and Peek, 2014) (Supplementary Table S2) once daily for five consecutive days for all 76 calves. The behaviour score was the total number of behaviour variables observed, a score of 1 being assigned to each indicator. The CRS was derived from assessment of four clinical signs (cough, nasal and ocular discharges, and ear

position) categorised into four (0 – 3) ordinal levels. The researcher recorded behaviour scores before assigning the CRS. Observations were made close to morning feeding time as this has been shown to be a time when calves are particularly active (Bokkers and Koene, 2001). BRD diagnosis and treatment decisions were made independently of the researcher by a single experienced on-farm calf caregiver, in accordance with the farm's normal operating procedures. This judgement was based on observing calves in their normal environment and measuring rectal temperature, as required to confirm diagnosis.

Statistical analysis

For each calf that had a BRD treatment event (n = 13) the behaviour and clinical scores for the 5 days preceding veterinary treatment were imported into a single file and analysed using SPSS software, version 26 (SPSS Inc., Chicago, IL). This analysis enabled us to retrospectively review the appearance of both clinical and behavioural indicators. A Friedman test was applied to estimate whether there were significant differences between time points for behaviour and clinical scores across the five days. Ordinal data presents challenges in analysis of repeated measures correlation. It could be highly misleading to analyse such data by combining repeated observations from several subjects and then calculating the correlation coefficient as if the data were one sample. Moreover, computing the correlation between variables separately at each time point ignores the dependencies between each pair of time points and potentially inflates alpha error by conducting multiple tests on the same dataset. Therefore, we applied an alternative method which involves conducting the analysis using a summary statistic for each variable in each subject which incorporates the change of the variable over time (Bland and Altman,

1995). Spearman rank test was applied to the median of the repeated measures for each calf across the 5 days preceding treatment to estimate the strength of the correlation between behaviour and clinical scores across subjects. A *P*-value of < 0.05 was considered statistically significant.

Results

Scoping review

After the systematic search and selection, 24 publications were included for qualitative synthesis: 7 studies related to evaluation of the effectiveness of antimicrobial treatments in BRD and 17 studies concerned behavioural indicators of BRD in behaviour research (Fig. 2). The behaviours identified were categorised inductively into groups, tabulated and assigned a behaviour code (1 – 17). The analysis identified four behaviour typologies associated with respiratory disease in calves: feeding, exploratory, activity and socialising (Table 1). Of the accessible papers reporting the effectiveness of antimicrobial treatments (*n* = 27), one-third (9/27) did not refer to any assessment of behaviour in the evaluation of treatment outcomes, one-third (9/27) included depressive-like state in outcome evaluations but did not characterise this further, and one-third (9/27) included depressive-like state and characterised it in terms of specific behaviours. In the latter studies, the behaviours were inadequately described and embedded into subjective composite assessments of an animal's depressive-like state referred to as depression or clinical attitude scores (e.g. Tennant *et al*., 2014). The behaviours most frequently described were isolation from the group (4/9), reduced activity (4/9) and increased lying time (3/9).

298 ***Mapping to established animal welfare assessment frameworks***

299 The behavioural indicators identified corresponded with different characterisations of
300 the dimensions of welfare (Table 2), providing evidence in support of their
301 association with welfare states.

302

303 ***Concept elicitation interviews***

304 Participants (*n* = 42) were veterinarians (*n* = 19) and stockpersons (*n* = 23) from UK
305 (*n* = 20), US (*n* = 17) and Canada (*n* = 5) and represented dairy and a range of
306 different beef production systems including cow-calf, backgrounder, feedlot, veal and
307 seedstock (breeder) operations. Approximately three-quarters of participants (76%,
308 32/42) had over 10 years' experience and the majority were male (71%, 30/42). All
309 participants described themselves as the key decision maker in relation to BRD
310 treatment decisions. Inductive thematic analysis of the interview transcripts
311 generated three key themes: how the calf looks, how the calf reacts, and how the
312 calf carries out normal activities. The indicators elicited and representative interview
313 quotations are presented in Table 3. The detailed responses on topics such as
314 interactions with the feed source, oral manipulation of the artificial teat, suckling
315 behaviours and sham eating, provided potentially useful indicators of HRQL in BRD.
316 For example, one respondent suggested that sick calves 'come to the feed bunk but
317 they won't eat' and another described healthy calves 'bumping things around, being
318 a very active nurser'. Rumen fill, which is also related to feeding behaviour (Burfeind
319 *et al*., 2010), was suggested by livestock keepers, though it was not reported as an
320 indicator in our literature review. As seen from the examples in Table 3, most
321 indicators were described by participants as signalling an animal's emotional
322 experience of HRQL in both positive and negative valence. Bidirectionality was

implicit when it was described in neutral terms. The behaviours purportedly related to emotional wellbeing which emerged most frequently from participants' narratives included volume of feed intake, movement to feed, spatial proximity, motivation at feed and vigour

Pilot study

Thirteen calves required veterinary treatment during the 5-day period. All of the remaining 63 calves had clinical and behaviour scores of zero at all assessments. The number of calves showing each behaviour and CRS sign in the 5 days preceding veterinary treatment for respiratory disease is displayed in Supplementary Tables S1 and S2 respectively. Behaviour and clinical scores for the 5 days preceding treatment are summarised in Fig. 3. There were significant differences between time points for behaviour scores ($\chi^2 = 51.81$, df = 3, $P = <0.001$) and clinical scores ($\chi^2 = 38.96$, df = 3, $P = <0.001$) across the 5 days, i.e. for both clinical and behaviour scores, the median score for at least one of the time points differed from the other time points. Behaviour scores were observed up to 4 days prior to treatment, a median of 1.0 (IQR: 1.0 – 3.5) days before clinical scores. Drinking speed, level of activity and responsiveness towards humans were the earliest behavioural indicators (Supplementary Table S1). There was a moderate positive correlation between behaviour scores and clinical scores ($r_s = 0.59$, $P = 0.035$) across the 5 days preceding veterinary treatment.

Conceptual framework

346 A conceptual framework for assessment of health-related quality of life (HRQL) in
347 calves with respiratory disease, derived from the results of the scoping review,
348 concept elicitation interviews and pilot study is presented in Fig. 4.
349
350 **Discussion**
351 Scientific endeavour to evaluate animals' capacity for sentience (Kremer, 2020)
352 highlights the need for health and welfare assessment methods which incorporate
353 measures of emotional wellbeing. The objective of this study was to construct a
354 conceptual framework for assessment of HRQL, including emotional wellbeing, in
355 calves with respiratory disease. We used data from three sources to construct an
356 empirically-derived conceptual framework for assessment of HRQL in calves with
357 respiratory disease, based on indicators suitable for direct pen-side visual
358 observation. Previous studies (Cramer and Ollivet., 2020; Cramer and Stanton.,
359 2015; Cramer et al., 2019) have quantitatively assessed calf behaviour in BRD. This
360 study explored qualitatively, the indicators that veterinarians and stockpersons
361 consider to be important when assessing HRQL in calves with BRD. The proposed
362 framework features 23 putative indicators of HRQL distributed across two broad
363 interrelated domains – clinical signs and behavioural expressions likely to be
364 associated with emotional wellbeing.
365
366 ***Indicators suggested during interviews***
367 To inform the construction of our conceptual framework, we interviewed
368 veterinarians and stockpersons with extensive practical experience of managing beef
369 or dairy calves with respiratory disease across a range of different production
370 systems and countries. As expected, several indicators reported in the interviews,

such as feeding behaviour and reduced grooming behaviour, were also identified in the scoping review. The respondents provided relevant detailed suggestions for indicators associated with interaction with feed source, hair coat condition, specific characteristics of eye appearance, eye contact, rumen fill and stretching (pandiculation) that were not captured in the scoping review. One-third of interviewees reported hair coat condition as a useful indicator of wellbeing with one respondent commenting that calves with BRD are 'not looking after themselves'. As with goats, poor hair coat condition may be valuable as an indicator of welfare (Battini *et al*., 2015). Sunken appearance of the eyes was also an indicator for almost one-quarter of interview participants. It is recognised as a sign of dehydration and its magnitude forms the basis of clinical dehydration scores (e.g. Renaud *et al*., 2018). Vibrancy of eyes, described by interview participants as the eyes appearing 'clear', 'bright', 'dull' or 'glazed', is referred to in some calf health scoring systems as a sign of dehydration (e.g. Lowe *et al*., 2019). In the context of the interview narratives, some respondents also appeared to relate eye contact to the response to humans as a potential predator. It is possible that avoidance of eye contact, reported by one-fifth of interview participants, is an indicator of negative emotional valence in calves. In humans, changes in gaze behaviour are associated with affective disorders including depression (Suslow *et al*., 2020).

Pilot study

This step was conducted to examine the construct validity of 18 putative behavioural indicators as a composite index. The moderate positive correlation between behaviour scores and clinical scores across the 5 days preceding veterinary treatment was consistent with our *a priori* hypothesis and contributed evidence to

support their potential to measure HRQL. The observation of behavioural indicators prior to the appearance of clinical signs of BRD is consistent with previous findings using sensor technologies which showed that sick calves have longer lying bouts, longer total daily lying time, and fewer feeder visits with consumption, several days prior to clinical detection (Marchesini *et al*., 2018; Belaid *et al*., 2019; Haskell *et al*., 2019; Ramezanigardaloud *et al*., 2019).

Our results cautiously suggest that calves that did go on to develop clinical BRD demonstrated some behavioural indicators, specifically drinking speed, level of activity and responsiveness towards humans, that were potentially suitable as visual early warning indicators of respiratory disease in calves. This study was limited to an examination of these indicators for a HRQL tool. However, a systematic evaluation of the predictive value of these behaviours may warrant further investigation. For example, it is also important to determine the relationship between these behaviours and subclinical disease detected by thoracic ultrasound. Previous studies have reported that observations of some behaviours were not able to accurately identify calves with subclinical BRD (Cramer *et al*., 2019 and 2020).

Conceptual framework

The proposed conceptual framework explicitly defines the principal clinical and behavioural indicators of HRQL in BRD and how these can be grouped into two interrelated domains. Some clinical signs such as cough and nasal discharge when concurrent are pathognomonic features of respiratory disease. By contrast, all the behavioural expressions of emotional wellbeing and several clinical signs including posture, hair coat condition and rumen fill, are not disease-specific and are possibly

indicators of calf HRQL in general, not just in the specific context of BRD. The framework includes several indicators of HRQL in BRD described by experienced veterinarians and stockpersons, but not normally included in clinical scoring systems. These behaviours are often generic sickness-related signs that may not be a specific predictor of respiratory disease. It is, therefore, not surprising that they are not included in clinical scoring systems designed to identify calves requiring veterinary treatment. However, behavioural indicators, which are likely to be related to emotional state, would be relevant for a HRQL measurement instrument aimed at reflecting the animal's experience of BRD.

Evidence to support the construct validity of these behavioural indicators elicited during the interviews is sparse and of low quality, especially in the specific context of BRD. However, they are included to ensure the most complete conceptualisation of HRQL and should be investigated when the framework is applied to the development of new measures. If they do not make unique contributions to measurement of HRQL they can be omitted from a final measurement instrument. Monitoring behaviour to assess emotion can be challenging in that key indicators such as play, grooming or movements unique to feeding time might only occur infrequently or be influenced by individual personality traits (Neave *et al*., 2018). Moreover, while some behaviours, such as mutual grooming, are unequivocal in their emotional valence, the meaning of others such as competition at feeding can be more difficult to gauge (Cooper and Wemelsfelder, 2020). Several of the indicators in the conceptual framework, such as posture or movement to feed, may lend themselves to measurement using a qualitative behaviour assessment (**QBA**) approach in which the focus is the animal's expressive style of behaving (demeanour) rather than its specific behaviours, using

446 descriptors such as relaxed, enjoying, irritable or happy (Cooper and Wemelsfelder,
447 2020). QBA has been successfully applied to assess emotional wellbeing across a
448 wide range of species including livestock (Fleming *et al*., 2016) and has been
449 examined in health contexts such as lameness (Phythian *et al*., 2016) and
450 gastrointestinal parasitism (Grant *et al*., 2020) in sheep, and mastitis in dairy cattle
451 (de Boyer des Roches *et al*., 2018).
452
453 ***Limitations***
454 This study aimed to explore the potential indicators of HRQL in BRD suitable for
455 direct pen side visual observation that reflect the experience of the calf, rather than
456 to replace or refine existing clinical measures of BRD for which a 'gold standard'
457 clinical outcome can be defined. A conceptual framework was constructed by
458 applying a robust combination of quantitative and qualitative approaches consistent
459 with previous QL investigations (Tatlock *et al*., 2017, Wiseman-Orr *et al*, 2011).
460
461 Despite a rigorous literature search methodology to promote comprehensiveness,
462 some relevant studies may have been missed due to use of a single bibliographic
463 database and exclusion of grey literature from the review. Future research should
464 consider increasing the breadth of coverage of the search. For concept elicitation,
465 interviews and thematic analysis have been shown to achieve the greatest depth in
466 conceptual understanding (Humphrey *et al*., 2017; Rising *et al*., 2019). However, the
467 application of additional methods such as group concept mapping would have
468 provided a complementary approach for identifying measurement concepts. Group
469 concept mapping is a participatory mixed methods approach that uses an online
470 platform to integrate qualitative group processes with multivariate statistical analyses

to generate, structure and represent the content of a specific topic (Humphrey *et al*., 2017). A sole person was mainly responsible for performing the thematic analysis, which has potential to bias the results. However, this was mitigated by maintaining a reflexive approach throughout and the other authors evaluated each concept in relation to its study excerpts and performed a final recheck on the analysis. The pilot study assessed the construct validity of behavioural indicators by examining their convergent validity with clinical scores. Although the pilot study was a strength of this study, it was not without its limitations. Not all behavioural indicators were included because additional concepts were derived from the thematic analysis after the pilot validation began. The sample size was small, behaviours were examined as a composite index rather than separately, and there was potential for observer bias as the behaviour and clinical scores were not assigned independently. Moreover, the study examined the indicators in a single production setting, preweaned beef x dairy crossbred calves, which cannot be generalised to others. However, notwithstanding these limitations, the pilot validation methodology was sufficient to achieve the purpose intended.

Applications

The proposed conceptual framework has applications to guide the development of valid and reliable instruments to operationalise measurement of HRQL in BRD. These could enhance cattle health, welfare and lifetime productivity, and advance antimicrobial stewardship through improved disease management. The rigorous methodology applied to the construction of the proposed conceptual framework provides robust evidence to support the content validity of questionnaire measurement instruments derived from it. The next steps in this research agenda

include following established methodologies for item (i.e. question) generation, item reduction and response formatting to prepare a prototype questionnaire, and examination of its validity, reliability and other measurement properties, feasibility and utility in a range of different production settings and for different purposes such as dairy and beef systems. If farmers could be alerted to diseased animals earlier than is currently possible based on clinical signs alone, this would enable earlier treatment of diseased animals to prevent further spread of disease. HRQL measurement could also be applied to help inform decisions of when to treat, the selection of the most appropriate treatment(s) and the assessment of treatment outcomes. We suggest that an effective treatment strategy is one which, in addition to alleviation of clinical signs and control of the disease-causing organisms, also enhances the HRQL of an animal. Furthermore, the conceptual framework may guide the development of automated sensor technologies to support health and welfare assessments.

Conclusions

Using a combination of methods, this study has proposed a multidimensional concept of HRQL in BRD that includes behavioural indicators that may complement other indicators of disease. This included putative indicators derived from interviews with veterinarians and stockpersons who had extensive practical experience of managing calves with respiratory disease. The framework provides a foundation for advancing welfare assessments and informing instrument development and sensor technologies to improve BRD management.

Ethics approval

The Royal Agricultural University (RAU) Ethics Committee reviewed the concept elicitation interview (2019.0012) and the pilot validation study (2019.0131) protocols and gave favourable opinions. The study was conducted in compliance with their conditions. All interview participants provided handwritten or online informed consent before the interview, transcripts were anonymised and stored on a password protected device, and all contact details were stored securely before being deleted 30 days after interview.

Data and model availability statement

None of the data were deposited in an official repository. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Declaration of interest

None.

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852

853 **Table 1** Behaviours exhibited by calves with respiratory disease.

854

Typology	Description of behaviour	Study
Feeding	Fewer visits to feeder when feed is available (rewarded visits)	Hixson *et al*., 2018 Swartz *et al*., 2017
	Reduced drinking speed	Knauer *et al*., 2017
	Reduced volume of intake	Buhman *et al*., 2000 Hixon *et al*., 2018 Jackson *et al*., 2016 Johnston *et al*., 2016 Kayser *et al.*, 2019 Quimby *et al*., 2001
	Fewer visits to feeder when feed is not available (unrewarded visits)	Svensson and Jensen, 2007 Johnston *et al.*, 2016
	Avoidance of competition	Hixson *et al*., 2018
	Reduced head down duration	Jackson *et al.*, 2016
	Decreased rumination time	Marchesini *et al.,* 2018
Exploratory	Less likely to approach novel object	Cramer and Stanton, 2015
	Less time spent in proximity of novel object	Hixson *et al*., 2018
	Less likely to approach stationary human	Cramer and Stanton, 2015
Activity	Decreased number of steps/ less active	Baggott *et al*., 2011 Hanzlicek *et al.*, 2010b Marchesini *et al*., 2018 Swartz *et al*., 2017 Van Donkersgoed, 2012 Van Donkersgoed and Merrill, 2013a, 2013b White *et al*., 2012 White *et al*., 2015
	Increased lying time	Hanzlicek *et al*., 2010a Hanzlicek *et al*., 2010b Hixson *et al.*, 2018 Lechtenberg *et al*., 2011 Step *et al*., 2007 Tennant *et al*., 2014 Theurer *et al.*, 2013 Toaff-Rosenstein *et al*., 2016
	Less time at feeder	Baggott *et al*., 2011 Theurer *et al*., 2013 White *et al*., 2012
	Increased time standing inactive	Hixson *et al.,* 2018
Social	Fewer play incidents (head butting)	Hixson *et al.,* 2018
	Reduced self and social grooming	Hixson *et al*., 2018
	Isolation from the group	Lechtenberg *et al*., 2011 Van Donkersgoed, 2012 Van Donkersgoed and Merrill, 2013a, 2013b White *et al*., 2015

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856 **Table 2** Mapping of clinical and behavioural indicators of respiratory disease in calves against the attributes of five animal welfare assessment
857 frameworks to appraise correspondence.

Welfare assessment framework			Mapping of BRD indicators
Name	Principles	Provisions	
Five Freedoms	Freedom from hunger and thirst	Ready access to water and a diet to maintain health and vigour	1, 3
(FAWC, 1993)	Freedom from discomfort	By providing an appropriate environment	-
	Freedom from pain, injury and diseases	By prevention or rapid diagnosis and treatment	C
	Freedom to express normal behaviour	By providing sufficient space, proper facilities and appropriate company of the animal's own kind	8 – 12, 15 – 17
	Freedom from fear and distress	By ensuring conditions and treatment which avoid mental suffering	-
A Good Life in terms of the Five Freedoms	Freedom from hunger and thirst	Food should be a pleasurable experience	1 – 7
	Freedom from discomfort	Environments provided that animals seek out and enjoy	-
(FAWC, 2009)	Freedom from pain, injury and diseases	Adequate anaesthesia and pain relief should be provided	C
	Freedom to express normal behaviour	Positive behaviours such as play or social grooming	8 – 10, 14 – 17
	Freedom from fear and distress	No imposed circumstances in which animal is in fear or distress	-
Five Domains Model	Nutrition	Negative: Restricted food/water intake; unchanging diet; poor food quality; infrequent feeding	1 – 7
(Mellor and Beausoleil, 2015; Mellor, 2016)		Positive: Sufficient feed/water; varied and preferred food tastes, smells and textures	
	Environment	Negative: Extreme heat or cold; injurious hard surfaces; restricted space; smells of excrement	-
		Positive: Thermally comfortable; padded bedding; fresh air	
	Health	Positive: Acute or chronic injury; ill health; poor physical fitness; physically disabled	C, 11, 12, 14
		Negative: Injury fee; robust gut health; good fitness level	
	Behaviour	Negative: Restricted, barren, unvarying environment; threatening circumstances; no company	8 – 17

Welfare assessment framework			Mapping of BRD indicators
Name	Principles	Provisions	
	Mental state	Positive: Able to explore, herd and exercise extensively; able to socialise with others and play Negative: Thirst, hunger; heat or cold stress; physical and olfactory discomfort; boredom, frustration; pain, nausea, anxiety, helplessness, loneliness, depression, neophobia Positive: Pleasures of eating/drinking; pleasures of thermal physical and olfactory comfort; feeling the vitality of robust good health and physical fitness; rewarding engagement with exploration, herding and exercise; comfort and security of socialising with bonded others. Rewards of exercising agency and having a sense of control	C, 1 – 17
Three Orientations (Fraser et al., 1997, Webster *et al*., 2015; Mellor, 2016)	Biological functioning	Functionally based – health and normal body functioning	C, 1 – 3
	Affective state	Feelings and emotions – freedom from suffering in the sense of prolonged or intense pain, fear, hunger and other negative states	C, 1 – 17
	Natural living	Naturalness of conditions animal kept in – according to its nature, ability to perform natural behaviours	10, 11,12, 13, 14, 17, 18, 19
Welfare Quality®	Good feeding	Absence of prolonged hunger, absence of prolonged thirst	1 – 7
	Good housing	Comfort around resting, thermal comfort, ease of movement	-
(Welfare Quality, 2009; Manteca *et al*., 2012)	Good health	Absence of injuries, absence of disease, absence of pain induced by management procedures, such as castration, tail docking, dehorning, etc.	C
	Appropriate behaviour	Expression of appropriate social behaviour, such that there is a balance between negative aspects positive ones. Appropriate expression of other behaviours, such that there is a proper balance between negative aspects and positive ones. Good human-animal relationships, such that the animals do not fear humans. Positive emotional state.	8 – 12, 15 – 17

858

859 Indicators: C. Clinical signs; 1. Fewer visits to feeder when feed is available; 2. Reduced drinking speed; 3. Reduced volume of intake; 4. Fewer visits to
860 feeder when feed is not available (unrewarded visits); 5. Avoidance of competition; 6. Reduced head down duration; 7. Decreased rumination; 8. Less likely to
861 approach novel object; 9. Less time spent in proximity of novel object; 10. Less likely to approach stationary human; 11. Decreased number of steps/ less
862 active; 12. Increased lying time; 13. Less time at feeder; 14. Observation of standing inactive – stoicism; 15. Fewer play incidents (head-butting); 16. Less
863 likely to exhibit social grooming; 17. Isolation from the group. – No indicator mapped directly onto this attribute of the five animal welfare assessment
864 frameworks.

865 **Table 3** Representative quotations and indicators of health-related quality of life (HRQL) in calves with respiratory disease, derived from the
866 concept elicitation interview transcripts (*n* = 42). Concepts that supplement findings from the scoping review are marked with X.
867

Concept	*n* (%)	Representative quotation		
		Negative valence	Positive valence	
Domain 1: Clinical signs				
Theme 1: How the calf looks				
Rumen fill	8 (19%)	'If their flanks are sunk in at all it might suggest they haven't been eating' (8)	'How much fill they have, are they eating as much as everybody else?' (12)	X
Hair coat condition	14 (33%)	'Not looking after themselves so a bit of a rough coat' (6)	'They've got a good shine on the coat' (4)	X
Nasal discharge	27 (64%)	'Snotty noses like discharge around the nose' (5)	'If they're healthy and good, their noses are clean, but they're wet' (7)	
Spontaneous cough	14 (33%)	'Cough when they move. I always think it's worse when they cough, and they have to put their head down because it hurts.' (12)	'If they've stopped coughing then that's a good sign' (4)	
Respiratory rate/ effort	27 (64%)	'The farmer will see them breathing heavily or breathing fast and then obviously whenever we listen with a stethoscope you hear a lot more noise' (6)	'The breathing rate and effort would be returned to a more normal rate and normality' (6)	
Ocular appearance				
Discharge	4 (10%)	'Often discharge around the eyes.' (6)		
Vibrancy	9 (21%)	'I look at eyes a lot because you can pick out a calf… their eyes will be kind of glazed over a little bit' (7)	'Their eyes will be bright and clear' (10)	X
Sunken	10 (24%)	'Just a bit sunken eyed, maybe a bit dehydrated.' (5)	'Once they start feeding and getting their milk again, the eyes return to a normal position, you know more bulging rather than sunken into the head' (6)	X
Drooling saliva	4 (10%)	'Drooling at the mouth' (10)		X
Body posture	5 (24%)	'Standing there, with their back humped' (7)		

Concept	*n* (%)	Representative quotation		
		Negative valence	Positive valence	
Head carriage	20 (48%)	'One whose head carriage is slightly lower whether they be standing or whether they be lying down, and their head isn't listed up in a positive aspect.' (6)		
Ear carriage	25 (60%)	'That's a good clue if their ears are down then we know they're probably sick' (12)	'The drooping ears are back up and perky' (6)	
Domain 2: Behavioural expression of emotional wellbeing				
Theme 2: How the calf reacts				
Movement to feed	27 (64%)	'If it's feeding time and it's a bit shy about coming forward, then you know there's something wrong with it.' (4)	'It's with the other ones and as soon as you put the milk or pellets out it comes up with all of them' (5)	
Eye contact	8 (19%)	'…because they're a prey species, when they're sick they want to avoid any kind of appearance that they're sick …do they lower their head and try to walk away or do they make eye contact with the person who's checking and watch them.' (1)	'A calf will stand and turn and look at you if he's well' (6)	X
Responsiveness	21 (50%)	'If he's not well he doesn't give a **** that you're in the pen, does he? He's not interested in you' (4)	'Is it interacting with you when you're in there trying to do stuff? Is it chewing your clothes or is it just sitting in the corner just not doing anything?' (4)	
Competition at feeding	3 (13%)	'Slightly more vulnerable to being pushed off the teat by others.' (5); 'Not being aggressive, to push their way into the feed bunk' (10)	'If it can stand up to its mate where they are penned in lots of two.' (5)	
Engagement in play	18 (43%)	'Not wanting to butt around, you know, if somebody wants to pick on them they just go lay down or something maybe.' (12)	'If one decides to take off around the pen as they do, the rest of them are all skipping about, tails up, just sort of having a bit of a play' (6)	
Grooming	3 (7%)	'We do have some group grooming going on and then when they're just feeling sh***y they're not partaking' (3)		
Spatial proximity	24 (57%)	'Looking for animals that have isolated themselves.' (1)	'It's interacting with its pen mates. It's not segregated from them.' (6)	

Concept	*n* (%)	Representative quotation		
		Negative valence	Positive valence	
Theme 3: How the calf carries out normal activities				
Volume of feed intake	28 (67%)	'Recently there were a couple of calves I saw didn't finish their milk' (2); 'Calves that are nursing, the beef cows, those farmers do a very good job…they will also look at the cow's udder to determine whether she's been sucked out or not and so they'll appraise the appetite of the calf in that manner' (1)	'Drinking the full volume of milk offered…as well as eating other hay pellet hard feed' (6)	
Motivation at feed				
Speed of feeding	6 (14%)	'not drinking with much vigour' (6); 'the owner reported slow to drink' (6)	'…return of normal drinking speed' (3)	
Interaction with feed source	16 (38%)	'…calf latches on that teat … if they, every 20 or 30 seconds, maybe just pull off, stand back a bit, maybe even play with the teat before they start drinking, that would be a worry then' (5); 'Sometimes if calves are sick, they will come to the feed bunk, but they won't eat, they pretty much pretend to eat. You need to watch for those with their heads down but not actually really eating' (10)	'A normal calf is going to be nursing with what I call vigour, so very much up there with mumma, nuzzling her udder, bumping things around, being a very active nurser, kind of kicking those legs around a little bit, tails usually twitching' (11)	X
Time standing inactive	7 (17%)	'I'll watch them, because sometimes those sick calves they're just kind of standing there, inactive.' (8)	'You would see them having the time to rest and be willing to rest because some calves they're miserable and they just can't lay down and relax and, just like a person, you want to see that demeanour from the cattle.' (11)	
Lying time	21 (50%)	'Reluctant to get up…the calf growers would quite quickly recognise the calf that was reluctant to get up and wanted to stay there resting' (1); 'They don't feel like getting up out of bed like they should' (11)	'They should all get up at roughly the same time.' (6)	
Vigour	22 (52%)	'They're a little bit slower and they are at the back of the queue' (6); 'When a calf walks and	'You'll have more energy. They'll have more pop in their step' (8)	

Concept	*n* (%)	Representative quotation		
		Negative valence	Positive valence	
		he's picking up his feet. Just normal travelling across a pen or in a pasture…if they're dragging their feet, and it's not a very pronounced thing but they just don't have the energy to take a normal place with each step. It's a big indicator.' (11)		
Stretching	5 (12%)	'How does he get up? Does he stretch when he gets up or does he just wander and drift because it's too painful to stretch?' (4)	'When they stand the first thing we look for is a good stretch' (9)	X

868 Negative and positive valence refer to the subjective experience of the animal: pleasure (positive valence) or displeasure (negative valence) (Baciadonna et
869 al., 2018)

870 *n* = number of participants contributing to concept (out of a total of 42 interviews)

871 Numbers in parentheses refer to source participant demographics: (1) CA Beef Vet, (2) CA Veal Producer, (3) CA Veal Vet, (4) UK Dairy Beef Rearer, (5) UK
872 Dairy Farmer, (6) UK Mixed Vet, (7) US Backgrounder, (8) US Beef Vet, (9) US Cow-Calf Producer, (10) US Feedlot Producer, (11) US Mixed Vet, (12) US
873 Seedstock Producer

874 **** is used to replace some letters to avoid profanity

875

Figure captions

Fig. 1. Methodological approach to building the conceptual framework.

Fig. 2. Flow diagram of the systematic search process for the scoping review.

Fig. 3. Box-and-whisker plot of behaviour and clinical scores in the 5 days preceding treatment (*n* = 13). Horizontal bars indicate the median; boxes include first to third quartiles; whiskers show the 95% centiles; outliers are indicated by individual symbols. Behaviour score represents the sum of the total number of behaviours observed (Supplementary Table S1, maximum score = 18); Clinical score represents the score on the Wisconsin calf respiratory scoring system (CRS) (maximum score = 12) (McGuirk and Peek, 2014).

Fig. 4. A conceptual framework for measurement of health-related quality of life (HRQL) in calves with respiratory disease.