# Human-centered Artificial Intelligence: A Multidimensional Approach towards Real World Evidence

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Abstract: This study indicates the significance of a human-centered perspective in the analysis and interpretation of Real World Data. As an exemplary use-case, the construct of perceived 'Health-related Quality of Life' is chosen to show, firstly, the significance of Real World Data and, secondly, the associated 'Real World Evidence'. We settled on an iterative methodology and used hermeneutics for a detailed literature analysis to outline the relevance and the need for a forward-thinking approach to deal with Real World Evidence in the life science and health care industry. The novelty of the study is its focus on a human-centered artificial intelligence, which can be achieved by using 'System Dynamics' modelling techniques. The outcome – a human-centered 'Indicator Set' can be combined with results from data-driven, AI-based analytics. With this multidimensional approach, human intelligence and artificial intelligence can be intertwined towards an enriched Real World Evidence. The developed approach considers three perspectives – the elementary, the algorithmic and – as novelty – the human-centered evidence. As conclusion, we claim that Real World Data are more valuable and applicable to achieve patient-centricity and personalization if the human-centered perspective is considered 'by design'.



## 1 INTRODUCTION

The life science and health care industry is striving for a higher degree of patient-centricity and personalization. The necessary investments are significant and expose healthcare systems worldwide to high cost-pressure (Marwaha et al., 2018). To address the explosive investments/cost growth, 'outcome-based payment' has emerged – as a very promising pricing model. The model requires that any payment/pricing is associated with the effectiveness of a product for a dedicated patient.

Measuring the results of a patient treatment is commonly carried out with the help of Randomized Clinical Trials (RCTs) that take place in a highly controlled and regulated laboratory environment (Mahajan, 2015). It has been under discussion for about ten years that an increasing portion of such measurements can be achieved alternatively through the analysis of data from the 'real world', the so-called Real World Data (RWD). One idea is to process the vast amounts of digital patient data with cutting-edge technologies like Artificial Intelligence (AI).

Unfortunately, results based on AI-analytics are worthless if industry-specific regulatory bodies (e.g., the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA)) do not accept them as evident data sources. There are a few references from the regulatory bodies, which discuss the application of RWD and the associated data evidence, the so-called Real World Evidence (RWE). The influential FDA elaborated as one of the first institutions a leading guidance on how to prove RWE and launched a framework for a RWE program (FDA, 2017, 2018). In Europe, the PRIority MEdicines (PRIME) scheme recognizes electronic data from patient registries or health records in order to identify unmet medical needs (Davis et al., 2018). Both are promising indications that regulators may permit the use of RWD if RWE is proven (Marwaha et al., 2018).

By definition, (treatment) effectiveness is the extent to which an intervention produces beneficial outcomes under ordinary day-to-day circumstances



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(Khan et al., 2011). Whereas some therapeutic effects − the 'hard factors' can be quantified quite easily, other effects are difficult to assess – we call them the 'soft factors'. Patterns for hard factors are for example pulse, blood sugar or blood pressure. For the soft factors, it is more difficult to extract patterns but there exists a general accepted concept, that will be used in this study: perceived 'Health-related Quality of Life' (HRQoL) − a human-centered factor defined as patients' perception of their own health status (Asadi-Lari et al., 2004; Jin et al., 2008).

From the affected patient's perspective, soft factors, like perceived HRQoL are crucial, because they largely determine the essence of life (Asadi-Lari et al., 2004; Jin et al., 2008). However, determining perceived HRQoL is a challenging endeavour as it can be driven by multiple individual sources and factors, such as age, sex, type of disease or personality (Bengtsson et al., 2018; Ekundayo et al., 2018).

At this point, AI can be used to analyse sets of RWD to quantify perceived HRQoL. However, can an algorithm provide evidence about human´s essence of life? From this question, we derive our hypothesis that AI alone is not sufficient to create evidence for perceived HRQoL. That is why we postulate a multidimensional approach, which combines AI with human-centered intelligence.

The objectives of this study are (1) as a pre-condition to point out a suitable definition for RWD and RWE, (2) to stress the relevance and to sketch a multidimensional approach for analysing RWD to determine perceived HRQoL, (3) to guide future research by developing a systematic, method-based procedure and putting forward a research agenda.

In terms of research methodology, first we settled on an iterative approach and used hermeneutics for a detailed literature review. For this, we used recommendations of Boell and Cecez-Kecmanovic (2014) as well as Tranfield et al. (2003). The repeated steps of searching, acquiring, analysing, and interpreting were focused on science databases like Web of Science (all journals), and Google Scholar (top journals). Then, we enriched the findings by adapting knowledge, practical experience and work from regulatory bodies. The main queries we combined to find relevant sources related to the topics 'Real World Data', 'Real World Evidence', 'Big Data' (as RWD is a specific set of big data) in combination with 'Health Care', 'Life Science', 'Pharmaceutical Industry', 'Artificial Intelligence' and 'Systems Dynamics' . The last term is chosen as technique to disclose human-centered perspectives.

The remainder of the paper is structured as follows. In chapter 2, we discuss key terms and causalities of RWD and RWE. Chapter 3 summarizes challenges and risks associated with RWD. The need for the multidimensional approach is outlined in chapter 4. Chapter 5 sketches the components of the developed procedure and the associated 'Indicator Set' derived with Systems Dynamics techniques. Lastly, chapter 6 concludes the results and shows further research intentions.

## 2 BACKGROUND

Data may be regarded as factual, for example in the form of figures, percentages or statistics. Evidence is data of relevance, which additionally demonstrates that it supports a particular conclusion. For RWD this means that specific data sets may be relevant, but not mandatorily sufficient to prove RWE. Therefore, there is a need to separate RWD and RWE to ensure exploitability, handling and compliance criteria of RWE itself. This has important implications on how RWD and RWE will be interpreted by regulators and accepted in the course of RCTs.

In the context of life science and health care, RWD can be defined as data relating to patients' health status. In addition, RWD refers to data on the delivery of healthcare that is commonly retrieved from a variety of sources (FDA, 2017). This includes data elements captured in a patient's electronic health record (EHR) in a hospital or in an insurance company. It entails data on claims processes as well as data collected directly from patients or various providers in the course of an observational study. Aside from clinical settings, the definition extends to self-generated patient data (e.g., in-home monitoring devices, wearable technologies, fitness trackers) and data from registries that support various aspects of care studies and research (FDA, 2017). It may also include data on contextual metrics, such as patient's exposure and socio-economic indicators (WHO, 2010; Padilla et al., 2016). Importantly, this baseline definition does not preclude the incorporation of routinely collected data based on RCTs (Berger et al., 2017a).

In contrast, Hubbard and Paradis (2015) defined RWE as evidence derived from RWD through application of research methods. RWE can further be defined as clinical evidence regarding the use and potential benefits or risks of a medical product derived from RWD analysis (FDA, 2017).

According to Berger et al. (2017a) RWE is not simply 'anecdotes' based on RWD – it involves data

curation, validation, and standardization to ensure that the data themselves are adequately 'fit-for-purpose'. It requires thoughtful study designs to assess the effects of the treatments on the outcomes of interest, and an understanding of the context, in which the treatments are used.

Berger et al. (2017a) additionally emphasize that the outlined definition of RWE reflects evidence generation that is broader than passively collected observational data and retrospective analytical approaches. It conceptually enables the prospective capture of a wider variety of data, and utilization of study designs that are embedded in clinical practice but retain randomization. This definition of RWE does not characterize good versus bad evidence and does not specify what 'kind' of RWE is suitable for regulatory decisions. Therefore, rigorous RWE should be able to provide insight into questions that are difficult, infeasible, unethical, or cost-prohibitive when addressed with traditional RCTs.

Once approval has been obtained from the regulatory authorities, both RWD and the associated RWE can contribute to a safer and more effective patient profile. Such a profile with proven RWE is increasingly valuable for patients and providers compared to evidence only available from traditional RCTs. Both – RWD and RWE – can be developed through applications that capture information of patient-related data and evidence for decision-making and labelling (Berger et al., 2017a; Bipartisan Policy Center, 2016).

To conclude the discussion, figure 1 visualizes the considerations for generating RWE, which are 'fit for a specific (regulatory) purpose'.

## 3 CHALLENGES AND RISKS

Even though the application of RWD – as a complementary or even substituting approach to classical RCTs – holds great potential, numerous hurdles need to be overcome. For example, the lack of clear guidance on the inquiry and use of RWD and associated evidence may lead to biased conclusions with potential of adverse consequences for decision-making regarding the efficacy and safety of new and promising health technologies (Berger et al., 2017a).

RWD are based on real, everyday conditions of individuals and their exploitation was inconceivable just a few years ago. Today, for example sensor data from fitness bands/apps or from social media platforms are created daily in incredible quantity and variety. The interest of the life science and health care industry in pioneering for RWD is closely linked to the search for alternative ways of developing and approving new drugs, not least in order to have methods that also allow research into drugs for rare diseases.

Promising opportunities, however, come along commonly with risks associated in the area of patients' interests with corresponding highly regulated processes. Despite increasing recognitions for the value of RWD and even though there are definitions (chapter 2), a common understanding and a harmonized body of language in the field of RWD and RWE are lacking (Makady et al., 2017a).

As elaborated in chapter 2, a well-accepted definition refers to RWD as data collected in a non-RCT setting. A considerable number of definitions diverge from this concept and frequently there is no official or institutional definition for RWD in use. This may lead to potential issues when decision-making is based on RWD (Makady et al., 2017a).

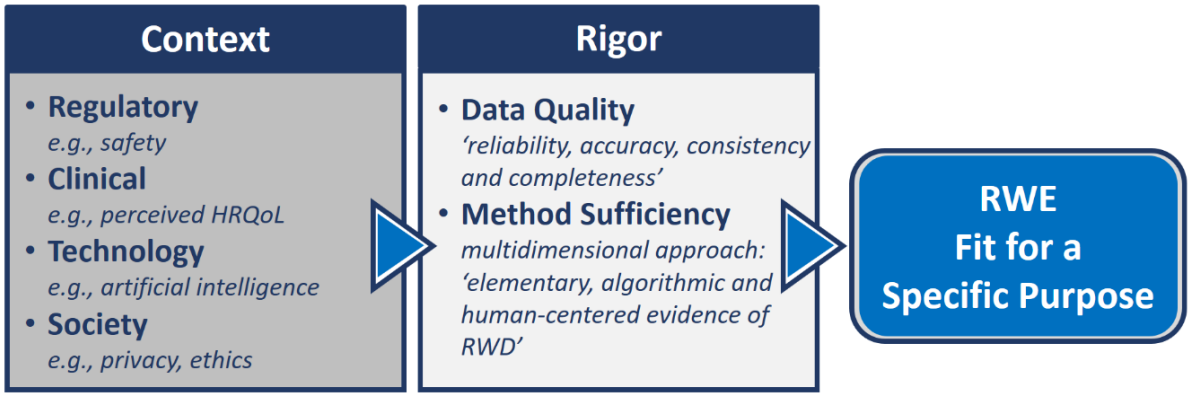


Figure 1: Fit for purpose RWE (adopted from Berger et al., 2017a).

Further, policies for the use of RWD notably differ across contexts and agencies. Such variations might discourage the application of RWD for drug approval (Makady et al., 2017b). According to the World Health Organization's (WHO) global observatories for eHealth from 2015, only 17% of the member states surveyed (i.e. 21 of 125) enforced a policy or strategy to regulate the use of big data in their health sectors (WHO, 2016).

Currently, there are multiple public and private efforts to digitize and aggregate health information from e.g., administrative claims, EHR, or laboratory tests. However, whereas these RWD promise insights that are more robust into what works in health care, there are various impediments. Most important in this respect is the facilitation of greater openness among public and private stakeholders to collaboration, connecting information and data sharing, with the goal of making robust data accessible to all researchers (Berger et al., 2015).

There are a number of issues when collecting RWD, for example the lack of good quality, sufficient representative or complete databases, the presence of many asymptomatic cases in RWD, more chances of bias and confounding in prospective real-world studies (Mahajan, 2015).

Not least, regulatory burdens from the European Union (EU), the General Data Protection Regulation (GDPR) must be taken into account (European Union, 2016). This law entered into force in 2018 and has global reach and implications with respect to how companies manage and share personal data after collection. This means companies need to establish strict procedures for handling personal data; an active data protection, e.g., to deal with the 'right to be forgotten' (GDPR, article 17) needs to be established. Nevertheless, good procedural practices are emerging for RWD, which strengthen decision makers' confidence in the related evidence (Berger et al., 2017b).

Based on the discussions around RWD, we aggregated the associated risks into three areas and put them in relation to the expected extent of industry transformation (figure 2). The aggregated risk areas visualized in figure 2 are 'Compliance Controversies', 'Registration Failure', and 'Business Model Disruption'. In the following, we discuss significant differences and dependencies with regard to the tree risk areas.

**Compliance Risks.** The inner layer of figure 2 deals with the regulatory requirements − data-driven RWD compliance. It is essential for the life science and health care industry to familiarize itself with upcoming requirements and recommendations of regulatory bodies to prove, establish and audit the company-specific conformity; this includes e.g., monitoring of potential contractors. The use of RWD without sound knowledge and continuous monitoring (governance) carry the risk of punishable compliance violations.

**Registration Risks.** The middle layer of figure 2 emphasizes that the use of RWD can lead to adjustments in the approval processes of drugs and in the design of clinical trial setups. Companies preparing to leverage RWD effectively, including RWE's evidence will be able to respond proactively to changes in the near future and surely gain competitive advantage. In conclusion, the focus here is set on process changes in the development and approval of new drugs and/or therapies.

**Business Model Risks.** The outer layer of figure 2 shows that RWD have the potential to disrupt (not only) the life science and health care industry. RWD will develop into a critical success factor: Those in possession of RWD and able to prove RWE and, in addition, have the knowledge and competence for their evaluation will probably dominate the market in the near future. This area focuses on potential new competitors (e.g., Apple and its Smart Watch) entering the market as well as new disruptive business models in the life sciences and health care industry.

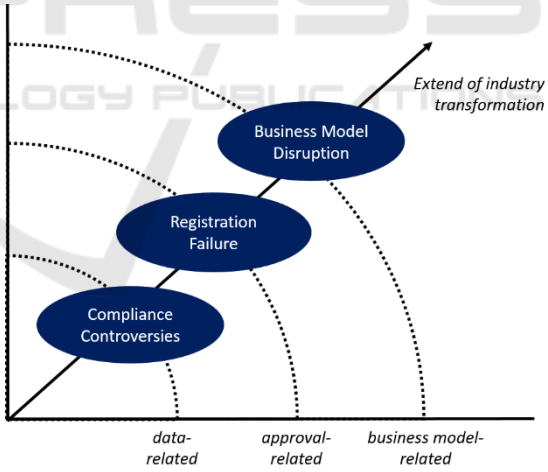


Figure 2: Risk areas of RWD.

In conclusion, our focus is on regulatory and legal requirements for RWD protection of personal data and proof of data integrity to provide RWE. The latter is subject to special attention by the FDA (FDA, 2016, 2017, 2018), United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA), and various other regulatory bodies. This means that at the latest in an audit which is scoped to RWE, companies need to provide information e.g., based on

technical justification and corresponding scientific rationale to prove that their analytical results based on RWD are compliant (related to conceivably various regulatory requirements).

## 4 MULTIDIMENSIONAL APPROACH

The use of RWD promises enormous potential for many areas of the life sciences and health care industry (Greenfield, 2017); there are clear chances that it may possibly disrupt the industry in the wake of potential new competitors, like Apple (e.g., heart study conducted by Apple (2018)).

Considerable research work has just been initiated focusing on the use and analysis of RWD in health care. AI is the technique of choice in many studies to analyse the large amount of RWD. RWD resp. big data in health care is generally regarded as crucial for building (new) models of disease progression and improved efficiency (cost effectiveness) of existing clinical trial setups (Vayena et al., 2018).

In certain areas, the application of AI algorithms has already outperformed experienced health care professionals. One example is the identification of skin cancer based on dermatologic image recognition (Haenssle et al., 2018). Unfortunately, the use of AI entails unsolved disadvantages. As an example, AI algorithms are criticized for their 'black box' results, not giving insights into the pathways/algorithms that lead from input data to output results (Forbes, 2018).

Another, still unresolved challenge regarding AI based results is the correct understanding of 'soft factors' related to human´s behaviour: AI algorithms are not foreseen to (properly) interpret figurative uses of human´s language such as metaphors and irony.

Also the assignment of meaning to symbols or behaviour is a challenge − there is a hidden side of language and communication that requires at least extra-linguistic knowledge (Moreno and Redondo, 2016; Lu et al., 2018).

According to Moreno and Redondo (2016), figurative language is used to about 20% in social media conversations. This means that about 20% of the language is (at least) currently impossible to be interpreted via AI techniques.

To conclude, while AI is extremely powerful in extracting statistically significant patterns from data, there are serious limitations to whole-brain functions and associated underlying meanings and perceptions. Despite this serious deficiency, many innovations today rely heavily on automated data analytics, not exclusively but more and more often, based on AI algorithms, without considering the fact that data evidence can be achieved only with a combination of hard and soft factors. Figure 3 shows the dependencies between hard and soft factors, in particular the state of RWE (based mainly on hard factors) and future perspectives with increasing consideration of soft factors.

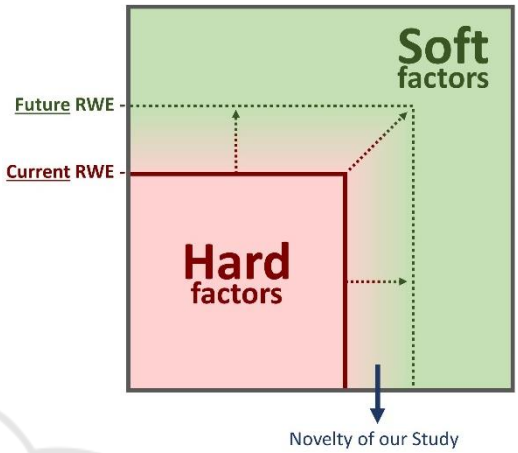


Figure 3: Hard and Soft factors of RWE.

For the life science and healthcare industry, the abstract construct of perceived HRQoL is a substantial criterion for evaluating the impact of products and treatments. As an example, perceived HRQoL relies on RWD and is strongly dependent on RWE. It is mandatory to question the methodologies and techniques used to collect RWD and to show RWE, which lead to future decisions. Therefore, we postulate that approaches that focus on the analysis of RWD and associated RWE need to incorporate the strengths of artificial and human intelligence 'by design'. Such a multidimensional method will significantly enhance the use of RWDs for the following reasons:

- Artificial Intelligence (AI) – is strong in revealing correlations and extracting statistically valid patterns, whereas
- Human Intelligence (HI) – is strong in revealing causalities by creating system-related sense-making and contextual scenarios, considering symbols or behaviour.

The two complementary approaches have the potential to cross-fertilize and replenish each other. The results can be developed iteratively, so that outcomes based on AI and HI are merged and finally reach a level where it is possible to measure the effectiveness of treatments beyond the hard factors (related to AI), stretching out to a validated analysis

of soft factors (related to HI). With this approach, for example the concept of perceived HRQoL can be supported with an increased validity of the analysed RWD.

Finally, our multidimensional approach aims to achieve three levels of evidence, which we refer to 'elementary', 'algorithmic' and 'human-centered' evidence of RWD. The elementary level addresses the challenges to ensure accuracy, consistency and completeness of the data collected. The algorithmic evidence is achieved with the help of AI algorithms, whereas the human-centered evidence will rely on a method, which puts humans in the center. For the last one, we chose 'System Dynamics' as the appropriate methodology which is introduced in the following chapter. Figure 4 shows the emerging level of evidence over time by applying our suggested multidimensional or multilevel approach.

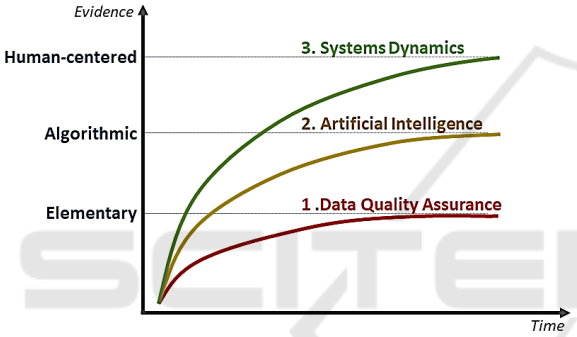


Figure 4: Levelled Multidimensional Approach.

In the following chapter we explain each component of our approach, we enrich the use of AI in combination with RWD providing a more systemic and holistic perspective. Our novel multidimensional approach will be reflected on the derived indicators necessary to gather information about perceived HRQoL.

# 5 COMPONENTS OF APPROACH

While the first level of our multidimensional approach establishes the basis for further research steps, the subsequent levels for building evidence (algorithmic and human-centered levels) need to be performed iteratively.

## 5.1 Elementary Evidence

The basis for establishing elementary evidence is to assure a governed data quality. The prerequisite is the access to trustworthy and comprehensible RWD.

It is of high relevance that the selected RWD is of sufficient quality, with the consequence that data assurance needs to be proven using procedures that are subject to a recognised procedural guideline based on regulatory requirements. This results in an 'assurance quality seal', which verifies in particular the accuracy, consistency and completeness of the relevant RWD − a key when dealing with patient-centered material. From an audit perspective, to achieve an assurance quality seal for RWD, accurate and traceable data management and related governance procedures is a prerequisite. In a first step, evidence criteria for the assurance quality seal need to be determined. The evidence criteria will be used for a RWE assessment. The results determine whether the selected RWD source can be used ('go') or if data quality improvement procedures must be performed, or if another set of data needs to be selected and audited ('no go').

The result is an assurance quality seal, the elementary RWE that builds the foundation for subsequent steps; we categorize this level of RWE as 'maturity-level-1' or elementary evidence (figure 4).

## 5.2 Algorithmic Evidence

The tempting idea of AI aims to simulate human (-like) intelligence within machines, more specifically computerized systems. This is termed as 'general AI', which includes the replication of human emotions and reasoning. By contrast, 'narrow AI' is used to describe technologies that conduct specific tasks similarly, or even better, than humans (Jones et al., 2018). Even though AI has recently gained a lot of attention, the idea and term was coined in 1955 (McCarthy et al., 1955).

A closely related approach is 'Machine Learning' (ML) which refers to 'the study of computer algorithms that can learn complex relationships or patterns from empirical data and make accurate decisions.' (Jones et al., 2018). ML methods can be divided in a.) supervised learning and b.) unsupervised learning. While a.) implies the need to train the rules and models based on existing knowledge (e.g. training data, structures), b.) does not rely on predefined data or structures (Moreno and Redondo, 2016).

A very prominent group of AI algorithms are the Neural Networks (NN) (Jones et al., 2018). The example outlined in chapter 3 in which AI was used for dermatologic image recognition is based on convolutional NNs. There are currently numerous software solutions available that offer numerical high-performance calculations (e.g., the open source

software library 'TensorFlow' and the application programming interface 'Keras').

Another branch of AI is Natural Language Processing (NLP), which supports to understand, learn, interpret and produce human language content. NLP draws from many disciplines, including computer science and computational linguistics; it is the 'art' to manage the understanding between human communication and computers. NLP supports human-human communication, human-machine communication, or both by analysing learning and producing content from a large quantity of data (Hirschberg and Manning, 2015). In addition, NLP can be used to extract information from unstructured text such as clinical notes, or RWD from patient's interest groups (Murff et al., 2016; Jiang et al., 2017).

The initial part for algorithmic evidence is built on indicators that analyse and interpret structured as well as unstructured RWD. As previously elaborated, the shortcomings of AI require the validation and further elaboration of the indicators on which the applied algorithms rely on. This is important to judge if the AI-based results considered both - hard and soft factors - to achieve the desired level of RWE.

Because our developed approach has an iterative character, the indicators and data-driven explanations discovered at level 2 - the algorithmic evidence - will serve as initial input for level 3 (section 5.3); consequently, the level-3-output will be returned for subsequent iterations of (supervised) learning based on AI algorithms. With this approach, we create a complementary linkage of level-2- and level-3-outcomes, which will leverage the RWE. Results of the level-2- activities are the 'maturity-level-2-' or algorithmic evidence: AI-generated indicators subsequently can be used as input for the level-3-exercise to achieve the desired level of human-centered evidence (see figure 4).

## 5.3 Human-centered Evidence

As already outlined, the causalities of social interactions are indispensable to understand complex situations (e.g., language metaphors, irony, symbols, signs, behaviour). Therefore, as a complementary technique to the algorithmic evidence we considered the 'Systems Dynamics' (SD) technique as sufficient to collect human-centered indicators. The methodology itself is generic and can be applied to various other contexts (Van den Belt, 2004); for example in management research and practice (Lane, 1992; Repenning, 2002; Rudolph et al., 2009).

The idea of the SD technique is a 'systems thinking' based analysis, which takes a step back from the level of single events and attempts to develop structural explanations of system behaviour.

So-called 'Causal Loop Diagrams' (CLDs) - shown exemplarily in figure 5 - are used to describe feedback loops; core building blocks of CLDs are variables and causal relationships between them (von Kutzschenbach et al., 2018).

Every loop represents a feedback system, whereas the loops can be categorized as either positive /reinforcing (labelled as 'R') or negative/balancing (labelled as 'B'). The causal relationships between the variables of a system are indicated as links - visualized as arrows. Our example in figure 5 shows that the variable 'Growing Action' is expected to increase (+) variable 'Results', and vice versa. However, the changes of 'Results' are expected to increase (+) the third variable named 'Slowing Action', which is expected to decrease (−) 'Results' again. The 'II' sign indicates assumed time delays between causes and effects. The loops spoil the distinction between the driver and the driven, cause and effect, because, as time progresses, each variable plays both roles. All loops together show the overall.

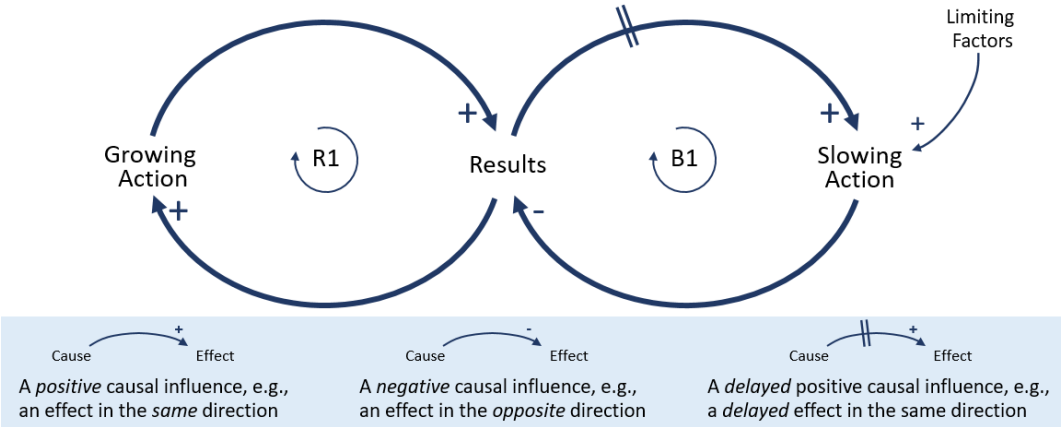


Figure 5: Generic Example of a CLD Diagram (adopted from Kutzschenbach et al., 2018).

systems behaviour (von Kutzschenbach et al., 2018).

These SD modelling techniques can be applied to validate the previously generated set of AI indicators. The data-driven approach from level 2 is expected to lead to explanations - indicators - that would be used on level 3 to design the variables and links of a CLD. This CLD would represent a system explaining the behaviour of perceived HRQoL and its influencing as well as influenced variables

Appreciating the complex and fuzzy nature of the perceived HRQoL, the AI-approach (level 2) will be validated and enhanced by 'Group Model Building' (GMB).

When applying SD, GMB is a proven way of engaging multi-stakeholder perspectives in the development of causal-loop diagrams and simulated dynamic model (Scott et al., 2016).

With these activities, we create a dynamic model, which will be refined and corrected until it is saturated. This is a sense-making, human-centric and collaborative action; with the GMB approach, we are able to involve various stakeholders with different perspectives and experiences. The outcome, the 'SD AI indicator set', is grounded on a dynamic SD model, which allows simulations of different scenarios. The worked out 'SD AI indicator set' must be regularly merged with the data-driven insights based on AI algorithms (level 2); the associated governance processes must be additionally defined.

The result of the level-3-activities is the human-centered evidence, which means a set of AI-generated indicators, which are complementarily and iteratively enriched with the GMB-generated indicators of HRQoL.

# 6 CONCLUSION AND OUTLOOK

At the beginning of this study, we claimed that the exclusive use of AI to analyse and interpret RWD and to achieve reasonable RWE for a selective dataset is not sufficient. We showed (figure 1) that the 'fit for purpose' to obtain RWE is depending on various factors like regulatory, clinical, technology and society perspectives as well as other considerations, in particular data quality and the sufficiency of the used and combined methods.

Thereafter, major challenges associated with the use of RWD have been categorized by three areas - compliance, registration and business model risks (figure 2). Compliance risks are data-related and refer to challenges along the assurance and governance of RWD. Registration risks refer to product-related challenges that might occur due to adapted approval and development procedures once RWD become an accepted means to prove drug effectiveness. Finally, business model risks have been pointed out as RWD have the potential to disrupt the life science and healthcare industry.

Next, we addressed current trends to analyse RWE with the help of AI techniques when trying to demonstrate RWE. We concluded that, due to shortcomings of current data-driven techniques, there is a need for a multidimensional approach. We selected and applied the concept of perceived HRQoL to discuss our novel approach towards RWE.

Unlike pure hard factors (relatively easy to analyse and measure with AI techniques), the construct of perceived HRQoL is mostly determined by soft factors - which are difficult to analyse and quantify. Soft factors are not measurable via AI exclusively; however, it is our claim that the soft factors will be increasingly considered in future decision-making related to RWE (see figure 3).

Thus, our developed and proposed approach has the potential to contribute to one of the major challenges of NLP - the 'soft side' of text and human perceptions. Existing techniques mainly rely on text fragments in which opinions/sentiments are explicitly expressed (e.g., polarity terms and their co-occurrence frequencies) (Cambria et al., 2016).

As an agenda for further research, a feasibility study to test and apply the suggested procedures is desired. As unit of analysis, patient interest group data from a dedicated therapeutic area could be used. In the scope of such a future study, the authors would aim to limit the focus on assessing perceived HRQoL. The design, development and validation of four artefacts with relation to figure 4 is being considered:

1. Development of a quality assurance level (a 'quality seal') for the elementary evidence for RWD resulting in a maturity-level-1-evidence.
2. AI-generated indicators to provide perceived HRQoL algorithmic evidence (level 2) and as input for human-centered evidence resulting in a maturity-level-2-evidence.
3. 'SD AI indicator set' - a set of robust indicators gathered via SD technique and passed back to the AI-generated indicators resulting in a maturity-level-3-evidence.
4. 'RWE Framework' - a prototypical frame-work, which contains all relevant steps to achieve RWE for a selective set of RWD – perceived HRQoL − associated with the 'SD AI indicator set'.

These results could trigger a multiplier effect and form the basis for future research. First, the concept of using a three-layered multidimensional procedure

and an evidence providing quality seal can be used in various AI related contexts to improve AI based results, not at least in providing RWD evidence. Second, the created artefacts could be generalized for a broader use. More specifically, the concept of a combined methodically sound set of AI indicators based on hard- and soft factors could become a standard approach for the AI discipline. Third, the 'RWE Framework' could be applied on further RWD sources to show data evidence in other areas.

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