The Terminology Conflict on Efficacy and Effectiveness in Clinical Trials on Health-Related Quality of Life

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Method Article

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Abstract

Background: The Health-Related Quality of Life (HRQoL) is one of the essential outcome dimensions in clinical research. In recent years, we have studied the difference between Efficacy and Effectiveness. When examining studies on HRQoL, we have noticed the incongruence of the terminology used. In this paper we analyze the characteristics of form and function in clinical studies that assessed the Health-Related Quality of Life and suggest to challenge the used terminology under either Experimental Study Conditions (Efficacy) or Real World Conditions (Effectiveness).

Methods: We analyzed 100 free available publications of clinical studies listed in PubMed between April 2015 and August 2016 which assessed quality of life as an outcome. In these 100 studies we analyzed characteristics of form and function of clinical studies assessing HRQoL. Characteristics of form were 'description of the objective of the study', 'differentiation of HRQoL as primary or secondary endpoint', 'use of the terms 'Efficacy' or 'Effectiveness' to describe the assessed outcome' and 'numbers of described inclusion and exclusion criteria'. Characteristics of function were 'specification of 'Randomised Controlled Trial'', 'description of the study design as 'pragmatic'' and 'description of the HRQoL measurement instruments used'.

Results: Our results showed that there is no congruent strategy for the description of HRQoL studies. In 91% of the examined studies the assessment of the HRQoL was part of an experimental trial. In many cases no uniform definitions of the terms Efficacy and Effectiveness were used and thus no clear distinction was made between Experimental Study Conditions and Real World Conditions. In 38% of all studies the assessment of HRQoL was described as secondary endpoint.

Discussion: We discuss the use of Experimental Study Conditions and Real World Conditions in measuring HRQoL. Furthermore, other occurring errors when measuring HRQoL are analysed. A possible solution is presented with the concept of the 'Pragmatic Controlled Trial', which is conducted under everyday conditions. The assessment of survival in an RCT makes sense to provide the 'Proof of Principle' by demonstrating the investigated treatment can indeed prolong survival. In contrast, a 'Proof of Principle' in HRQoL research may not be the appropriate information for selection of a particular treatment.

Introduction

The Health-Related Quality of Life (HRQoL) is one of the essential outcome dimensions in clinical research. It represents a multidimensional construct which consists of the three sub-aspects of physical health, mental well-being and social integration. Mostly, it focuses on the subjective view of the patient on his health status [1].

Improvement or maintenance of HRQoL is considered an important indicator for the success of interventions. Especially in chronic diseases the description of the HRQoL is of considerable importance, since life expectancy is permanently increasing due to successful treatment, amongst other things [2,3]. For these and other reasons, an optimal assessment of the HRQoL is essential and has been the subject of research in recent years.

Nevertheless, the optimal method of the assessment of HRQol is still a matter of discussion [4,5,6,7,8,9]. Examples for unsolved problems are the inadequate definition of the HRQoL, the dimensions to be measured as well as the choice of instrument. We learned from the architects and designers of buildings that both form and function of a concept should be described according to the principle 'form follows function' [10, 11]. We used this principle in the following to explain the importance of the appropriate sequence in designing a clinical trial.

We presumed that authors who investigate the effect of a treatment on HRQoL will be interested in the effects under Real World but not Experimental Study Conditions.Therefore, it may be expected that most of these HRQoL studies use the function of an observational or pragmatic study for assessment of the endpoint under Real World Conditions. The corresponding form of an observational study is a non-experimental i.e. non-randomized trial.

Based on this presumption, the aim of this study was to confirm our assumption that the concepts of Efficacy and Effectiveness are only rarely considered for the description of treatment effects on HRQoL.

Methods

To answer our study question we analyzed 100 free available publications of clinical studies listed in PubMed between April 2015 and August 2016 which assessed quality of life as an outcome. End of August 2016 we conducted a PubMed search with the search parameters 'trial' and 'quality of life' in their titles. The first 100 freely available studies listed here were included in the analysis. It was assumed that the investigation of quality of life in clinical studies always involves HRQoL. In these 100 studies we analyzed characteristics of form and function of clinical studies assessing HRQoL. According to the recommendation of architects and designers we started with the description of the functions of studies followed by the description of the study forms.

Study functions:

- Description of the objective of the study.

To analyze the aim of the study we primarily examined the end of the introduction followed

by the abstract or the method section of the paper.

Here we report whether a clear study question was described or not. A clear study question

was confirmed when all three of the criteria modified according to David Sackett et al. [12]

were reported: 1. Patient and problem, 2. Intervention (+ comparator if relevant) and 3. Outcome.

- Differentiation of HRQoL as primary or secondary endpoint of the study or not stated.

- Use of the terms 'Efficacy' or 'Effectiveness' (effects under Experimental Study Conditions (ESC) or Real World Conditions (RWC)) to describe the assessed outcome, neither 'Efficacy' nor 'Effectiveness' or both terms used synonymously.

- Numbers of described inclusion and exclusion criteria.

Study forms:

- Specification of 'Randomised Controlled Trial' ('RCT') or other than 'Randomised Controlled Trial' (Non-'RCT').

- Description of the study design as 'pragmatic'. All other studies that were not explicitly named 'pragmatic' were classified as other than 'pragmatic' trial.

- Description of the HRQoL measurement instruments used as generic or disease-specific.

Papers were downloaded as pdf documents and analyzed following the mentioned criteria. Some of the publications were updated during the project or were no longer freely available thereafter. In these cases, the updated versions were carefully compared with the previous versions and it was found that the aspects relevant to us were not changed. The complete references of the 100 articles can be found in the online supplementary appendix A.

Results

15 of the 100 publications were only study protocols and 85 were reports of completed studies. 14 were published in 2017 (updated versions), 64 in 2016 and 22 in 2015. The details of the reported results are listed in the appendices B and C.

Characteristics for description of the study functions:

Description of the objective of the study:

No clear study question was observed in about 40% of the 100 papers. We consider this a serious problem that requires further discussion. However, a detailed analysis is beyond the scope of this paper and will be reported in a separate publication. We also observed considerable variation in the terminology used for describing the objective of the study and will include a discussion of this aspect in our next publication.

A detailed list of the identified study questions can be found in appendix D.

Differentiation of HRQoL as primary or secondary endpoint of the study:

The HRQoL was assigned as primary endpoint in 29 studies (29%) (including eight study protocols) and as secondary endpoint in 38 studies (38%) (including seven study protocols). In 33 studies (33%) no information was provided for the description of the primary endpoint or it was not clear from the description whether the HRQoL was chosen as the primary or secondary endpoint.

Classification as 'Efficacy' or 'Effectiveness' trial:

In 14 (14%) of the examined studies (including one study protocol) it was described that 'Efficacy' of a therapy was measured. 25 studies (25%) (including seven study protocols) reported that 'Effectiveness' of a therapy was measured. In 60 studies (60%) (including six study protocols) no specification of 'Efficacy' or 'Effectiveness' was described. In one study (1%) (study protocol) the terms 'Efficacy' and 'Effectiveness' were used synonymously.

Numbers of described inclusion and exclusion criteria:

Both inclusion and exclusion criteria were reported in 69 (69%) of 100 studies (including 15 study protocols). Only inclusion but no exclusion criteria were reported in six studies (6%). There was no publication that reported only exclusion but no inclusion criteria, but there were 25 (25%) publications that reported neither inclusion nor exclusion criteria. Inclusion criteria were reported in detail in 75 (75%) of 100 publications (including 15 study protocols). The median number of explicitly reported inclusion criteria in these 75 documents was four with an IQR (interquartile range) of three to five. Exclusion criteria were described in 69 (69%) of 100 publications, the median number of explicitly reported exclusion criteria being four with an IQR of two to six. A more detailed version of the data on inclusion and exclusion criteria in the 100 HRQoL studies has already been published previously [13].

In summary, the four aspects that describe the functions of a study are frequently not reported. The objective of the study was not clearly defined in 40%, the primary or secondary endpoint was not differentiated in 33%, the dimension (Efficacy or Effectiveness) was not defined in 60% and the selection of patients (inclusion or exclusion criteria) was not defined in 25% of all examined studies. We can conclude that in 60% of these papers at least one of the important functional criteria was not reported.

Characteristics for description of the study forms:

Specification of 'Randomised Controlled Trial' ('RCT') or other than 'Randomised Controlled Trial' (Non-'RCT'):

In this category we differentiated two categories: studies which were described as 'Randomized Controlled Trial' and any other type of study except 'Randomized Controlled Trial'.

91 (91%) of the studies (including 15 study protocols) were designated as 'RCTs'. Nine trials (9%) were not designated as 'RCTs'.

In Table 1a we demonstrate the high variability of different coincidences of the terms 'Efficacy' or 'Effectiveness' or 'used synonymously' or 'not defined' and of the terms 'RCT'/other than 'RCT'.

Terms used to describe the assessed outcome dimension	'RCT'	Non-'RCT'	Total
'Efficacy'	14	0	14
'Effectiveness'	23	2	25
Both terms used synonymously	1	0	1
Not defined	53	7	60
Total	91	9	100

Table 1a: Numbers of studies assessing Health-Related Quality of Life (n=100) which used the terms 'Efficacy' or 'Effectiveness' or used both terms synonymously or did not define the described outcome dimension.

RCT: Randomised Controlled Trial.

Specification as 'pragmatic' or other than 'pragmatic' trial:

All of the 100 studies were classified as 'pragmatic' or other than 'pragmatic' studies. Six (6%) of the studies (including two study protocols) were described as 'pragmatic' mostly in the method section. These six trials were also named 'randomized' in the title. More precisely five studies were called 'Randomized Controlled Trial' [14 - 18] and one study was called 'Randomized Clinical Trial' [19]. To report the details of the used terminology we found that one study [14] was named a 'Pragmatic Randomized Trial', three studies [15 - 17] (including two study protocols) a 'Pragmatic (...) Randomized Controlled Trial', one study [19] a 'Pragmatic (...) Randomized Clinical Trial' and one study [18] a 'Pragmatic (...) Controlled Trial'. In none of these six studies an explanation of the meaning of 'pragmatic' was described.

The remaining 94 studies are summarized as other than 'pragmatic' trials. These 94 studies include 85 'RCTs' and nine Non-'RCTs'.

Terms used to describe the assessed outcome dimension	'Pragmatic'	Other than 'pragmatic'	Total
'Efficacy'	1	13	14
'Effectiveness'	4	21	25
Both terms used synonymously	0	1	1
Not defined	1	59	60
Total	6	94	100

Table 1b: Numbers of studies assessing Health-Related Quality of Life (n=100) which used the terms 'Efficacy' or 'Effectiveness' or both synonymously or did not define the described outcome dimension for presentation of data in an 'pragmatic' (observational) or any other type of study.

The following 2x2 table describes the 'RCT'/Non-'RCT' studies versus the studies designated as 'pragmatic'/other than 'pragmatic':

	'RCT'	Non-'RCT'	Total
Other than 'pragmatic'	85	9	94
'Pragmatic'	6	0	**6**
Total	**91**	**9**	**100**

Table 2: Number of studies assessing Health-Related Quality of Life (n=100) which were classified as 'pragmatic'/other than 'pragmatic' and which were designated as 'RCT' or Non-'RCT'. The bold figures represent the indicated numbers of studies. The remaining numbers were calculated. We identified six of 100 studies that were named 'pragmatic' und simultaneously 'RCT'. Additional nine studies that were Non-'RCTs' were classified other than 'pragmatic'. These numbers are shown as red figures in our table. This table seems to identify an oxymoron in terminology.

RCT: Randomised Controlled Trial.

Description of the HRQoL measurement instruments used:

In all 100 studies the used instruments for assessment of HRQoL were described. In 28 studies (28%) (including two study protocols), only generic measurement instruments were used. In 55 studies (55%) (including eight study protocols) only disease-specific measurement instruments were used. In 17 studies (17%) (including five study protocols) both types of measurement instruments were used.

Discussion

The aim of our project was to challenge the used terminology for the description of HRQoL under either Experimental Study Conditions (ESC) or Real World Conditions (RWC). These two conditions are defined by the terms Efficacy (effects of a therapy under ESC, 'Proof of Principle') or Effectiveness (effects of a therapy under RWC) [20,21,22].

The measurement of HRQoL is - in addition to survival - one of the most important indicators for central questions to be answered in health care. The clear definition of the objectives of these measurements is just as important as the applicability of the assessed results to everyday clinical practice.

Experimental versus Real World Conditions:

According to Sir Archie Cochrane and Sir Austin Bradford Hill we should differentiate between three objectives of a clinical study: Efficacy (or 'Proof of Principle'), Real World Effectiveness and Value [23]. Efficacy describes if an innovative intervention can work at all (under ESC). Effectiveness addresses whether or not an innovative intervention that was efficacious will also be effective i.e. useful when assessed under everyday Real World Conditions (RWC). The third of these objectives describes the subjective perception of the observed value either from the perspective of an individual person or the society. It is obvious that the first objective must be assessed under ESC, because all confounders that could influence the effect of an intervention were excluded for 'Proof of Principle'. The gold standard for this type of study is an RCT (Randomized Controlled Trial). The results of the second and third objective will only be meaningful when assessed under Real World but not under Experimental Study Conditions. To achieve this, a pragmatic study design is necessary (see below).

Table 3 shows the differences between Experimental Study Conditions and Real World Conditions.

Experimental Study Conditions (ESC)	Real World Conditions (RWC)
Performance of a human experiment. **Aim to gain new knowledge** („Proof of Principle').	Implementation of health services. **Aim to provide care to patients.**
Assessed in an **RCT** (**R**andomised **C**ontrolled **T**rial) measuring the **Efficacy** of a therapy.	Assessed in a **PCT** (**P**ragmatic **C**ontrolled **T**rial) measuring the **Effectiveness** of a therapy.
Conclusion of a liability insurance.	No liability insurance needed.
Institutional review board approval to minimize the risks of experimental therapy and guarantee data protection. Informed consent required.	Approval by institutional review board required to guarantee data protection. Informed consent required.
Selection of **one primary endpoint.**	Selection of **several equally important endpoints.**
Definition of inclusion **and** exclusion criteria.	Definition of inclusion but **not** of exclusion criteria.
Randomisation.	Stratification according to risk and endpoint.

Table 3: Differences between Experimental Study Conditions and Real World Conditions.

Primary versus secondary endpoint:

Furthermore, it is clearly defined that an experimental study such as an RCT can provide a reliable answer only to the primary endpoint. This is because the study question and the 'Power Calculation' are adapted to the primary endpoint. The secondary endpoint represents a new study hypothesis. Consequently, it is not possible to obtain in a single experimental study reliable results on the primary and secondary endpoint. In a (observational and descriptive) pragmatic study, it is possible to select several equally important endpoints, e.g. HRQoL, adverse effects and costs [24].

Problems identified in hrQoL studies:

Our results clearly demonstrate that there is no congruent strategy for the description of HRQoL studies. In most of the examined studies (91%) the assessment of the HRQoL was part of an experimental trial ('RCT'). In many cases no uniform definitions of the terms Efficacy and Effectiveness were used and thus no clear distinction was made between ESC and RWC.

In 38% of all studies the assessment of HRQoL was described as secondary endpoint. When HRQoL is used as secondary endpoint it can only be hypothesized that the efficacious treatment may influence the HRQoL.

According to our currently accepted standards in clinical research a well-designed tool for assessment of Efficacy is available but not yet for the assessment of Effectiveness. As we have developed a tool for assessment of RWC we can use both methods to get the appropriate answers to two different questions.

Proposed solution:

A possible solution can be derived from the rules of designers, whose theorem 'form follows function' defines the requirement that the function of a new product e.g. a new building or a new study result (purpose) must first be defined before a decision can be made on the design (form) of this product e.g. of the new building or clinical study [11,25].

As a proposal we offer the concept of a 'PCT' ('Pragmatic Controlled Trial') [24,25]. If a new intervention – for example a chemotherapy – is being tested, the Efficacy ('Proof of Principle') should be provided as a first step under ESC in an RCT to answer the question 'Can it work?' [23]. This step should be completed to demonstrate the expected effect on the primary endpoint – for example survival.

Once this 'Proof of Principle' has been provided, two and more endpoints – for example survival and HRQoL – can be measured in a pragmatic study ('PCT') [25] conducted under everyday conditions (RWC), to prove the Real World Effect of the chemotherapy on these two endpoints, e.g. to answer the second question: 'Does it work?' [23].

This second step is essential, since the desired effects of the therapy are influenced by disturbing factors that are unavoidable in everyday life (e.g. comorbidities, patient preferences). This second step cannot be carried out within the framework of an experimental study. In order to actually adhere to everyday conditions, it is neither possible to randomize nor to exclude patients who need to be treated in everyday life.

Declarations

Conflict of interest:

The authors have no conflicts of interest to declare

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References

1. Robert Koch-Institut (Hrsg.). Allgemeines zu Gesundheitsbezogener Lebensqualität, https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GesundAZ/Content/G/Gesbez_Lebensqualitaet/Inhalt/Lebensqual Last access May 01, 2019
2. Katz S: The science of quality of life. Journal of chronic diseases, 459-463 (1987)
3. Statistisches Bundesamt (Hrsg.). Gesundheitsbericht für Deutschland. http://www.gbe-bund.de/gbe10/abrechnung.prc_abr_test_logon?p_uid=gast&p_aid=0&p_knoten=FID&p_sprache=D&p_suchstring=819 (20.01.2020)
4. Bullinger M: Das Konzept der Lebensqualität in der Medizin – Entwicklung und heutiger Stellenwert. Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen, 97-103 (2014)
5. Gill T M, Feinstein A R: A critical appraisal of the quality of quality-of-life measurements. The Journal of the American Medical Association, 619-626 (1994)
6. Haraldstad K, Wahl A, Andenaes R, Andersen J R, Andersen M H, Beisland E, Borge C R, Engebretsen E, Eisemann M, Halvorsrud L, Hanssen T A, Haugstvedt A, Haugland T, Johansen V A, Larsen M H, Loevereide L, Loeyland B, Kvarme L G, Moons P, Norekval,T.M., Ribu L, Rohde G E, Urstad K H, Helseth S, network L: A systematic review of quality of life research in medicine and health sciences. Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation, 2641-2650 (2019)
7. Kohlmann T: Measuring quality of life: as simple as possible and as detailed as necessary. Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen, 104-110 (2014)
8. Moons P, Budts W, De Geest S: Critique on the conceptualisation of quality of life: a review and evaluation of different conceptual approaches. International journal of nursing studies, 891-901 (2006)
9. Radoschewski M: Gesundheitsbezogene Lebensqualität - Konzepte und Maße. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz, 165-189 (2000)
10. Schipper R: 5 characteristics of bauhaus art, architecture and design. https://www.catawiki.com/stories/5263-5-characteristics-of-bauhaus-art-architecture-and-design. Last access Mar 24, 2020.
11. Porzsolt F, Jauch K W, Kaplan R M: 100 Years BAUHAUS Dessau/Germany: What designers of clinical studies can learn from designers and architects of BAUHAUS Dessau and hochschule für gestaltung ulm/Germany. Int J SurgProced, 133 (2020)
12. Sacket D L, Straus S L, Richardson W S, Rosenberg W, Haynes R B: Evidence-based medicine. How to practice and teach EBM. Edinburgh: Churchill Livingstone (2000)
13. Porzsolt F, Wiedemann F, Becker S I, Rhoads C J: Inclusion and exclusion criteria and the problem of describing homogeneity of study populations in clinical trials. BMJ evidence-based medicine, 92-94 (2018)
14. Edmonds S W, Cram P, Lou Y, Jones M P, Roblin D W, Saag K G, Wright N C, Wolinsky F D, PAADRN Investigators: Effects of a DXA result letter on satisfaction, quality of life, and osteoporosis knowledge: a randomized controlled trial. BMC musculoskeletal disorders, 369-016-1227-0 (2016)
15. Slok A H, Kotz D, van Breukelen G, Chavannes N H, Rutten-van Molken M P, Kerstjens H A, van der Molen T, Asijee G M, Dekhuijzen P N, Holverda S, Salome P L, Goossens L M, Twellaar M, In 't Veen J C, van Schayck O C: Effectiveness of the Assessment of Burden of COPD (ABC) tool on health-related quality of life in patients with COPD: a cluster randomised controlled trial in primary and hospital care. BMJ open, e011519-2016-011519 (2016)
16. Espie C A, Luik A I, Cape J, Drake C L, Siriwardena A N, Ong J C, Gordon C, Bostock S, Hames P, Nisbet M, Sheaves B, G Foster R, Freeman D, Costa-Font J, Emsley R, Kyle S D: Digital Cognitive Behavioural Therapy for Insomnia versus sleep hygiene education: the impact of improved sleep on functional health, quality of life and psychological well-being. Study protocol for a randomised controlled trial. Trials, 257-016-1364-7 (2016)
17. Klinkhammer-Schalke M, Lindberg P, Koller M, Wyatt J C, Hofstadter F, Lorenz W, Steinger B: Direct improvement of quality of life in colorectal cancer patients using a tailored pathway with quality of life diagnosis and therapy (DIQOL): study protocol for a randomised controlled trial. Trials, 460-015-0972-y (2015)
18. Coulton S, Clift S, Skingley A, Rodriguez J: Effectiveness and cost-effectiveness of community singing on mental health-related quality of life of older people: randomised controlled trial. The British journal of psychiatry: the journal of mental science, 250-255 (2015)
19. Braamse A M, van Meijel B, Visser O J, Boenink A D, Cuijpers P, Eeltink C E, Hoogendoorn A W, van Marwijk Kooy M, van Oppen P, Huijgens P C, Beekman A T, Dekker J: A randomized clinical trial on the effectiveness of an intervention to treat psychological distress and improve quality of life after autologous stem cell transplantation. Annals of Hematology, 105-114 (2016)
20. Schwartz D, Lellouch J: Explanatory and pragmatic attitudes in therapeutical trials. Journal of chronic diseases, 637-648 (1967)
21. Grimes D A, Schulz K F: An overview of clinical research: the lay of the land. Lancet (London, England), 57-61 (2002)
22. Thiese M S: Observational and interventional study design types; an overview. Biochemia medica, 199-210 (2014)
23. Haynes B: Can it work? Does it work? Is it worth it? The testing of healthcareinterventions is evolving. BMJ, 652-653 (1999)

24. Porzsolt F, Weiß C, Weiß M, Müller A G, Becker S I, Eisemann M, Kaplan R M: Versorgungsforschung braucht dreidimensionale Standards zur Beschreibung von Gesundheitsleistungen – Teil 2. Monitor Versorgungsforschung, 53-60 (2019)
25. Porzsolt F, Eisemann M, Habs M, Wyer P: Form follows function: pragmatic controlled trials (PCTs) have to answer different questions and require different designs than randomized controlled trials (RCTs). Zeitschrift für Gesundheitswissenschaften, 307-313 (2013)

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