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IDENTIFYING THE CONCEPTS CONTAINED IN OUTCOME MEASURES OF CLINICAL TRIALS ON FOUR INTERNAL DISORDERS USING THE INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH AS A REFERENCE.

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1. Deutsche Zusammenfassung

Ziel: Systematische Identifizierung und Vergleich der Konzepte aus Outcome-Instrumenten, die in klinischen Studien mit Patienten mit Chronischer Ischämischer Herzkrankheit, Diabetes Mellitus, Adipositas und Obstruktiver Lungenkrankheit einschließlich Asthma enthalten sind, unter Anwendung der Internationalen Klassifikation der Funktionsfähigkeit, Behinderung und Gesundheit (ICF) als Referenz.

Methoden: Lokalisation publizierter randomisierter, kontrollierter Studien der Jahre 1993 bis 2003 in Medline und Selektion nach zuvor definierten Kriterien. Die Outcome-Instrumente der Studien wurden extrahiert und die in ihnen enthaltenen Konzepte wurden über sogenannte „Linking Rules“ dem Kategorien-System der ICF zugeordnet.

Ergebnisse: 166 Studien mit Patienten mit Chronischer Ischämischer Herzkrankheit, 227 mit Diabetes Mellitus, 428 mit Adipositas und 253 mit Obstruktiver Lungenkrankheit wurden eingeschlossen. Zehn verschiedene „Health-status“ Fragebögen wurden aus den Studien mit Chronischer Ischämischer Herzkrankheit, 19 aus Studien mit Diabetes Mellitus, 47 aus Studien mit Adipositas und 39 aus Studien mit Obstruktiver Lungenkrankheit extrahiert.

In jedem Erkrankungsbereich konnten mindestens 75% (range 75-92%) der extrahierten Konzepte dem Kategorien-System der ICF zugeordnet werden. In den Studien mit Diabetes Mellitus und Adipositas waren die am häufigsten angewandten ICF-Kategorien ‘Allgemeine Stoffwechselfunktionen’ (b540), in

Studien mit Obstruktiver Lungenkrankheit ‘Atmungsfunktionen’ (b440) und in Studien mit Chronischer Ischämischer Herzkrankheit ‘Herzfunktionen’ (b410).

Schlussfolgerung: In allen vier Erkrankungsbereichen bestanden die meisten Studien aus pharmakologischen Studien, die auf klinisch relevante Paramenter und nicht auf die Funktion fokusierten. Die ICF stellt eine nützliche Referenzsystem zur Identifizierung und Quantifizierung von Konzepten aus Outcome-Instrumenten klinischer Studien dar.

2. Abstract

Objectives: To systematically identify and compare the concepts contained in outcome measures of clinical trials on chronic ischemic heart disease, diabetes mellitus, obesity and obstructive pulmonary disease, including asthma using the International Classification of Functioning, Disability and Health (ICF) as a reference.

Methods: Randomized controlled trials between 1993 and 2003 were located in MEDLINE and selected according predefined criteria. The outcome measures were extracted and the concepts contained in the outcome measures were linked by so called “linking rules” to the ICF.

Results: 166 trials on chronic ischemic heart disease, 227 trials on diabetes mellitus, 428 trials on obesity and 253 trials on obstructive pulmonary disease were included. 10 different health status questionnaires were extracted in chronic ischemic heart disease, 19 in diabetes mellitus, 47 in obesity, 39 in obstructive pulmonary disease. Across conditions at least 75% (range: 75-92%) of the extracted concepts could be linked to the ICF. In diabetes mellitus and obesity the most used ICF- categories were ‘general metabolic functions’ (b540), in obstructive pulmonary disease ‘respiratory functions’ (b440) and in chronic ischemic heart disease ‘heart functions’ (b410).

Conclusions: In all four health conditions the majority of studies were drug trials focusing on clinically relevant parameters and not on functioning. The ICF

provides a useful reference to identify and quantify the concepts contained in outcome measures used in clinical trials.

3. Introduction

Each of the four general internal disorders, chronic ischemic heart disease (CIHD), chronic obstructive pulmonary diseases (COPD) with asthma, diabetes mellitus (DM) and obesity (OB) carries a high burden of disease. Ischemic heart disease is projected to become the leading cause, and chronic obstructive pulmonary disease, the fifth leading cause of disability-adjusted life years (DALYs) (Murray, Harvard Univerity Press 1997). Obesity is already considered to be the fifth most serious risk factor for disease burdens measured in DALYs (WHO 2002), and diabetes mellitus is responsible for 1.9% of all DALYs in developed countries (Murray, Lancet 1997). Thus, these conditions are highly relevant to most clinically active physicians and other health professionals. In a survey on the competencies that should be addressed in a medicine core clerkship, coronary artery disease, chronic obstructive pulmonary disease, and diabetes mellitus were among the disease-specific clinical competency areas warranting highest priority (Bass 1997).

Ischemic Heart Disease (IHD), which most commonly refers to coronary-artery disease, may present either as an acute syndrome, like unstable angina and acute myocardial infarction or chronic stable angina. Chronic stable angina is the initial manifestation of chronic ischemic heart disease (CIHD) in approximately one half of the patients (Elveback 1986, Kannel 1972).

The most typical and common symptoms and limitations of functioning in patients with chronic stable angina are substernal/chest discomfort, which occurs predictably and reproducibly at a certain level of exertion and is relieved

by rest or nitroglycerine (Kannam 2003, Podrid 2003) and “exercise intolerance” – activity-limitations, like reduced walking distances. However, there are atypical symptoms, such as shortness of breath (dyspnea), (left) arm pain on exertion, and worsening heart failure, also referred to as “ischemic or anginal equivalent” (Gibbons, Circulation 2003 & J Am Coll Cardiol 2003). Silent (asymptomatic) ischemia is, however, a most common manifestation of CIHD (Prakash 2003, Deedwania 1991).

From a psychosocial perspective, IHD is associated with a decreased quality of life (Westin 1997). Psychological problems are well known and common in CIHD patients, including depression, anxiety, irritability, sexual difficulties, and problems within the family (Eaker 1988, Orth-Gomer 1998, Orth-Gomer 2000). Annually health care costs for CIHD in the US was estimated in 2002 at 111,8 billion dollar (NIH-NHLBI 2002- Morbidity & Mortality chartbook).

Current recommendations for the treatment of CIHD focus on two major goals: first, to increase the “quantity” of life (prevent myocardial infarction and death) and second, to improve the quality of life (by reducing symptoms related to angina/ischemia) (Gibbons, Circulation 2003 & J Am Coll Cardiol 2003, Balady 2000). The recognition of the importance of systematically assessing symptoms and functional limitations to optimize the management of CIHD has led to the development and use of a number of condition-specific health-status measures such as Quality of Life after Myocardial Infarction (QLMI) (Lim 1993), Seattle Angina Questionnaire (SAQ) (Spertus 1995) and Angina pectoris Quality of Life Questionnaire (Marquis 1995). These specific instruments are often combined with generic instruments as the Medical Outcomes Study Short Form 36 (SF36) (Ware 1992), the Sickness Impact Profile (Bergner 1981), the

Nottingham Health Survey (Hunt 1985). Recently the American College of Cardiology and the American Heart Association reviewed the use and the properties of currently available health-status measures for patients with CIHD (Gibbons, Circulation 2003 & J Am Coll Cardiol 2003).

Diabetes mellitus (DM) is a chronic metabolic disease caused by a relative or absolute insulin deficiency (Skyler 1997). It can be present for up to 9-12 years before initial clinical diagnosis (Harris 1992). Microvascular disease progresses during this time, causing 15% to 20% of patients to have retinopathy (Harris 1992, Hamman 1989) and 5% to 10% to have polyuria at the time of diagnosis (Haffner 1989). Diabetic Patients have high rates of hypertension, dyslipidemia, and obesity, major reasons for their 2- to 4-fold higher rates of cardiovascular disease (Roman SH 1997). At time of diagnosis Diabetic symptoms that may be seen are thirst, polyuria, fatigue, general malaise, infections, and blurred vision. Over time patients with DM also develop symptoms and limitation of functioning related to major microvascular (i.e., retinopathy, nephropathy, neuropathy, diabetic foot problems) and macrovascular (i.e., cardiovascular disease, cerebrovascular disease, and peripheral vascular disease) complications (Stratton 2000, Foster 1998). These long-term complications of Diabetes have a considerable effect on quality of life (Koopmanschap 2002, UKPDS 1999). Psychological problems in DM patients include depression, anxiety, fatigue, eating disorders, changes in sexual functions (Pita 2002, Jacobson 1996, Hörnquist 1995). Reduced quality of life is apparent in general well-being; family life effects, arising from a lack of acceptance and support from family members; social effects, such as reduced

social function due to feelings of isolation and withdrawal (Koopmanschap 2002, Assal 1995). U.S. Health care costs attributable to diabetes have exceeded $100 billion each year (American Diabetes Association 2003).

Current recommendations for the medical treatment of DM primarily focus on the close measurement and regulation of blood sugar. In addition, symptoms related to diabetic complications should be closely monitored (Clark 2000). The recognition of the importance of systematically assessing symptoms and functional limitations to optimize the management of DM has led to the development and use of a number of condition-specific health-status measures such as the Diabetes Quality of Life Questionnaire (DCCT Research Group 1988) or the Audit of Diabetes Dependent QOL (Bradley 1999). Condition-specific instruments are often combined with generic health status instruments such as the EQ-5D (Brooks 1996) and so called dimension-specific measures such as the Beck Depression Inventory (Beck 1961) and the Cognitive Failures Questionnaires (CFQ) (Broadbent 1982). A recently-published review of health-related quality of life measurements in DM shows the wide variety of generic, diabetes-specific, and psychological measures that have been used in diabetic patients (Luscombe 2000).

Obesity (OB) is the excessive accumulation of adipose tissue to an extent that health is impaired. Obesity is usually determined using body mass index (BMI). A BMI $\geq$ 30 kg/m^2 correlates strongly with obesity-related comorbid conditions and mortality (Aronne 2002, WHO 1998). The etiology of this complex, multifactorial condition comprises biologic, genetic, emotional, social and cultural factors (McTigue 2002, NIH-NHLBI 2000). The major dangers of

obesity on a person's functioning and health includes the increased risk of hypertension, dyslipidemia, type II diabetes mellitus, coronary-artery disease, stroke, gall-bladder disease, osteoarthritis, sleep apnea, and respiratory problems, as well as certain types of cancer (Pi-Sunyer 1993; NIH-NHLBI 2000). Symptoms and limitations of functioning commonly associated with morbid obesity are dyspnea, hip and knee pain, low back pain (Heo 2003, Yancy 2002, Barofsky 1997), fatigue/decreased energy (Stoohs 1994), sleep disturbance (Ropka 2002), gastroesophageal reflux (Locke 1999) and urinary incontinence (Dwyer 1988). From a psychosocial perspective, obesity is associated with a decreased quality of life (Yancy 2002, Fontaine 1996; Fine 1999). Astonishingly the obese population manifest no more psychological disturbance than do non-obese populations; however, obese persons who seek treatment may be more likely than non-treatment-seeking obese persons to experience psychological disturbance and eating disorders (Fitzgibbon 1993, Foster 1994). Nevertheless the social and psychological burden of obesity is considerable (Rand 1991). Discrimination at work, in public, and interpersonally is common (Stunkard 1992, Rand 1990, Klesges 1990). Obese persons are regarded as "dirty" ,"lazy", "stupid", "cheating", "lying" and "ugly" (Kushner 2000, Staffieri 1967). In contrast to other chronic physical conditions obesity often results in negative economic and social consequences, such as lower income and lower marriage rates (Gortmaker 1993). U.S. Health care costs attributable to obesity amounted in 1995 to 92,2 billion dollars (Wolf 1998).

Current recommendations for the medical treatment of obesity primarily focus on the close measurement and regulation of BMI, waist circumference, blood pressure, blood sugar and serum lipids (Aronne 2002). In addition,

therapeutic interventions should aim at symptoms related to obesity, patients functioning and well-being (Ropka 2002, NIH-NHLBI 2000 – The practical guide.). The recognition of the importance of systematically assessing symptoms and functional limitations to optimize the management of obesity has led to the development and use of a number of condition-specific health-status measures such as the Impact of Weight on Quality of Life Questionnaire (IWQOL), Obese specific quality of life (Le Pen 1998) or the Obesity related well-being (Mannucci 1999). Obesity-specific instruments are often combined with generic health status instruments such as the SF-36 (Ware 1992) and so called dimension-specific measures including measures of depression (Beck Depression Inventory) (Beck 1961), self esteem (Rosenberg 1965) and comorbidities such as arthritis (WOMAC) (Bellamy 1988) and daytime sleepiness (Johns 1991). The North American Association for the Study of Obesity (NAASO 2002) recently published a supplement showing the wide variety of generic, obesity-specific, and psychological measures that are used in obese patients.

Chronic Obstructive Pulmonary Diseases (COPD) and asthma the most common conditions associated with chronic airflow limitations. COPD and asthma differ with regard to age, risk factors, course, and treatment (Pauwels 2001, NIH-NHLBI 2002 - Asthma). However, both conditions share many symptoms and functional limitations.

COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response (NHLBI/WHO 2003).

The most typical and common symptoms in patients with COPD are chronic cough, sputum production, wheezing and shortness of breath (firstly only upon exertion, later on at rest) (NHLBI/WHO 2003). Cough and sputum production can precede the development of airflow limitations by many years. Limitation of functioning is mostly due to dyspnea reducing daily activities such as fostering oneself, outdoor activities and hobbies. Psychological problems such as anxiety, depression, low self-esteem, poor social relations, difficulties in coping with chronic lung disease, and reduction in self-efficacy contribute to the handicap of advanced respiratory disease (ACCP/ACVPR 1997, Ries 1995, Carrieri-Kohlman 1996). Fear of dyspnea-producing activities may further limit the patient's ability to participate in activities of daily living. Reduced self-efficacy may also burden the family and lead to conflicts due to new or increased responsibility for bathing, dressing and meal preparation (Sexton 1985). Annually health care costs for COPD in the US was estimated in 2002 at 32,1 billion dollar and for asthma patients 14,0 billion dollar (NIH-NHLBI 2002-Morbidity & Mortality chartbook).

Current recommendations for the treatment of COPD focus on prevention of disease progression and reduction of mortality as well as on relief of symptoms, improvement of exercise tolerance and emotional function (health-related quality of life) (Pauwels 2001).

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. A widespread, but variable airflow obstruction is often reversible either spontaneously or with treatment (NIH-NHLBI 2002 - Asthma). The most typical and common symptoms in patients with asthma are recurrent episodes of coughing, wheezing, chest tightness and difficult breathing, particularly at night or in the early morning. Important triggers that may cause asthma exacerbation are allergens, respiratory infections, air pollutants, excise and hyperventilation, weather changes, foods, food additives, drugs and extreme emotional expression such as laughing, crying, anger or fear (NIH-NHLBI 2002 - Asthma). Limitations of functioning consist in problems with physical activities such as sports, hurrying, going upstairs and shopping. Allergens may cause difficulties with daily activities such as household chores, outdoor activities and hobbies. Environmental stimuli, such as cigarette smoke, strong smells, and troublesome weather condition, may limit family activities and visiting friends (Juniper - Curr Opin Pulm 1999). Considerable numbers of patients report regular sleep disturbances (Strachan 2000) and often feel tired. Health-Related Quality of Life (HRQoL) in patients with occupational asthma is even poorer than in patients, whose asthma is not of occupational origin (Malo 1993). Emotional stresses are “fear of not having medications available”, “afraid of getting out of breath”, “concerned about the need to use medications” and “frustration” (Juniper 1992). Asthma has been documented as a major cause of absence from work (Department of Health and Human Services 2000). Uncontrolled asthma in one family member can impede the economic effectiveness of other family members (Weiss 1992). Time spent caring for the

asthmatic person and obtaining medicines, as well as high medical bills can cause substantial burden for entire families.

Current recommendations for the treatment of asthma focus on the best possible lung function as well as on no restriction on activities, including sports and freedom from symptoms day and night (NIH-NHLBI 2002 - Asthma). The recognition of the importance of systematically assessing symptoms and functional limitations to optimize the management of COPD and asthma has led to the development and the use of a number of condition-specific health-status measures such as the Chronic Respiratory Questionnaire (CRQ) (Guyatt 1987), the St. George's Respiratory Questionnaire (Jones 1991) and the Asthma Quality of Life Questionnaire (Juniper - Chest 1999). These specific instruments are often combined with generic instruments such as the Medical Outcomes Study Short Form 36 (SF36) (Ware 1992), the Sickness Impact Profile (Bergner 1976) and the Nottingham Health Survey (Hunt 1985).

A number of organizations, including the American Thoracic Society (ATS 1999 Pulmonary Rehabilitation, ATS 1999 Dyspnea), the American College of Chest Physicians, the American Association of Cardiovascular and Pulmonary Rehabilitation (ACCP/AACVPR 1997), and the National Heart, Lung, and Blood Institute collaborating with WHO (WHO 2001), have reviewed the use and the properties of currently available health-status measures for COPD.

As described above, a large number of clinical tests as well as generic, symptom- or dimension- and condition-specific (Bowling 2001, Guyatt 1993) health status measures have been developed and are used in clinical practice

and clinical trials on internal disorders to describe and evaluate functioning and health as well as therapeutic benefit.

Based on the new International Classification of Functioning, Disability and Health (ICF) (WHO 2001), it is now possible to identify and compare concepts contained in different outcome measures (i.e. HRQoL Questionnaires), in addition to clinical and physiological outcome measures.

The International Classification of Functioning, Disability and Health (WHO 2001) is a multipurpose classification belonging to the WHO family of international classifications. The overall aim of the ICF is to provide a unified and standard language and framework for the description of health and health-related states.

The ICF has two parts, each containing two separate components. Part 1 covers FUNCTIONING and DISABILITY and includes the components: Body Functions (b) and Structure (s) and Activities and Participation (d). Part 2 covers CONTEXTUAL FACTORS and includes the components: Environmental Factors (e) and Personal Factors.

In the ICF classification, the letters b, s, d, and e, which refer to the components of the classification, are followed by a numeric code starting with the chapter number (one digit), followed by the second level (two digits) and the third and fourth levels (one digit each). The component letter with the suffix of two, three, or four digits corresponds to the code of the so-called categories. Categories are the units of the ICF classification. Within each chapter, there are individual two-, three- or four-level categories.

As a classification, ICF does not model the “process” of functioning and disability. However, the ICF can be used to describe the process of functioning

and disability. Functioning is an umbrella term encompassing all body functions, activities and participation. Disability is an umbrella term for impaired body functions and structures, activity limitations and participation restrictions. Any description of the process of functioning and disability is always made within the context of environmental and personal factors.

The objective of this systematic review was to identify and compare the frequency of concepts contained in the outcome measures of randomized controlled trials (RCTs) for interventions in general internal disorders using the ICF as a reference tool.

4. Methods

4.1 Design

A systematic review was performed with the following three steps: step 1, selection of studies, step 2, outcome measures extraction and step 3, linkage of the concepts contained within the outcomes measures to the corresponding categories of the ICF. Step 3 was done by two independent reviewers.

4.1.1 Step 1: Selection of Studies

In step 1, selection of studies, randomized control trials (RCTs) between the years 1993-2003 were located in MEDLINE®, Silver Platter, 2000 Edition,

by using Dickersin et al's (1994) highly precise search strategy (sets 1-8). Thereafter, the Dickersin search was combined with four condition-specific search strategies using the 'and' operator.

To locate CIHD- trials, the title and abstract terms 'coronary thrombosis', 'coronary stenosis', 'coronary arteriosclerosis', 'angina unstable', 'angina pectoris', 'coronary disease' were combined using the 'or' operator. To locate DM- trials, the title and abstract term 'Diabetes Mellitus' and 'Diabetes Mellitus' in all subheadings were combined using 'or' operator. To locate OB-trials, the explode- function 'obesity-morbid' including all subheadings and the title and abstract terms 'obesity', 'obese', 'overweight' were combined using 'or' operator. To locate OPD- trials, the explode-function for 'lung-disease-obstructive', 'Asthma- Exercise- Induced', 'Status-Asthmaticus', 'Bronchial-Hyperreactivity', 'and 'Respiratory-Sounds' including all subheadings, the combined term 'chronic obstructive' and 'lung' or 'pulmonary' or 'airway*', and the single terms 'bronchit*', 'emphysem', 'COPD', 'COAD', 'asthma*' and 'wheez' were combined using the 'or' operator. All searches were limited to English articles. The abstracts were checked applying general and condition-specific eligibility criteria. For the selected trials the original study reports were ordered and reviewed applying again the same eligibility criteria. The finally included studies entered step II of the review.

A study met general eligibility, if the study design was a RCT, the experimental intervention had a therapeutic aim, and the outcome measures had to be evaluated on patients, and if none of the following exclusion criteria were fulfilled: reviews, secondary analyses, psychometric studies, primary prevention studies (healthy population at risk), mode of action studies, and

studies with mixed population. In the case of multiple publications, the paper with the highest impact factor was included.

To identify the appropriate study population in each health condition condition-specific eligibility criteria were applied. To select persons with CIHD, the terms angina pectoris, coronary arteriosclerosis, coronary stenosis and coronary thrombosis have to be reported to describe the study population. Populations with 'old' myocardial infarction (acute infarction older than 12 months), aneurysm of the heart, coronary artery aneurysm or silent myocardial ischemia were excluded. Further exclusion criteria were the following MESH Terms: Syndrome X, coronary aneurysm, coronary restenosis, coronary vasospasm, angina pectoris variant. To select persons with DM, the term diabetes mellitus has to be reported to describe the study population. Specific populations with prediabetic states or gestational diabetes were excluded. To select persons with OB, the diagnosis of obesity has to be reported to describe the study population. Populations with coronary heart disease, stroke, osteoarthritis and diabetes mellitus Type I and II were excluded. To select persons with OPD, the diagnosis of asthma or chronic obstructive pulmonary disease (chronic bronchitis and/or pulmonary emphysema) has to be reported to describe the study population. Upper obstructive respiratory tract disease and airways obstruction in lower respiratory tract due to diseases with known etiology and specific pathology (e.g. cystic fibrosis, lung cancer, bronchiolitis obliterans) were excluded. Persons aged below 18 years were excluded in each health condition considered.

4.1.2 Step 2: Outcome Measures Extraction

In step 2, outcome measures extraction, all types of outcome measures including clinical tests, single item measures on different domains, biochemical, physiologic, imaging tests, biopsy as well as questionnaires were extracted. If the items of a questionnaire were not specified in the publication, we attempted to obtain the questionnaire by reference checking, searches in databases or books on health status measures (Mc Dowell 1996, Salek 1999), email-consultation with the developers of the questionnaire in demand, and Internet Searches, and then the items were extracted. Only questionnaires available in English language were included. Additionally, study population characteristics (disease duration, disease-subsets, etc.) and the type of experimental intervention (drug-, surgery-, non-pharmacologic treatment including complex rehabilitative, physical, complementary, nutritional, educational and psychological therapy, and combination of these categories) were extracted.

4.1.3 Step 3: Linkage of the Concepts

In step 3, linkage of the concepts contained within the outcomes measures to the corresponding categories of the ICF, the concepts contained within the outcome measures were extracted and linked to the most specific ICF- category by two independent health professionals according to a recently developed set of 10 linking rules (Cieza 2002).

Concepts of outcome measures that could not be linked to the ICF were documented and classified in two ways: 1) If a concept of an outcome measure

was not sufficiently specified to make a decision which ICF- category the concept should be linked to, the ‘not definable’ option was chosen (linking rule 9). To give an example, unspecified concepts such as ‘functional status’, ‘health’, ‘disability’ or ‘symptoms’ were considered not to be definable for linking. 2) If a concept of an outcome measure was not represented by the ICF, the option ‘not covered’ was chosen (linking rule 10). To give an example, concepts such as ‘plans about committing suicide’, ‘killing’ extracted from the BDI (Beck Depression Inventory) (Beck 1961) or ‘Do you look forward to the future’ from the DHP (Diabetes Health Profile Questionnaire) (Meadows KA 1996) were considered not to be covered by the ICF. Also personal factors such as age and weight are not covered. Consensus between the two health professionals was used to decide which ICF category should be linked to each item/concept of the questionnaires. To resolve disagreements between the two health professionals concerning the selected categories, a third person trained in the linking rules was consulted. In a discussion led by the third person, the two health professionals that linked the item stated their pros and cons for the linking of the concept under consideration to a specific ICF category. Based on these statements, the third person made an informed decision.

Additionally, to control the plausibility of the linkage procedure the concepts of the outcome measures assigned to the same single ICF- category were analyzed (e.g. the concepts ‘not able to make a start’, ‘having little interest in things’, ‘feeling full of pep’, ‘having trouble resisting one’s craving’ which were linked to the ICF- category ‘energy and drive functions’ (b130)).

4.2 Analyses

Descriptive statistics were used to examine the frequency of ICF-categories linked to the concepts contained in the outcome measures. Large-scale-cross tables generated from a SQL-database (Structured Query Language-Server 2000) were thereby analyzed. If one and the same ICF-category was assigned repeatedly in a study, the category was counted only once.

ICF-categories are presented on the second level. If a concept of an outcome measure was linked to a third or fourth level ICF-category, the overlying second level category was considered. The ICF is organized in a hierarchical scheme, so that the lower-level category shares the attributes of the higher-level category (WHO 2001). Only ICF-categories with a frequency equal or greater than 10% are shown (preset frequency).

5. Results

5. 1 Step 1: Selection of Studies

For each of the four health conditions, the number of studies located by the search strategy (step 1), the number of studies preliminarily selected by abstract checking, the number of studies selected after screening the original papers, and the number of studies included in the review are presented in Table I. For OPD, only 25% of the studies selected after screening the original papers were included in the review. This 25% of studies was selected randomly.

Table I: Selection of Studies

	CIHD	DM	OB	OPD
Studies located by the search strategy	345	815	1382	3731
Studies preliminary selected by abstract checking	260	334	519	2174
Studies selected after screening the original papers	166	227	428	1014
Studies included in the review	166	227	428	253*

CIHD: Chronic ischemic heart disease, DM: Diabetes mellitus, OB: Obesity, OPD: Obstructive pulmonary disease.
* Randomly included studies out of 1014 selected studies

5. 2 Step 2: Outcome Measure Extraction

In step 2, for CIHD 11 different questionnaires were identified, 10 fulfilled the inclusion criteria and could be linked (different versions of a questionnaire were considered as one and the same questionnaire). These 2 condition-specific questionnaires, 5 dimension-specific questionnaires (on dimensions such as pain, locus of control, depression, anxiety, coping, etc.) and 3 generic questionnaires were chosen as outcome measures. Exclusively 6 studies contained one or more questionnaires. The Physical Symptoms Distress Index (Anderson 1999) was included in two studies, all other questionnaires in one study each. Most often used clinical and physiological outcome measures referred to cardiovascular parameters (i.e. blood pressure, heart rate, ECG-changes, anginal symptoms, nitroglycerine consumption, arrhythmia, cardiac output and volumes, exercise test parameters, arterial lesions and stenosis, myocardial infarction) and laboratory tests (i.e. haematology, coagulation parameters, lipids, creatininekinase). Also variables such as mortality, length of stay, revascularisation and adverse events were frequently reported study outcomes. Pharmacologic treatment was the most frequently used intervention

type with a prevalence of 88% (n= 146 studies), followed by invasive surgery and minimal invasive surgery with 7,8% (n= 13 studies) and 3,6% (n= 6 studies), respectively. Standard medical care, nutritional therapy, active physical therapy, gene therapy and education were each found in less than 3% of the 166 studies (3%; 3%; 1,8%; 1,2%; 1,2%). 153 studies (92,2%) examined the efficacy of one intervention type; only 11 studies (6,6%) examined the efficacy of two intervention types. The efficacy of three and four intervention types were examined in one study (0,6%) each.

In DM 25 different questionnaires were identified, 19 fulfilled the inclusion criteria and could be linked. These 6 condition-specific questionnaires, 10 dimension-specific questionnaires and 3 generic questionnaires were chosen as outcome measures. At least one health status questionnaire per trial was selected in 21 (9,25%) of the studies. The most frequently used questionnaire was the Medical Outcomes Study 36 Items Short Form Health Survey SF-36 (Ware 1992) with a prevalence of 1,8% (n= 4 studies). Most often used clinical and physiological outcome measures referred to laboratory parameters for metabolic and renal functioning (i.e. glucose, HbA1c, C-peptide, lipids cholesterol, trigyceride, fatty acids, insulin, albumin, creatinine, filtration rates), nutritional parameters (i.e. caloric intake, eating habits), cardiovascular parameters (i.e. heart rate, blood pressure, ECG-changes, ischemic symptoms) and also clinical events such as reaction to hypoglycemia, physical activity and compliance. Also variables such as adverse events, length of stay, body measurements (i.e. BMI, weight, fat distribution) were frequently reported study outcomes. Drug treatment was the most frequently used intervention type with a prevalence of 83,7% (n= 190 studies), followed by nutritional therapy with

14,5% (n= 33 studies) and education with 11,5% (n= 26 studies). Active physical therapy, psychological intervention, standard medical care, minimal invasive surgery and passive physical therapy were each found in less than 4% of the 227 studies (3,5%; 2,6%; 2,2%; 1,8%; 0,4%). 188 studies (82,8%) examined the efficacy of one intervention type, 34 studies (15%) of two intervention types. Three and four intervention types were examined in three (1,3%) and two (0,9%) studies respectively.

In OB 96 different questionnaires were identified, 47 fulfilled the inclusion criteria and could be linked, including 3 condition-specific questionnaires, 35 dimension-specific questionnaires and 9 generic questionnaires were chosen as outcome measures. At least one health status questionnaire per trial was selected in 116 or 27,1% of the studies. The most frequently used questionnaires were the Beck Depression Inventory BDI (Beck 1961), Block Food Frequency questionnaire (Block 1992) and Three-Factor Eating Questionnaire TFEQ (Stunkard 1985) with a prevalence of 5,8% (n= 25 studies), 3,5% (n= 15 studies) and 3,5% (n= 15 studies), respectively. Most often used clinical and physiological outcome measures referred to nutritional parameters (i.e. caloric intake (fat/protein/carbohydrate), eating habits), body measurements (i.e. BMI, weight, waist circumference, bodily fat distribution) cardiovascular parameters (i.e. heart rate, blood pressure, exercise tests), laboratory parameters (i.e. cholesterol, triglyceride, HDL, LDL, fatty acids, glucose, insulin, thyroid function, metabolic rate), lung function (i.e. FEV1, FVC, peak expiratory flow rate, lung volumina parameters, ventilation rate, oxygen consumption/uptake, carbon dioxide production, respiratory quotient) as well as physical activity, sleep, fatigue and pain. Also patient compliance and adverse

events were frequently reported study outcomes. Nutritional therapy was the most frequently used intervention type with a prevalence of 55,8% (n= 239 studies), followed by drug treatment with 54% (n= 231 studies), active physical therapy with 22% (n= 94 studies), psychological intervention with 20,6% (n= 88 studies) and education with 18% (n= 88 studies). Surgery, complementary medicine, standard medical care and passive physical therapy were each found in less than 6% of the 428 studies (5,4%; 0,9%; 0,5%; 0,2%). 197 studies (46%) examined the efficacy of one intervention type, 146 studies (34,1%) of two intervention types and 68 studies (15,9%) of three intervention types. Four and five intervention types were examined in 14 (3,3%) and two (0,5%) studies respectively.

For OPD 39 different questionnaires were identified, fulfilled the inclusion criteria and could be linked, including 16 condition-specific, 17 dimension-specific questionnaires and 6 generic questionnaires were chosen. At least one health status questionnaire per trial was selected in 64 or 25% of the studies. The most frequently used questionnaires were the Asthma Quality of Life Questionnaire (Juniper 1999), Chronic Respiratory Questionnaire (Guyatt 1987) and St. George's Respiratory Questionnaire (Jones 1991) with a prevalence of 6% (n= 15 studies), 5% (n= 13 studies) and 4% (n= 10 studies), respectively. Most often used clinical and physiological outcome measures referred to lung function (i.e. FEV1. FVC, peak expiratory flow rate, lung volumina parameter), blood gas analysis (i.e. paCO2, paO2, pH), VO2max,) cardiovascular parameters (i.e. heart rate, blood pressure), exercise test parameters, on demand medication and symptoms like dyspnea, chest tightness, coughing, or wheezing. Also variables such as sleep and fatigue as well as adverse events

were frequently reported study outcomes. Drug intervention was the most frequently used intervention type with a prevalence of 74% (n= 187 studies). Non-drug intervention types as pulmonary rehabilitation, muscle training, homeopathy, diet and health education were presented in 26% (n=65) of the studies. Due to computer problems the detailed percentages are not available anymore. Only in one study two intervention types have been compared.

5.3 Step 3: Linkage of the Concepts

In step 3, at least 75% (range: 75-92%) of the extracted concepts could be linked to the ICF across all four conditions. At most 5% (range 3-5%) of the concepts were considered not to be definable, and at most 21% (range: 3-21%) of the concepts were considered not covered by the ICF.

In CIHD a total of 2805 concepts were extracted from the outcome measures; 2110 or 75% of concepts could be linked to the ICF, 112 or 4% of concepts were considered not to be sufficiently specified for an assignment to the ICF ('not definable option'), and 583 (21%) of concepts were considered to be not covered by the ICF. In DM a total of 3409 concepts were extracted; 2848 concepts (84%) could be linked to the ICF, 166 concepts (5%) were considered not to be sufficiently specified, and 395 concepts (12%) were considered to be not covered by the ICF. In OB a total of 16034 concepts were extracted; 12914 concepts (81%) could be linked to the ICF, 527 concepts (3%) were considered not to be sufficiently specified, and 2593 concepts (16%) were considered to be not covered by the ICF. In OPD a total of 8266 concepts were extracted; 7611

(92%) concepts could be linked to the ICF, 378 concepts (5%) were considered not to be sufficiently specified, and 277 concepts (3%) were considered to be not covered by the ICF.

For all four conditions 83,5% of the concepts within the outcome measures could be linked to the ICF. Of those which could not be linked 12,6% were not covered and 3,9% were not sufficiently defined.

The broadest spectrum of ICF-categories with frequencies over 10% was found in OPD, the narrowest in DM. In all four conditions the most used categories were condition-specific and focused on the component 'body-function':

Table II: Relative frequency in percentage of International Classification of Functioning, Disability and Health (ICF)- categories linked to the concepts contained in the outcome measures for the ICF- component 'Body Functions'

ICF Cluster Code	Title	CIHD n=166	DM n=227	OB n=428	OPD n=253*
b126	Temperament and personality functions				13
b130	Energy and drive functions			21	13
b134	Sleep functions			17	38
b152	Emotional functions			21	25
b160	Thought functions			13	
b280	Sensation of pain	16		13	23
b410	Heart functions	87	22	28	17
b415	Blood vessel functions	11			
b420	Blood pressure functions	46	37	39	
b430	Haematological system functions	33	21	12	
b435	Immunological system functions				13
b440	Respiration functions			11	86
b450	Additional respiratory functions				31
b455	Exercise tolerance functions	43		21	31
b460	Sensations associated with cardiovascular and respiratory functions				51
b525	Defecation functions				11
b530	Weight maintenance functions			14	
b535	Sensations associated with the digestive system				14
b540	General metabolic functions	25	95	65	13
b545	Water, mineral and electrolyte balance functions		15	18	
b555	Endocrine gland functions		15	22	
b610	Urinary excretory functions	16	32		

CIHD: Chronic ischemic heart disease, DM: Diabetes mellitus, OB: Obesity, OPD: Obstructive pulmonary disease.
* Randomly included studies out of 1014 selected studies

The ICF categories with the highest relative frequencies are in CIHD 'heart functions' (b410), in DM and OB 'general metabolic functions' (b540) and in OPD 'respiratory functions' (b440). Most of the concepts linked to these categories represented paraclinical tests, i.e. ECG-change in CIHD was linked to b410, spirometry in OPD to b440 and in OB different laboratory tests to b540. The most used ICF-categories throughout all four conditions were heart functions (17-87%) and general metabolic functions (13-95%).

Within the ‘activities and participation’ component the most prevalent categories were ‘looking after one's health’ (d570) in CIHD, DM and OB, being the only category for CIHD and DM reaching the preset 10 percent level. OPD covered a large spectrum of this component with slight accentuation on 'walking' (d450) and 'moving around in different locations' (d570). Further important categories were i.e. ‘recreation and leisure’ (d920), ‘doing housework’ (d640), ‘washing oneself’ and ‘changing basic body position’ (d410).

Table III: Relative frequency in percentage of International Classification of Functioning, Disability and Health (ICF)- categories linked to the concepts contained in the outcome measures for the ICF- component ‘Activities and Participation’

ICF Cluster Code	Title	CIHD n=166	DM n=227	OB n=428	OPD n=253*
d350	Conversation				10
d410	Changing basic body position				14
d430	Lifting and carrying objects				11
d450	Walking			10	29
d455	Moving around				21
d460	Moving around in different locations				25
d510	Washing oneself				15
d540	Dressing				13
d550	Eating			10	
d570	Looking after one’s health	25	33	57	
d620	Acquisition of goods and services				13
d640	Doing housework				19
d650	Caring for household objects				13
d910	Community life				10
d920	Recreation and leisure			13	20

CIHD: Chronic ischemic heart disease, DM: Diabetes mellitus, OB: Obesity, OPD: Obstructive pulmonary disease.
* Randomly included studies out of 1014 selected studies

Within the ‘environmental factors’ component ‘Products or substances for personal consumption’ (e110) was present in CIHD, OB and OPD. In OPD

further categories were ‘climate’ (e225), ‘time-related changes’ (e245) and ‘air quality’ (e260). In DM there were no “environmental” categories with frequencies over 10%.

Table IV: Relative frequency in percentage of International Classification of Functioning, Disability and Health (ICF)- categories linked to the concepts contained in the outcome measures for the ICF- component ‘Environmental Factors’

ICF Cluster Code	Title	CIHD n=166	DM n=227	OB n=428	OPD n=253*
e110	Products or substances for personal consumption	13		16	41
e225	Climate				12
e245	Time-related changes				28
e260	Air quality				11

CIHD: Chronic ischemic heart disease, DM: Diabetes mellitus, OB: Obesity, OPD: Obstructive pulmonary disease.
* Randomly included studies out of 1014 selected studies

Within the ‘body structure’ component, ‘structure of cardiovascular system’ (s410) was present in CIHD and ‘structure of the trunk’ (s760) in OB.

Table V: Relative frequency in percentage of International Classification of Functioning, Disability and Health (ICF)- categories linked to the concepts contained in the outcome measures for the ICF- component ‘Body Structure’

ICF Cluster Code	Title	CIHD n=166	DM n=227	OB n=428	OPD n=253*
s410	Structure of cardiovascular system	49			
s760	Structure of trunk			13	

CIHD: Chronic ischemic heart disease, DM: Diabetes mellitus, OB: Obesity, OPD: Obstructive pulmonary disease.
* Randomly included studies out of 1014 selected studies

6. Discussion

Using the ICF as a reference it was possible to identify and quantify the concepts within the outcome measures used in RCTs for interventions in CIHD, DM, OB and OPD. Most concepts within the outcome measures could be linked to the ICF. Those, which could not be linked, were mostly not covered by the ICF. In these cases the content of the concepts did not lie in the defined universe of the ICF. This was most often the case for adverse events. Further more, health related status measures on dimensions such as personal factors are not covered by the current ICF and could therefore not be linked. Concepts referring to personal factors included ”habit” (i.e. ‘stop smoking’, ‘stop drinking’ (Scaling of Life Changes; Lundberg 1976)) or ”attitudes towards oneself” (i.e. ‘how useful is your education for your personality’, ‘no matter I am talking to, I am always a good listener’ (Life Satisfaction Index, Campbell 1976)). Similarly, “perception of surrounding” (i.e. ‘would you say it is safe to go out walking around here at night’ (Life Satisfaction Index, Campbell 1976)), and concepts on patient satisfaction (i.e. “How satisfied are you with …”) are beyond the ICF and could not be linked. Only a small portion of concepts was not specified in enough detail for an assignment.

The broadest spectrum of ICF categories with frequencies over 10% was found in OPD, the narrowest in DM. In all four conditions the most used categories were condition-specific and focused on the component 'body-functions': The ICF categories with the highest relative frequencies are in CIHD ‘heart functions’ (b410), in DM and OB 'general metabolic functions’

(b540) and in OPD 'respiration functions' (b440). Most of the concepts linked to these categories represented paraclinical tests, i.e. ECG-change in CIHD was linked to b410, spirometry in OPD to b440 and in OB different laboratory tests to b540. The most used ICF categories throughout all four conditions were heart functions (17-87%) and general metabolic functions (13-95%). Within the 'activities and participation' component the most prevalent categories were 'looking after one's health' (d570) in CIHD, DM and OB, being the only category for CIHD and DM reaching the preset 10 percent level. OPD covered a large spectrum of this component with slight accentuation on 'walking' (d450) and 'moving around in different locations' (d460). Further important categories were i.e. 'recreation and leisure' (d920), 'doing housework' (d640), 'washing oneself' (d510) and 'changing basic body position' (d410).

Within the 'environmental factors' component the category 'products or substances for personal consumption' (e110) was present in CIHD, OB and OPD. In OPD further categories were 'climate' (e225), 'time-related changes' (e245) and 'air quality' (e260). There were no "environmental factors" categories with frequencies over 10% in DM. Within the 'body structures' component, the category 'structure of cardiovascular system' (s410) was present in CIHD and the category 'structure of the trunk' (s760) in OB.

The outcome measures used in the studies influence the spectrum and the frequency of concepts linked to the ICF categories. The choice of the outcome measures on its part may depend on the intervention and the subset of patients studied. The results of this systematic review therefore have to be interpreted with caution and are to be put into perspective. In all

health conditions the majority of studies were drug trials focusing on clinically relevant parameters and not functioning.

Although it is beyond the scope of this paper to discuss whether the outcome measures used and therefore the concepts linked to the ICF in this study are appropriate for specific study questions and whether or not they adequately represent the patient experience, these findings reflect that in drug trials there is a lack of awareness regarding the importance of patients functioning (physical, emotional and social). There is growing evidence that correlations between clinical measures and how patients feel and how they are able to function in daily activities are only weak to moderate (Bendtsen 2003, Juniper 2002, Moy 2001, Juniper 1995). Outcome Research has shown that through the assessment HRQoL in addition to physiological parameters it is more likely to develop interventions that do not simply correct physiological abnormalities but truly improve health (Conners 2002). Our findings also indicate a need to define ”what should be measured” in RCTs to allow a more comprehensive and comparable comparison of patient populations across studies and interventions.

7. Conclusion

In conclusion, the ICF provides a useful reference to identify and quantify the concepts within the outcome measures used in RCTs for interventions in CIHD, DM, OB and OPD.

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9. Attachment (Anhang):

9.1 ICF-Definitions :

Body functions are the physiological functions of body systems (including psychological functions).

Body structures are the anatomical parts of the body such as organs, limbs and their components.

Impairments are problems in body function or structure such as a significant deviation or loss.

Activity is the execution of a task or action by an individual.

Participation is involvement in a live situation.

Activity limitations are difficulties an individual may have in executing activities.

Participation restrictions are problems an individual may experience in involvement in life situations.

Environmental factors make up the physical, social and attitudinal environment in which people live and conduct their lives.

9.2 Curriculum Vitae

Persönliche Daten

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10/96-06/98	Assistenzärztin: Psychiatrie, Klinikum Rechts der Isar der TU München
10/96	Vollapprobation
04/95-09/96	ÄiP: Innere Medizin, Hôpital du District de Moutier/Schweiz

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10/93-09/94	Praktisches Jahr: Neurochirurgie (Mc Gill University of Montreal) Allgemeine Chirurgie (Hôpital Universitaire de Montréal) Innere Medizin (Bezirksspital Grosshöchstetten/Schweiz) Neurologie (Universitätsklinik Benjamin Franklin/Berlin)
1991-1993	Praktika: Allgemeinmedizin (3 Monate im Hôpital de Bafang/Kamerun) Innere Medizin (3 Monate), Neurologie (2 Monate), Anästhesie (1 Monat)

Ausbildung

03/88-10/94	Medizinstudium an der Universität Bonn und der FU Berlin
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09/72-07/87	Grundschule/Gymnasium Icking (Bayern)
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Besondere Kenntnisse

Auslandserfahrungen:	4 Jahre in der Schweiz, Kanada, Kamerun (Assistenzarzt-Stelle, PJ, Famulaturen, Schüleraustausch)
Sprachkenntnisse:	Englisch und Französisch fließend in Wort und Schrift, Grundkenntnisse Spanisch
EDV-Kenntnisse:	MS Office, Internet
Psychologie:	Berufliche Erfahrungen in Verhaltenstherapie und Psychodrama
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München, den 15.05.2004