CORE-MD

Coordinating Research and Evidence for Medical Devices

The CORE-MD findings on the utility of PROMS

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What is the regulatory utility of patient-reported outcomes?

Objectives:

- to analyse the use of Patient-Reported Outcome Measures (PROMs) in trials, studies, of high-risk cardiovascular, orthopaedic, and diabetic medical devices.
- to provide the perspective of patients on their high-risk medical devices.

Methods:

- We performed a systematic literature review,
- We surveyed patients' and carers' views through a Delphi study, survey, and focus groups.

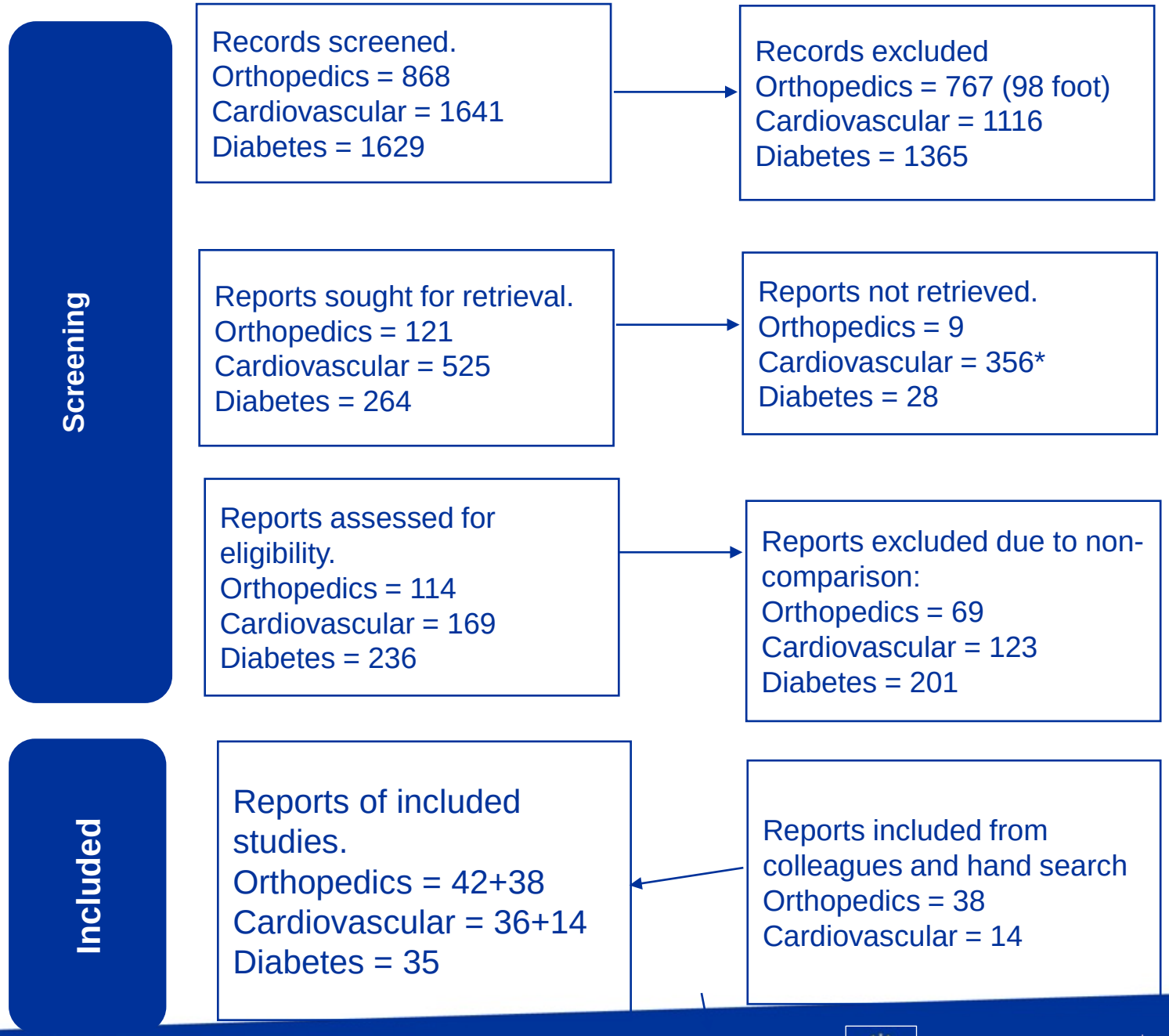
Literature review

- PROSPERO registered; PRISMA protocol for systematic reviews
- Data sources: MEDLINE, CINAHL, and Cochrane trials database
- Period of search: 2000–2023
- Search terms: 3 blocks: PROMS, devices / implants, condition (cardiology, orthopedic and diabetes)
- Inclusion criteria: RCT or observation studies, English-language, at least 3 months follow-up.
- Exclusion criteria: pharmaceuticals, rehabilitation, case-reports, expert statements.

Additional information

- Studies identified within other areas of CORE-MD that related to use of PROMS
- A manual, backward, snowballing search of the reference lists was performed to identify specific device related PROMS that had not emerged in the review.

Following Identification of studies via databases



Many PROMs being used: orthopedic device trials

GENERIC PROMS	freq	Pre-mkt	Core set	CONDITON SPECIFIC	freq	Pre-mkt	Core set
EQ-5D	25		X	Western Ontario and McMaster Universities Arthritis Index (WOMAC)	16	X	
SF-12 (VR-12)	9		X	Oxford Knee Score (OKS)	12		
SF-36	6	X		Oxford Hip Score (OHS)	11		
				Harris Hip Score (HHS)	9		
Non-validated / single item				Knee Injury and Osteoarthritis Outcome Score (KOOS)	9	X	X
Satisfaction VAS	18		X	Hip Disability and Osteoarthritis Outcome Score (HOOS)	7	X	X
Numeric pain rating scale	37	X	X	UCLA activity /function score	5		
VAS rating of disability	1			KSS expectation / satisfaction	2		
Disability index: self-admin	1			Forgotten Joint Score	1		
Questions about noise	1			Paffenbarger physical activity	1		
Unnamed questionnaire	1			Intermittent and Constant Osteoarthritis Pain (*ICOAP*)	1		

PROMs in cardiovascular device trials

ADULT GENERIC	freq	Pre-mkt	Core set	ADULT CONDITION SPECFIC	freq	Pre-mkt	Core set
SF-36	17	#		**Kansas City Cardiomyopathy Questionnaire** KCCQ*	4	#	#
SF-12	3		#	**Minnesota Living with Heart Failure Questionnaire** MLHFQ*	1	#	
EQ-5D	6	#		KCCQ-12	1		
HADS	5			Seattle Angina Questionnaire	1	#	
EQ-VAS	2			EuroQoL-HF	1		
State-Trait Anxiety Inventory (STAI)	2			Cardiac Anxiety Questionnaire (CAQ)	1		
PHQ-9	1		#	**MODIFIED for children**			
Profile of Mood States (POMS)	1			Patient scar assessment questionnaire (PSAQ)	1		
Quality of Well Being Schedule	1	#					
WHOQoL-Bref	1						
Satisfaction	1						
MODIFIED				**DEVICE SPECIFIC**			
"A short QoL questionnaire"	1			Florida Patient Acceptance Survey (FPAS)	3		
Karolinska questionnaire	1			Florida Shock Anxiety Scale (*FSAS*)	1		
NHQ /SF-36	1			Implanted Device Adjustment Scale (IDAS)	2		

*MDDT qualified

Types of PROMs and utility and composition: orthopedic device trials

PROM Outcome	Generic	Specific	Combination
Primary n=22	80% (25)	100% (31)	64% (14)
Secondary n=20	70% (21)	60% (17)	45% (9)

PROM Outcome	Pain	Satisfaction	QoL	Phy function/ activity	Social Activity/ADL	Emotional
Primary n=22	81% (20)	41% (9)		95% (24)	73% (16)	54% (13)
Secondary n=20	80% (17)	35% (10)		90% (25)	60% (13)	65% (17)

% related to the number of studies
(numbers in brackets represent the number of different PROMS used - 14 studies were used multiple PROMS)

FDA
Medical Device Development Tools (MDDT)

The MDDT program is intended to *facilitate device development by providing an efficient means for collecting the information to support regulatory submissions.*

patient-reported outcome measures (PROMs)

- Qualified PROMs can be used across multiple medical device submissions and manufacturers.
- Medical device sponsors can be sure that evidence provided will be accepted without the need to reconfirm the suitability and utility of the tool within the same context of use.

Example 1: - **Kansas City Cardiomyopathy Questionnaire** (KCCQ) (2000)

23-items (also -12); 2-week recall.

Domains:

- Symptom,
- Physical Limitation,
- Social Limitation,
- Quality of Life (QOL)
- Overall Summary Score.

- (NB KCCQ Qualification does not include Self-efficacy or symptom stability.)

Utility:

- evaluation of safety and effectiveness.
- component of a primary or secondary endpoint

Kansas City Cardiomyopathy Questionnaire (KCCQ-12)

e following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following estions. There are no right or wrong answers. Please mark the answer that best applies to you.

Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Activity	**Extremely** Limited	**Quite a bit** Limited	**Moderately** Limited	**Slightly** Limited	**Not at all** Limited	Limited for other reasons or did not do the activity
a. Showering/bathing	O	O	O	O	O	O
b. Walking 1 block on level ground	O	O	O	O	O	O
c. Hurrying or jogging (as if to catch a bus)	O	O	O	O	O	O
	1	2	3	4	5	6

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Construct Validity Assessments of the KCCQ

Domain	Reference Measure	Statistics	Validity Type,Analysis
Physical Function	1) 6 minute walk test, 2) NYHA class, 3) SF-36 physical 4) MLHFQ physical	1) r = 0.48** 2) r = -0.65** 3) r = 0.84** 4) r = 0.65**	Convergent validity, r=Spearman correlation coefficient
Symptom	NYHA class (I, II, III, IV)	Mean score diff: F=51.3** Linear trend: F=142.2**	Convergent Validity ANOVA
Social Limitation	1) NYHA class 2) SF-36 social scale	1) r = 0.62 ** 2) r = -0.57 **	Convergent validity Correlation
Quality of life	1) SF-36 general health 2) NYHA	1) r = 0.45 ** 2) r = -0.64 **	Convergent validity Correlation
KCCQ Overall Summary	1) NYHA class 2) Survival or hospitalization	1) Mean diff: F=41.9** Linear trend: F=156.8** 2) Mean diff 34.1 vs. 52.1**	Convergent & discriminant validity ANOVA, 2-sample t-test

Example 2: - Minnesota Living with Heart Failure Questionnaire (MLHFQ) (1987)

21 adverse effects of heart failure over the previous 4 weeks; 6-point rating scale

Questions ask about hospital admissions, medical costs, working to earn living, sexual activities and other problems eg:

Did your heart failure prevent you from living as you wanted during the past month by -

1. causing swelling in your ankles or legs?
2. making you sit or lie down to rest during the day?
3. making your walking about or climbing stairs difficult?

Utility:

- evaluation of safety, efficacy and effectiveness.

Evidence: internal, external reliability, convergent, divergent and predictive validity.

Example 3: Device specific instrument: Florida Patient Acceptance Survey (FPAS) (2005)

We want to understand what it is like for you to live with a medical device. Below are some statements that describe living with a medical device.

Factors:

1: Return to Function
2: Device-Related Distress
3: Positive Appraisal
4: Body Image Concerns

Structure:

15 items, present time; 5-point Likert scale Disagree/agree; 4 factors

Evidence: convergent validity with SF-36 & discriminant validity between different devices.

Factor analysis to identify domains.

Other aspects of the utility:

different ways to identify important change;

follow-up schedules

PROMS	Significant or important change	Baseline	6 Weeks	3 Mths	6 Mths	9 Mths	12 Mths	24 Mths	36 Mths Annually Thereafter
Subjective pain VAS (Clement 2021)	20-point (on a 100-point scale) improvement / unstated/trend	X	X	X	X		X	X	X
OKS (Moorthy 2020)	published MCID values	X			X			X	
SF-36 Mental and Physical Component Scores (Baktir et al 2016; Beaupré 2007;)	Statistically significant mean improvement from baseline	**X**	X	X	**X**		**X**	X	X
KCCQ (Lefevre et al. 2010)	using 0.05 as the minimum clinically important difference (MCID).	X					X		
MLHF (Acker et al. 2006)	Mean difference (<0.05)	X		X	X	X	x		
Florida Patient	cut-off score of 67			X					

How are PROMs used in device evaluation and regulatory decision-making?

- PROM instruments contribute to understanding of the real-world effects, satisfaction and acceptance (eg KCCQ, FPAS).
- PROMs are also used to identify adverse events and events that occur outside of the normal clinical visit times (eg MLHFQ).
- PROMs as intermediate endpoints.

PROMs may also have utility for:

- selection of clinical study subjects or to stratify patient population by predicted risk;
- study population enrichment;
- defining adverse events;
- developing post-market surveillance methodologies

Challenges to incorporating PROs in trials

1. Budget and time challenges related to generating sufficient evidence for a PRO, - process barriers, such as protocol implementation and site training.
2. Availability of PRO interpretation guidelines.
3. Lack of psychometric evidence - requiring further studies making it more time-consuming and costly to include PROs in trials.

4. Lack of clarity about evidence requirements.–

   Stakeholders are uncertain about:

   - what and how much evidence is necessary
   - the priorities for PROM evidence generation

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Multi-stakeholder workshop: Patient experience data in medicines development and regulatory decision-making

A common understanding on 'patient experience data', patient engagement, patient preferences and patient reported outcomes.

2022 CDRH issued guidance on the use of PROMs in medical device clinical trials

Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation

Guidance for Industry and Food and Drug Administration Staff, And Other Stakeholders

Document issued on January 26, 2022.

Advice from scientific societies: ISPOR

- Establishing Evidence in **Newly Developed** PROMS for Medical Product Evaluation Part 1
- Outcomes (PRO) Instruments for Medical Product **Evaluation** Part 2
- Use of Existing Patient-Reported Outcome (PRO) Instruments and Their **Modification**
- **Pediatric** PROMS for Research to Support Medical Product Labeling
- PROM and Observer-Reported Outcome Assessment in **Rare Disease** Clinical Trials
- Measurement **Equivalence between Electronic and Paper-Based** PROMS
- **Validation of Electronic Systems** to Collect PROMs- for Clinical Trial Teams
- Principles of Good Practice for the **Translation and Cultural Adaptation** of PROMS

www.core-md.eu

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ESC

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EAP European Academy of Paediatrics
Paediatric Section of U.E.M.S

EPF European Patients Forum

LUMC Leiden University Medical Center

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Region Uppsala

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