THE USE OF PATIENT REPORTED OUTCOMES IN MEDICAL DEVICES

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ABSTRACT

OBJECTIVES

The use of patient reported outcomes (PROs) in medical device studies have been increasing and signals a shift towards value-based purchasing in Europe. Currently, there is no requirement to include PROs in medical device studies for regulatory purposes in Europe or the United States (US). However, the Food and Drug Administration's Center for Devices and Radiological Health (CDRH) issued a report in 2016-2017 encouraging the use of PROs in medical devices. This study investigates the use of PROs in medical devices in clinicaltrials.gov to assess the frequency and type of PROs used.

METHODS

Using clinicaltrials.gov, clinical trials were identified using device as a search term and filtering by study phase (phase 3 and 4), recruitment status (not yet recruiting, recruiting, enrolling by invitation, active not recruiting, completed, unknown status), and funding (industry). The primary and secondary endpoints were reviewed for PROs once the trials were identified. Trials were excluded if PROs were not used as a study outcome, or if the study was suspended, terminated, or withdrawn.

RESULTS

Two hundred studies (n=15 phase 2/3, n=102 phase 3, n=83 phase 4) were identified. Twenty three (12%) studies started in 2017 or later. Seventy-eight (39%) of the studies included a PRO as a primary or secondary outcome. Eighteen percent of the studies (n=36) included a PRO as a primary outcome and 34% (n=67) studies included PROs as secondary outcome. A variety of PROs were used including both general and disease-specific measures. Fifteen studies included a pain PRO.

CONCLUSIONS

Although many publications indicate an increase of PRO use in medical device studies, findings from this research demonstrate that most studies in this space are not including PROs.

Background

- As there is currently no requirement to include patient centered outcomes (PCOs) in medical device studies for approval in Europe or the United States (US), the increasing inclusion of PCOs in the approval process may be due to a competitive market and the need for device manufacturers to demonstrate value of their product beyond clinical safety and efficacy.[1]
- Patient reported outcomes (PROs) measure patients' experiences and are increasingly being incorporated in device studies. Between 2009 and 2015, a > 500% increase was observed in the number of device studies that included PROs in the US.[2]
- The US Food and Drug Administration (FDA) launched the Medical Device Development Tool Program in 2017 to encourage and help manufacturers incorporate PROs into their studies and the Food and Drug Administration's Center for Devices and Radiological Health (CDRH) issued their guidance with these details in 2017.
- The first PRO measure to be qualified under the program was the Kansas Cardiomyopathy Questionnaire (KCCQ) in 2017 and additional PRO submissions were encouraged.[2]
- Additionally, the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) agreed that quality of life measures should be included as primary health outcomes.[2]
- The CDRH also upgraded its appropriate PRO use as evidence to inform regulatory decisions from ancillary data to a secondary or primary study endpoint.[2]

OBJECTIVE

- To investigate the inclusion of PROs in medical devices in clinialtrials.gov and to assess the frequency and type of PROs used.

METHODS

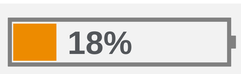
- Using clinicaltrials.gov, clinical trials were identified by searching for 'device' and filtering for:
  - Study phase (phase 3 and 4)
  - Recruitment status (not yet recruiting, recruiting, enrolling by invitation, active not recruiting, completed, unknown status)
  - Funding (industry).
- Primary and secondary endpoints were reviewed for PROs once the trials were identified.
- Trials were excluded if PROs were not used as a study outcome, or if the study was suspended, terminated, or withdrawn.

RESULTS

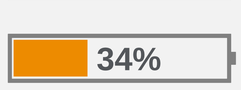
Overview

- A total of two hundred studies were identified following the inclusion/exclusion criteria.
- There were n=15 studies in phase 2/3, n=102 studies in phase 3, and n=83 studies in phase 4.

Seventy-eight (39%) of the 200 studies included a PRO as a primary or secondary outcome.



Thirty-six (18%) studies included a PRO as a primary outcome



Sixty-seven (34%) studies included a PRO as a secondary outcome

- Twenty three (12%) studies were started before 2017. Of the 23 studies, n=7 (30%) studies included a PRO as a primary endpoint and n=14 (61%) studies included a PRO as a secondary endpoint.
- Of the 177 studies started in 2017 or later, n=29 (16%) studies included a PRO as a primary endpoint and n=52 (29%) studies included a PRO as a secondary endpoint.
- The most common indications for the studies evaluated were cardiac (n=52) and pulmonary (n=23; Table 1)

.. **Table 1.** Indication of Studies

Indication (n)			
Cardiac (n=52)	Growth hormone (n=5)	Multiple sclerosis (n=2)	Uterine fibroids (n=1)
Pulmonary (n=23)	Venous leg ulcers (n=3)	Growth disorder (n=2)	Device latency (n=1)
Diabetes (n=12)	Urinary (n=3)	Hepatitis (n=1)	Hernia (n=1)
Autoimmune (n=11)	Headache (n=3)	Intubation (n=1)	Event marker (n=1)
Ear, nose, throat (n=9)	Wound (n=2)	Obesity (n=1)	Sleep (n=1)
Eye (n=9)	Aneurysm (n=2)	Catheter/vascular (n=1)	Flu/vaccine (n=1)
Cancer (n=8)	Hematology (n=2)	BPH (n=1)	Osteoporosis (n=1)
Women's issues (n=8)	GI (n=2)	Restless leg syndrome (n=1)	Osteoarthritis (n=1)
Skin/aging (n=8)	Teeth, jaw (n=2)	Low back wrap (n=1)	Hydrocephaleus (n=1)
Pain (n=5)	Parkinson (n=2)	Orthopedic (n=1)	Infection (n=1)
Spinal (n=5)	HIV (n=2)	Snoring (n=1)	

- Of the 78 studies that included PROs as a primary or secondary endpoint, 13 (17%) were for cardiac and 8 (10%) were for pulmonary.
- Table 2 presents the number of studies with PROs for each indication.

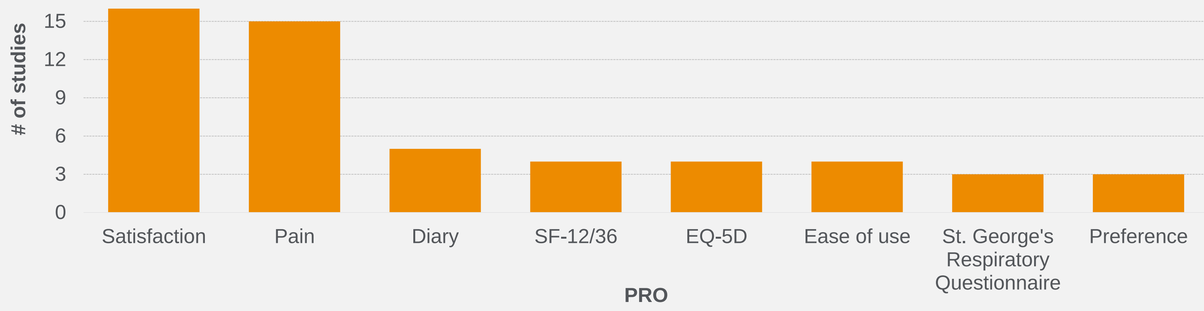
Indication	No. of studies with PROs
Cardiac	13 (17%)
Pulmonary	8 (10%)
Ear, nose, throat	6 (8%)
Diabetes	5 (6%)
Skin/aging	5 (6%)
Pain	5 (6%)
Women's issues	4 (5%)
Spinal	4 (5%)
Growth hormone	4 (5%)
Cancer	3 (4%)
Urinary	3 (4%)
Autoimmune	2 (3%)
Venous leg ulcers	2 (3%)

Indication	No. of studies with PROs
Multiple sclerosis	2 (3%)
Headache	1 (1%)
Wound	1 (1%)
Hematology	1 (1%)
GI	1 (1%)
Teeth, jaw	1 (1%)
Parkinson	1 (1%)
Growth disorder	1 (1%)
BPH	1 (1%)
Restless leg syndrome	1 (1%)
Snoring	1 (1%)
Hernia	1 (1%)
Osteoporosis	1 (1%)

Patient-reported outcomes included

- A variety of PROs were used including both general and disease-specific measures.
- The most frequently (as defined as ≥3 studies) included PROs are presented in Figure 1. Other PROs included as primary and secondary endpoints are also listed.
- Sixteen studies included a patient satisfaction questionnaire. The majority (n=14, 88%) of the satisfaction questionnaires were included as a secondary endpoint.
- Fifteen studies included a pain PRO, either as a visual analogue scale or numerical rating scale. Nine of these studies (60%) included the pain PRO as a primary endpoint.
- Patient diaries pertaining to symptoms (such as, rhinorrhea score, daily symptom) were administered in five studies.
- The majority of PROs identified were disease-specific or uncommonly used PROs such as the single sided deafness questionnaire.

Figure 1. Most frequently PROs included in medical device studies



Other PROs included as primary endpoints:

1. Neck Disability Index
2. International Prostate Symptom Score
3. Epsworth Sleepiness Scale
4. Restless Legs Syndrome Quality of Life instrument
5. St. George's Respiratory Questionnaire
6. Parkinson's Disease Questionnaire-39
7. Zurich Claudication Questionnaire
8. Overactive Bladder Questionnaire
9. Life Quality Index
10. Injection Pen Assessment Questionnaire
11. Abbreviated Profile of Hearing Aid Benefit
12. Multiple Sclerosis Impact Scale-29
13. Snoring Severity scale
14. Global Aesthetic Improvement scale
15. Dry mouth VAS
16. Morning diary congestion/obstruction symptoms

Other PROs included as secondary endpoints:

1. Patient global impression of change
2. St. George's Respiratory Questionnaire
3. Cystic Fibrosis Questionnaire
4. Mood and anxiety questionnaire
5. Rhinosinusitis Disability Index
6. MOS Sleep-R
7. Kansas City Cardiomyopathy Questionnaire
8. Night and day cough score
9. Hospital Anxiety and Depression scale
10. Insulin Delivery System Questionnaire
11. Walking impairment questionnaire
12. Zurich Claudication Questionnaire
13. Injection experience questionnaire
14. Diabetes Distress Scale
15. Lifestyle Questionnaire
16. Quality of Life in Neurological Disorders

Assessment of the most frequently used PROs: Pain and Satisfaction

- Pain and satisfaction instruments are commonly used in clinical trials.
- Pain is a prominent symptom among PRO label claims and is a straightforward symptom to assess.
  - Due to the variations on pain scales, several publications have reviewed and supported the usefulness, reliability, and validity of these scales, including VAS and NRS.[3, 4, 5]
- Variations on satisfaction PROs are also available and include frequently used PROs such as Treatment Satisfaction Questionnaire for Medication[6]. Treatment satisfaction provides insight on patient's perspective on the current treatment and may provide a opportunity for differentiation among alternative treatments.
  - More frequently, satisfaction PROs are developed specifically for the condition. The satisfaction PROs assessed in this study were listed primarily as patient satisfaction or treatment satisfaction.

LIMITATIONS

- Some PROs listed as endpoints may be home grown and not specified. As such, not all the PROs were identifiable and may not be classified appropriately.
- Accuracy of data obtained are based on how PROs are listed in clinicaltrials.gov. In some studies, assessment of the PRO was difficult due to its description. For example, one PRO was named 'quality of life questionnaires' and was listed as the secondary endpoint in NCT03725306.
- Assumptions were made in classifying the PROs (e.g., daily recordings were assumed to be implemented as diaries).
- In this research, only PROs were included. No other PCOs such as clinician-reported outcomes, performance outcomes, or observer outcomes were included in this evaluation.

CONCLUSIONS

- Given that only 39% of the total studies included a PRO, data obtained may be a point of differentiation (e.g., one-quarter of studies for cardiac devices included PROs and could use be used as a differentiator if the device appreciably improves the PRO scores).
- Due to the competitive market, this point of differentiation may be viewed as an added-value by various stakeholders including payers, healthcare systems, and providers. Although 48% of the payers in the U.S. and 78% of payers in ex-US felt that PRO data could impact decision making when considering one pharmaceutical product over another.[7]
- Since the release of CDRH in 2017, there is an increased inclusion of PROs as primary or secondary endpoints in clinical trials.
- Although there is an increased use of PROs in medical device studies, findings from this research demonstrate that the majority of studies in this space are not including PROs.
- Providing further guidance and a "fit-for-purpose" framework for assessing development and validation evidence for PROs may aid manufacturers to develop or modify a PRO to facilitate their conduct and reporting of a study.
- Future research may include evaluating the frequency of ClinROs used in medical devices and evaluating if market success of the devices are enhanced due to the inclusion of PROs.

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