**A STANDARD SET OF VALUE-BASED PATIENT-CENTERED
OUTCOMES FOR PANCREATIC CARCINOMA: AN
INTERNATIONAL DELPHI SURVEY**

Journal:	<i>Annals of Surgical Oncology</i>
Manuscript ID	Draft
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
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A STANDARD SET OF VALUE-BASED PATIENT-CENTERED OUTCOMES FOR PANCREATIC CARCINOMA: AN INTERNATIONAL DELPHI SURVEY

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Background:

Global health systems are shifting toward value-based health care (VBHC) to improve patient outcomes in the face of rising health care costs. The challenge is to identify standardized outcome measurements that allow the optimal monitoring and comparison of the quality of care, in order to optimize medical practices and patient pathways. A common outcomes definition is required, including medical results (CROMs, Clinical Reported Outcomes Measurements) and quality of life components that matter most to patients (PROMs, Patient Reported Outcomes Measurements), particularly important for severe pathologies with short life expectancy like pancreatic cancer. The aim of this work was to create standardized metrics that could be used for outcomes analysis of pancreatic cancer care.

Methods:

A multidisciplinary working group (WG) was assembled. A systematic review was conducted to collect the most used outcomes in pancreatic cancers clinical studies. A total of 570 studies published in the last ten years were reviewed; 3370 outcomes, including CROMs, and PROMs, were listed and prioritized. The WG reached a consensus on key outcomes, proposed groupings for CROMs and PROMs, identified existing questionnaires which could be used for PROMs collection and set the timeline for data collection. To refine and validate the final outcomes set an international external committee completed a Delphi process (two rounds both for CROMS and PROMs).

Results:

After the systematic literature review, the WG selected 102 outcomes (92 CROMs/10 PROMs) to submit to the international Delphi vote committee. In total, 89 outcomes (78 CROMs/11 PROMs) were retained. For PROMs the WG and the international external committee chose a validated questionnaire, the Fact-Hep, that covers all of the 11 selected PROMs.

Conclusions:

A standardized set of outcome measures that need to be validated through international health outcome comparisons and quality-of-care assessments was built. Pilot projects are underway to test and optimize the approach in real-life conditions.

INTRODUCTION:

Pancreatic cancer is the second most common digestive cancer in the United States, where approximately 44,000 new cases occur each year. In Europe, pancreatic cancer accounts for 2.8% of cancers among men and 3.2% among women, making it the sixth most common cancer [1]. Based on GLOBOCAN 2012 estimates, pancreatic cancer is the cause of more than 331,000 deaths per year, which represents the seventh leading cause of cancer-related deaths worldwide, with a five-year survival rate of less than 5% [2]. Despite the availability of newer and more effective chemotherapy regimens, the survival rate associated with this disease has remained consistently low.

Radical surgery is the only potential curative treatment for pancreatic cancer [3]. Despite the availability of newer and more effective chemotherapy regimens, prognosis of pancreatic cancer remains grim for most patients. Hence the importance of providing outcomes that really matter for this patient population.

Global health systems are shifting to value-based health care (VBHC) to drive better health outcomes in the face of rising care costs [4,5]. The challenge is to identify standardized outcome metrics that allow the optimal monitoring and comparison of the quality of care, in order to optimize medical practices and patient pathways. A common outcomes definition is required, including medical results (CROMs, Clinical Reported Outcomes Measurement) and also quality of life components that matter most to patients (PROMs, Patient Reported Outcomes Measurement). This is particularly important for severe pathologies with short life expectancy like pancreatic cancer [6].

Although several standardized datasets have been developed to measure both clinical and patient-oriented value-based health outcomes in the context of cancers of the breast [7], colon [8], lung [9], and prostate [10,11], standardized outcome measurement sets for pancreatic cancer are not currently available.

The aim of this work was to develop a standardized outcome measurement set that would be used in an outcomes analysis of pancreatic cancer pathways, to monitor patient quality of life and better meet patients expectations, and to identify and align on the best practices between the different care centers.

MATERIALS AND METHODS:

Working Group

A multidisciplinary working group (WG) of 20 people was assembled. The WG was composed of physicians (hepatobiliary pancreatic (HBP) surgeons, medical oncologists, gastroenterologists), paramedical personnel (nurses, dieticians, caregivers), patient, patient representative, administrative staff, and healthcare consultants. The WG was set up to prepare a Delphi process to validate the outcomes metrics set.

Review of Clinical Trials and Outcomes pre-selection

A systematic literature review of outcomes used in pancreatic cancers clinical trials was carried out by searching the *clinicaltrials.gov* database. Phase II, III or IV studies published in the last ten years on pancreatic cancer adult population were considered.

A total of 570 clinical studies were selected and reviewed. The studies listed 3370 outcomes, including CROMs (3168 items) and PROMs (201 items). After a first review 92 CROMs and 10 PROMs were selected by the WG (**Figure 1**).

Outcomes Structuring

CROMs were divided into 2 parts:

- A baseline set with 4 categories: 1) demographic factors, 2) clinical characteristics, 3) diagnostic methodology, and 4) therapeutic strategy (**Table 1**).
- A follow-up set with 3 categories: 1) treatment-related complications, 2) survival and disease control indicators, 3) evidence of relapse or disease progression. The final list of outcomes is listed in **Table 2**.

PROMs were grouped into health domains by the WG members using a method inspired by Macefield et al. [12] and Van Rijssen et al. [13]. Quality of life (QOL) and functioning items were encompassed in 5 categories: 1) physical well-being, 2) family and social well-being, 3) emotional well-being, 4) functional well-being, and 5) current symptomatology (**Table 3**).

Validation committee and process

An international external validation committee (VC) was formed to complete a Delphi process to refine and validate the final set (**Figure 1**). The VC comprised 93 persons and included patients, HPB surgeons, radiologist, psychiatrist, oncologists, nurses, dieticians, psychologist (**Table 4**). The Qualtrics platform was used to create and distribute questionnaires, and 4 rounds (2 for CROMs, 2 for PROMs) were carried out between the 31st of January and the 15th of June 2018.

Outcomes validation

Questionnaires in the first two rounds focused on the validation of CROMs. Participants had to answer the following question: "Please indicate if you would like to add or exclude the following variables in the final standard set". Participants could justify their choices during the first round. Only the variables reaching a threshold set at 85% of the addition rate were retained for the final standard set; those under a threshold at 15% were not retained; those between 15% and 85% had to be voted again in the second round. In the second round, the arguments from the first round were presented to the participants, and only the variables reaching 85% were retained.

Questionnaires in the second two rounds focused on the validation of PROMs.

In the first round, the outcomes were listed, with examples (questions extracted from existing questionnaires). The VC was asked to select the most relevant outcomes. Only the variables reaching a threshold set at 85% of the addition rate were retained for the final standard set; those under a threshold of 15% were not retained; those between 15% and 85% had to be voted again in the second round. In the second round, only the variables reaching 85% were retained. Participants chose the most suitable existing questionnaire in relation to their PROMs selection.

Set timeline

To finalize the deployment preparation, the WG decided to define a timeline for outcomes collection (patient record for CROMs, questionnaires for PROMs), to suit to the different care episodes.

RESULTS:

The WG defined the scope of the project as including all patients with stage I to IV invasive pancreatic cancer in accordance with the American Joint Committee of Cancer staging system, regardless of type or intent of treatment received, including those who did not receive therapy. Patients undergoing treatment with investigational agents were excluded because such studies have their own specific outcome assessments.

CROMs

Baseline items were included to allow for cross-treatment and cross-center comparison. The demographic factors included sex, date of birth, weight, height, units of weight and height, and family history of pancreas-related cancer. Baseline clinical factors prioritized for inclusion were the Eastern Cooperative Oncology Group (ECOG) score performance status, presence of comorbidities, and the level of alcohol and/or tobacco consumption [14]. The Charlson Comorbidity Index was selected for comorbidity

reporting [15]. The different methodologies used to verify the diagnosis were included, as well as the date of the tests.

Several baseline diseases and tumor factors were also included: nature and date of onset of cardinal symptoms, amount of weight loss, duration of weight loss evolution, tumor location, and clinical TNM stage. The items related to the therapeutic strategy were grouped as follows: a) general strategies (multidisciplinary care, intention of treatment and type of treatment selected) and b) specific strategies (surgical treatment, radiotherapy treatment, chemotherapy treatment and the need for an approach to biliary drainage).

Follow-up items were included to monitor the trends of medical outcomes.

Treatment-related event measures focused on short-term complications of treatment, including type and severity. An algorithmic evaluation to determine severity was developed based on the grading systems of the Clavien-Dindo classification for surgical complications [16] and the Common Terminology Criteria for Adverse Events for radiation therapy and chemotherapy (Version 4.0) [17]. The causes of postsurgical complications related to pancreatic surgery (pancreatic fistula, gastroparesis, hemorrhage) were evaluated separately and classified according to their severity [18,19,20]. Similarly, the implementation of nutritional support and the need for new admissions were selected from the proposed variables.

The following measures were included for survival and disease control: overall survival, cause-specific survival, recurrence-free survival, progression-free survival, and need for readmission. For patients receiving neoadjuvant therapy or surgery, pathological complete response and margin status were included because they would be able to serve as intermediary outcomes, proxies of survival, and short-term indicators of surgical quality.

The occurrence, method of diagnosis, date of relapse (for patients treated with curative intent) or progression (for patients treated with palliative indication) were also included in the follow-

up variables. These events are reported as they were identified and are considered a new baseline point.

A total of 78 CROMs were selected, with response referentials and administration timeline (Tables 1 & 2).

PROMs

The final PROMs set (Quality Of Life, functioning, and symptom measures) are listed in Table 3.

PROMs were recommended to be collected at baseline (when the patient treatment was defined) and then 1 month after treatment, 3 months, 6 months, 9 months, 1 year, 18 months, and annually up to 10 years after treatment, where possible.

A total of 11 PROMs were selected, with a validated questionnaire, the Fact-Hep [21], for outcomes collection.

DISCUSSION:

Until now, there was no widely validated standardized outcome measures for the follow-up of patients with pancreatic cancer. Our work aimed to build an innovative metrics set, in order to improve the quality and relevancy of care for patients, to facilitate comparison of results across treatments, between health care professionals (HCP) and centers around the world, and to support the research on this disease. The outcomes measurement could allow a wider vision of the care pathway.

A standardized set of metrics is a decision-support tool for care evaluation, which allows a real dialogue between care providers and patients and a personalized treatment strategy.

A comparison among centers can help to improve the care organization and a set of outcomes measurement can contribute to the identification of care priorities essential under constrained resources.

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3 Last, the continuous standardized outcomes assessment using real-time data together with the
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5 integration of patient's expectations (through the results of validated PROMs) could facilitate
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7 medical innovations since it would become easier to appreciate the variations of the different
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9 indicators related to the introduction of technological or organizational innovations.

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12 Outcomes reported by patients are becoming as important as the clinical results. A systematic
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14 review of the burden of pancreatic cancer in Europe showed that pancreatic cancer results in a
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16 98% loss of healthy life [22]. The severity of pancreatic cancer and the limited availability of
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18 effective treatment options [3] compel the medical community to prioritize patients' experiences
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20 and outcomes over objective medical results. Patient-centered outcomes reflect patients' life
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22 experience when dealing with their disease. The collection of PROMs has been shown to
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24 improve QOL and even overall survival in the context of other types of cancer [23]. The report
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26 of the *Centre Fédéral d'Expertise des Soins de Santé* (Bruxelles-Belgium) implements the
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28 application of results and experiences reported by patients (PROMs/patient-reported experience
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30 measures (PREMs)) for clinical and management purposes. The report specifies the three levels
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32 that are favored through its use: a) the relationship between the patient and his/her healthcare
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34 provider, to promote shared decision-making and patient-centered care (micro level); b)
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36 healthcare facilities, to contribute to the improvement of quality of care (meso level); and c) the
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38 public-policy level, to monitor and measure the performance of national health systems (macro
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40 level) [24].
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46 ***Feasibility and acceptability of outcomes measurement***

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49 A metrics set has to be accepted by all stakeholders in the care pathway. To do so, it is a matter
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51 of co-building these indicators with all actors; the patient was subsequently considered to be an
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53 "actor" of his/her pathway in the same way as the other stakeholders, taking part in the care
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55 pathway. In our strategy, this multidisciplinary and multi-professional team, with the presence
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57 of patients, patient associations, HCP in direct and long-term contact with patients, was
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respected within the working group and the international external committee. This presence highlighted patient experience and expectations beyond the medical expertise.

The metrics set has to be SMART (specific, measurable, achievable and realistic) and has to quantify the outcomes both in terms of CROMs and PROMs. Recently, the COPRAC study group established an international core set of PROMs that were selected by both patients and healthcare providers in the United States, Europe, and Asia [13]. In this study 8 categories of PROMs (general QOL, general health, physical capacity, ability to work and perform usual activities, fear of recurrence, satisfaction with services and care organization, abdominal complaints and relationship with partner or family) were included. Limit of the COPRAC study was not to define in detail each category content.

Our set aims to measure the outcomes in a valid and reliable manner and the VC considered that the most suitable questionnaire for assessing the selected PROMs and the Fact-Hep [21] was chosen. The FACT-Hep was developed in 1998 to measure health-related quality of life in patients with hepatobiliary cancers.

The WG determined a timeline for the CROMs and PROMs collection, balanced between the clinically relevant times (i.e.: new treatment needs to be tightly monitored) and pragmatic concerns faced by institutions and practices in regard to data collection (i.e.: patient's scheduled follow-up visits).

In conclusion, a standardized set of patient-centered outcome measures that need to be monitored for international health outcome comparisons and quality-of-care assessments was built for pancreatic carcinoma. The implementation of instruments that integrate the measurement of clinical parameters of treatment response and patient-reported outcomes, both in clinical research protocols and in routine medical practice, is a step forward to ensure that each patient receives the necessary and effective care in each setting and situation.

VBHC Pancreas Set

Figure 1

Figure 1: Systematic Outcomes Review Flow Chart

WG: *Working Group*

VC: *Validation Committee*

VBHC Pancreas Set

Table 1

Table 1: Clinical Reported Outcomes Measurement (CROMs) Baseline set

	PATIENT POPULATION	DETAILS	DATA SOURCE	TIMELINE
1. DEMOGRAPHIC FACTORS				
Sex	All patients	Patient Sex	Administrative data	Baseline (μ: baseline and follow-up)
Age		Date of Birth		
Weight ^μ		Unit of measurement (kg or lb)	Clinical abstraction	
Height		Unit of measurement (cm or ft)		
Family History of Cancer		First degree parent with Pancreas, Breast/Ovarian, Colon, Melanoma		
2. CLINICAL CHARACTERISTICS				
Patient Characteristics				
Score Performance (ECOG) ^μ	All patients	Eastern Cooperative Oncology Group (ECOG) Performance Status [14]	Clinical abstraction	Baseline (μ: baseline and follow-up)
Comorbidities ^μ		Charlon Comorbidity Index [15]		
Alcohol Consumption		Beverage-specific quantity and frequency (units per day)		
Tobacco use		Smoking Exposure (pack-year)		
Disease Characteristics				
Cardinal Symptoms	All patients	Onset date and nature of symptoms	Clinical abstraction	Baseline (μ: baseline and follow-up)
Weight Loss ^μ		Amount and time of evolution		
Tumor Location		Anatomical location of the tumor		
cTNM Stage		Preoperative staging of the disease		
3. DIAGNOSTIC METHODOLOGY				
CT-Scan	All patients	Test date (if applicable)	Administrative data	Baseline
MRI				
Endoscopic Ultrasound				
Biopsy				
4. THERAPEUTIC STRATEGY				
General				
Multidisciplinary Meeting	All patients	Meeting date (if applicable)	Clinical abstraction	Baseline + Follow-up
Intention of Treatment		Curative or palliative intent		
Type of Treatment Selected		Modality of treatment chosen		
Surgery				
ASA Score	Patients receiving surgery	Physical Status Classification System	Clinical abstraction	Follow-up
Date of Surgery		Specify the date of the intervention	Surgical Report	
Type of Surgery		Specify procedure performed		
Approach		Minimally invasive or open surgery		
Quality of Resection		Specify specimen margin status	Pathological Report	
Standardized Pathological Report		Completeness of recommended parameters		
pTNM Stage		Postoperative staging of disease	Administrative data	
Hospitalization Length		Admission and discharge dates		
Radiotherapy				
Type	Patients receiving neoadjuvant/palliative treatment	Start and finish date and treatment details (if applicable)	Clinical abstraction	Follow-up
Dose (cGy)				
Duration of treatment				
Chemotherapy				
Type	Patients receiving neoadjuvant/palliative treatment	Start and finish date and treatment details (if applicable)	Clinical abstraction	Follow-up
Duration of treatment				
Biliary Drainage				
Type ^μ	All patients	Placement date and technical details (if applicable)	Clinical abstraction	Baseline + Follow-up
Date of Treatment ^μ				

VBHC Pancreas Set

Table 2

Table 2: Clinical Reported Outcomes Measurement (CROMs) Follow-Up set

	PATIENT POPULATION	DETAILS	DATA SOURCE	TIMELINE	
1. TREATMENT-RELATED COMPLICATIONS					
Surgery-Related Complications					
Post-Surgical Complications	Patients receiving surgery	Clavien-Dido classification of surgical complications [16]	Clinical abstraction	Follow-up	
Pancreatic Leakage		International study group for pancreatic surgery [18-20]			
Gastroparesis					
Hemorrhage					
Transfusion					Blood transfusion requirements
Palliative/Neoadjuvant Treatment-Related Complications					
Tumor Response	All patients	No sign of residual cancer on diagnosis evaluation	Clinical abstraction	Follow-up	
Undesirable Effects		Common terminology criteria for adverse events V4.03 [17]			
Readmissions					
Need for Readmission	All patients	New admission at any time for any cause	Administrative data	Follow-up	
Date of Readmission					
2. SURVIVAL AND DISEASE CONTROL					
Overall Survival	All patients	Date of death	Administrative data	Long-Term Follow-Up (Annual follow-up from the first year of treatment)	
Cause-Specific Survival		Death attributed to pancreatic cancer			
Recurrence-Free Survival	Patients with curative intent	Local, regional, or distal recurrence	Clinical abstraction		
Progression-Free Survival	Patients with advanced disease	Disease progression			
Pathological or Clinical Complete Response	Patients receiving neoadjuvant treatment	No sign of residual invasive cancer of resected specimen or on diagnosis evaluation			
Need for Readmission	All patients	Evidence of margin involvement			
3. RELAPSE/PROGRESSION OF THE DISEASE					
Disease Relapse					
Relapse Date	Patients with curative intent	Onset date. Nature of event. Detection Method (clinical, imaging and/or pathological identification)	Clinical abstraction	Follow-up	
Method of Detection					
Disease Progression					
Progression Date	Patients with advanced disease	Onset date. Nature of event. Detection Method (clinical, imaging and/or pathological identification)	Clinical abstraction	Follow-up	
Method of Detection					

Table 3

Table 3: Patient Reported Outcomes Measurement (PROMs) set

	PATIENT POPULATION	DETAILS	DATA SOURCE	TIMELINE
1. PHYSICAL WELL-BEING				
Energy	All patients	Tracked via FACT-Hep [21]	Patient-reported source	Every follow-up control starting at baseline
Nausea				
Physical autonomy				
Pain				
Treatment Side Effect				
Illness perception				
Prostration				
2. FAMILY/SOCIAL WELL-BEING				
Relatives support	All patients	Tracked via FACT-Hep [21]	Patient-reported source	Every follow-up control starting at baseline
Relatives acceptance				
Communication with family and friends				
Satisfaction with sexual life				
3. EMOTIONAL WELL-BEING				
Sadness	All patients	Tracked via FACT-Hep [21]	Patient-reported source	Every follow-up control starting at baseline
Coping capacities				
Hope				
Nervousness				
Fearness				
4. FUNCTIONAL WELL-BEING				
Fitness for work	All patients	Tracked via FACT-Hep [21]	Patient-reported source	Every follow-up control starting at baseline
Work accomplishment				
Life enjoyment				
Illness acceptance				
Sleep quality				
QOL satisfaction				
5. SYMPTOMS				
General				
Fatigue	All patients	Tracked via FACT-Hep [21]	Clinical abstraction / Patient-reported sources	Every follow-up control starting at baseline
Fever				
Weight Loss				
Insomnia				
Jaundice				
Itching				
Change of physical appearance				
Back pain				
Dry mouth				
Gastrointestinal				
Abdominal Distension/Pain	All patients	Tracked via FACT-Hep [21]	Patient-reported source	Every follow-up control starting at baseline
Dietary Restrictions				
Nauseas and Vomiting				
Ability to Eat/Appetite Loss				
Bowel Function				
Stool Frequency	All patients	Tracked via FACT-Hep [21]	Patient-reported source	Every follow-up control starting at baseline
Diarrhea				
Constipation				
Fecal Continence				

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Table 4

Table 4: Composition of the Validation Committee

Expertise	n	%
HBP Surgeons	60	64.5%
Patients	8	8.6%
Nurses	8	8.6%
Medical Oncologists	8	8.6%
Dieticians	5	5.3%
Psychologist	1	1.1%
General Surgeon	1	1.1%
Psychiatrist	1	1.1%
Radiologist	1	1.1%
Region	n	%
Europe	46	49.5%
North America	17	18.3%
South America	16	17.2%
Asia	14	15.0%

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APPENDIX

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