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

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Complete List of Authors:	<p>Cherkaoui, Zineb; CHU Strasbourg, Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil</p> <p>González, Cristians ; Institute of Image-Guided Surgery (IHU Strasbourg), Université de Strasbourg, Strasbourg, 67091, France</p> <p>Wakabayashi, Taiga; Research Institute Against Digestive Cancer (IRCAD)</p> <p>Delattre, Bastien ; Integrated Health Solutions (IHS), Medtronic France, Boulogne-Billancourt, 92100, France</p> <p>Léost, Elodie ; Integrated Health Solutions (IHS), Medtronic France, Boulogne-Billancourt, 92100, France</p> <p>Serra , Sébastien ; CHU Strasbourg</p> <p>Huppertz, Jérôme ; CHU Strasbourg</p> <p>Klein, Francine; CHU Strasbourg</p> <p>Stéphan , Marie ; CHU Strasbourg</p> <p>Meyer , Jean-Michel; CISS Alsace (Collectif Inter associatif Sur la Santé) Strasbourg, France</p> <p>Schaff, Alain ; CHU Strasbourg, Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil</p> <p>Martinis, Elisa; CHU Strasbourg, Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil</p> <p>Bangoura, Elena; CHU Strasbourg, Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil</p> <p>Kieffer, Sophie; CHU Strasbourg, Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil</p> <p>Blanes-Brice, Sophie; CHU Strasbourg, Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil</p> <p>Haddad, Elham; CHU Strasbourg, Oncology Unit</p> <p>Deguio, Gabrielle ; Groupe Hospitalier Saint Vincent, Strasbourg, France</p> <p>Felli, Emanuele; Nouvel Hôpital Civil, General, Digestive, and Endocrine Surgery</p> <p>Pernot, Sophie; Institute of Image-Guided Surgery (IHU Strasbourg), Université de Strasbourg, Strasbourg, 67091, France</p> <p>Marescaux, Jacques; IRCAD-IHU University of Strasbourg, General, Digestive and Endocrine Surgery</p> <p>Mutter, Didier; CHU Strasbourg, Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil; Institute of Image-Guided Surgery (IHU Strasbourg), Université de Strasbourg, Strasbourg, 67091, France; Research Institute Against Digestive Cancer (IRCAD)</p> <p>Lugiez, Constance; Integrated Health Solutions (IHS), Medtronic France, Boulogne-Billancourt, 92100, France</p>

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	Pessaux, Patrick; CHU Strasbourg, Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil; Institute of Image-Guided Surgery (IHU Strasbourg), Université de Strasbourg, Strasbourg, 67091, France; Research Institute Against Digestive Cancer (IRCAD)

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

Zineb Cherkaoui¹, Cristians González², Taiga Wakabayashi³, Bastien Delattre⁴, Elodie Léost⁵, Sébastien Serra⁶, Jérôme Huppertz⁷, Francine Klein⁸, Marie Stéphan⁹, Jean-Michel Meyer¹⁰, Alain Schaff¹¹, Elisa Martinis¹², Elena Bangoura¹³, Sophie Kieffer¹⁴, Sophie Blanès¹⁵, Elham Haddad¹⁶, Gabrielle De Guio¹⁷, Emanuele Felli¹⁸, Sophie Pernot¹⁹, Jacques Marescaux²⁰, Didier Mutter²¹, Constance Lugiez²², Patrick Pessaux²³, IHU-VBHC Working Group.

Degrees and affiliations:

¹ MD,

Institute of Image-Guided Surgery (IHU Strasbourg), Université de Strasbourg, Strasbourg, 67091, France

Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg, France

SSPC (Simplification of Surgical Patient Care), UR UPJV 7518, University of Picardie Jules Verne, Amiens, France

email: zineb.cherkaoui@chru-strasbourg.fr

² MD,

Institute of Image-Guided Surgery (IHU Strasbourg), Université de Strasbourg, Strasbourg, 67091, France

Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg, France

email: cristians.gonzalez@ihu-strasbourg.eu

³ MD,

VBHC Pancreas Set

Manuscript revised

Research Institute Against Digestive Cancer (IRCAD), Strasbourg, 67091, France

email: taiga.wakabayashi@me.com

⁴ Consultant,

Integrated Health Solutions (IHS), Medtronic France, Boulogne-Billancourt, 92100, France

email: bastien.delattre@gmail.com

⁵ Patient-pathway Coordinator,

Integrated Health Solutions (IHS), Medtronic France, Boulogne-Billancourt, 92100, France

email: elodie.leost@medtronic.com

⁶ MD,

Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, 67091, Strasbourg, France

email: sebastian.serra@chru-strasbourg.fr

⁷ MD,

Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, 67091, Strasbourg, France

email: jeromehuppertz@gmail.com

⁸ Head nurse,

Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg, France

email: francine.klein@chru-strasbourg.fr

⁹ Nurse,

Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg, France

email: marie.stephan@chru-strasbourg.fr

¹⁰ Patient representative, President of CISS Alsace,

CISS Alsace (Collectif Inter associatif Sur la Santé) Strasbourg, France

email: jean-michel.meyer@cushabitat.fr

VBHC Pancreas Set

Manuscript revised

¹¹ Patient,

Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil, Hôpitaux Universitaires de
Strasbourg, Université de Strasbourg, Strasbourg, France

email: none

¹² Dietician,

Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil, Hôpitaux Universitaires de
Strasbourg, Université de Strasbourg, Strasbourg, France

email: elisa.martinis@chru-strasbourg.fr

¹³ Caregiver,

Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil, Hôpitaux Universitaires de
Strasbourg, Université de Strasbourg, Strasbourg, France

email: elena.bangoura@chru-strasbourg.fr

¹⁴ Nurse,

Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil, Hôpitaux Universitaires de
Strasbourg, Université de Strasbourg, Strasbourg, France

email: sophie.kieffer@chru-strasbourg.fr

¹⁵ Secretary,

Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil, Hôpitaux Universitaires de
Strasbourg, Université de Strasbourg, Strasbourg, France

email: sophie.blanes-brice@chru-strasbourg.fr

¹⁶ Nurse,

Oncology Unit, Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, 67091,
Strasbourg, France

email: elham.haddad@chru-strasbourg.fr

¹⁷ MD,

VBHC Pancreas Set

Manuscript revised

Groupe Hospitalier Saint Vincent, Strasbourg, France

email: gabrielle.deguio@gmail.com

¹⁸ MD,

Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg, France

email: emanuele.felli@chru-strasbourg.fr

¹⁹ Preclinical & innovation project manager,

Institute of Image-Guided Surgery (IHU Strasbourg), Université de Strasbourg, Strasbourg, 67091, France

email: sophie.pernot@ihu-strasbourg.eu

²⁰ MD, FACS, Hon FRCS, Hon JSES, Hon FASA, President of IRCAD, Chairman of the Institute of Image-Guided Surgery, WebSurg Editor-in-Chief,

Institute of Image-Guided Surgery (IHU Strasbourg), Université de Strasbourg, Strasbourg, 67091, France

Research Institute Against Digestive Cancer (IRCAD), Strasbourg, 67091, France

email: jacques.marescaux@ircad.fr

²¹ MD, PhD,

Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg, France

Institute of Image-Guided Surgery (IHU Strasbourg), Université de Strasbourg, Strasbourg, 67091, France

Research Institute Against Digestive Cancer (IRCAD), Strasbourg, 67091, FRANCE

email: didier.mutter@chru-strasbourg.fr

²² IHS Program Director,

Integrated Health Solutions (IHS), Medtronic France, Boulogne-Billancourt, 92100, France

VBHC Pancreas Set

Manuscript revised

email: constance.lugiez@medtronic.com

²³ MD, PhD,

Digestive and Endocrine Surgery Unit, Nouvel Hôpital Civil, Hôpitaux Universitaires de

Strasbourg, Université de Strasbourg, Strasbourg, France

Hepatobiliary and Pancreatic Surgical Unit, Nouvel Hôpital Civil (NHC), Strasbourg, France

Institute of Image-Guided Surgery (IHU Strasbourg), Université de Strasbourg, Strasbourg,

67091, France

Research Institute Against Digestive Cancer (IRCAD), Strasbourg, 67091, France

Unité Inserm UMR_S1110, Institut de Recherche sur les Maladies Virales et Hépatiques,

Strasbourg

Corresponding author, email: patrick.pessaux@chru-strasbourg.fr

Tel: +33 3 69 55 12 86

Fax: +33 3 69 55 17 45

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.

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

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

Feasibility and acceptability of outcomes measurement

A metrics set has to be accepted by all stakeholders in the care pathway. To do so, it is a matter of co-building these indicators with all actors; the patient was subsequently considered to be an "actor" of his/her pathway in the same way as the other stakeholders, taking part in the care pathway. In our strategy, this multidisciplinary and multi-professional team, with the presence of patients, patient associations, HCP in direct and long-term contact with patients, was

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

Contributors (Delphi participants) & Members of IHU-VBHC working group :

Name	Expertise	Country
Paulo AMARAL	HBP Surgeon	BRAZIL
Catherine ANTHONY	Dietetician	FRANCE
Raphael ARAUJO	HBP Surgeon	BRAZIL
Horacio ASBUN	HBP Surgeon	USA
Susan ATKINSON	Patient	USA
Elena BANGOURA	Caregiver	FRANCE
Marie-Pascale BATAILLE	Patient	FRANCE
Kimberly BERTENS	HBP Surgeon	CANADA
Sophie BLANÈS	Secretary	FRANCE
Javier BRICENO	HBP Surgeon	SPAIN
Hansen CARSTEN PALNAES	HBP Surgeon	DENMARK
Maria CATALINA MURSCH	Nurse	FRANCE
Clara CESARI-LOUSSOUARN	Psychologist	FRANCE
Zineb CHERKAoui	Resident in Digestive Surgery	FRANCE
Natalie COBURN	HBP Surgeon	CANADA
Fabrice COLIN	Patient	FRANCE
Claudius CONRAD	HBP Surgeon	USA
Vincent CORDELIER	Nurse	FRANCE
Francis CREWS	Patient	FRANCE
Vito DE BLASI	HBP Surgeon	LUXEMBOURG
Gabrielle DEGUIO	Geriatrician	FRANCE
Bastien DELATTRE	Consultant	FRANCE
Nicolas DEMARTINES	HBP Surgeon	SWITZERLAND
Kristine DENGsØ	Nurse	DENMARK
Mark DOHERTY	Medical Oncologist	CANADA
Elena FERNANDEZ	HBP Surgeon	FRANCE
David FUKS	HBP Surgeon	FRANCE
Armando GIL	HBP Surgeon	VENEZUELA
Veronica GOLDBARG	Medical Oncologist	FRANCE
Cristians GONZÁLEZ	Digestive Surgeon	VENEZUELA
Elham HADDAD	Nurse	FRANCE
Julie HALLET	HBP Surgeon	CANADA
Nathalie HAUSER	Nurse	FRANCE

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Supplementary file

Ruben HERNANDEZ	HBP Surgeon	VENEZUELA
Hugo HERRSCHER	Medical Oncologist	FRANCE
Ryota HIGUCHI	HBP Surgeon	JAPAN
Jens HILLINGSØ	HBP Surgeon	DENMARK
Paul HODY	Patient	FRANCE
Pauline HORN	Dietetician	FRANCE
Jerôme HUPPERTZ	Gastroenterologist	FRANCE
Naoki IKARI	General surgeon	JAPAN
Wataru IZUMO	HBP Surgeon	JAPAN
Emilie JACKY	Nurse	FRANCE
Shiva JAYARAMAN	HBP Surgeon	CANADA
Romane JENNER	Dietetician	FRANCE
Florence JEUNE	HBP Surgeon	FRANCE
Hironori KANEKO	HBP Surgeon	JAPAN
Takaaki KATO	HBP Surgeon	JAPAN
Suneil KHANNA	Medical Oncologist	CANADA
Sophie KIEFFER	Nurse	FRANCE
Francine KLEIN	Head nurse	FRANCE
Jean Emmanuel KURTZ	Medical Oncologist	FRANCE
Calvin LAW	HBP Surgeon	CANADA
Laura LAZARUS	Nurse	FRANCE
Myriam LEKEIR	Nurse	FRANCE
Elodie LÉOST	Patient-pathway Coordinator	FRANCE
Bruno LEMOS	HBP Surgeon	BRAZIL
Leonardo LIMA	HBP Surgeon	BRAZIL
Constance LUGIEZ	Integrated Health Solutions Program Director	FRANCE
Bernadette LUX	Patient	FRANCE
Guilherme MACHADO	HBP Surgeon	BRAZIL
Jacques MARESCAUX	Digestive Surgeon	FRANCE
Guillaume MARTEL	HBP Surgeon	CANADA
Lysiane MARTHEY	Medical Oncologist	FRANCE
Pablo MARTÍ-CRUCHAGA	HBP Surgeon	SPAIN
Elisa MARTINIS	Dietetician	FRANCE
Riccardo MEMEO	HBP Surgeon	ITALY
Jean-Michel MEYER	Patient representative, President of CISS-Alsace	FRANCE
Lise MUNK PLUM	Nurse	DENMARK

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Supplementary file

Cesar MUNOZ	Medical Oncologist	SPAIN
Didier MUTTER	Digestive Surgeon	FRANCE
Sulaiman NANJI	HBP Surgeon	CANADA
Amy O'CONNOR	Dietetician	CANADA
Akiko OMORI	HBP Surgeon	JAPAN
Pedro OSORIO	HBP Surgeon	BRAZIL
Fabrizio PANARO	HBP Surgeon	FRANCE
Fernando PARDO	HBP Surgeon	SPAIN
Lucio Lucas PEREIRA	HBP Surgeon	BRAZIL
Pierre PEREZ	Patient	FRANCE
Sophie PERNOT	Preclinical & innovation project manager	FRANCE
Patrick PESSAUX	HBP Surgeon	FRANCE
Yolanda QUIJANO	HBP Surgeon	SPAIN
Mariana RAMALLO	Psychiatrist	VENEZUELA
Nicolas REGENET	HBP Surgeon	FRANCE
Alexandre RESENDE	HBP Surgeon	BRAZIL
Fernando ROTELLAR	HBP Surgeon	SPAIN
Antonio SA CUNHA	HBP Surgeon	FRANCE
Rodrigo SANCHEZ CLARIA	HBP Surgeon	ARGENTINA
Daniel SANTANA	HBP Surgeon	BRAZIL
Rodolfo SANTANA	HBP Surgeon	BRAZIL
Alain SCHAFF	Patient	FRANCE
Lilian SCHWARZ	HBP Surgeon	FRANCE
Maja SEGEDI	HBP Surgeon	CANADA
Sébastien SERRA	Medical Oncologist	FRANCE
Pablo SERRANO	HBP Surgeon	CANADA
Masahiro SHIIHARA	HBP Surgeon	JAPAN
Olivier SOUBRANE	HBP Surgeon	FRANCE
Marie STÉPHAN	Nurse	FRANCE
Nobuhiro TAKESHITA	Medical Oncologist	JAPAN
Orlando TORRES	HBP Surgeon	BRAZIL
Melanie TSANG	HBP Surgeon	CANADA
Olivier TURRINI	HBP Surgeon	FRANCE
Shuichiro UEMURA	HBP Surgeon	JAPAN
Eliana VALLE	Radiologist	BRAZIL
Anna VAN OSCH	Dietetician	CANADA
Emilio VICENTE	HBP Surgeon	SPAIN

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Supplementary file

Annie VINCENT	Patient	FRANCE
Go WAKABAYASHI	HBP Surgeon	JAPAN
Taiga WAKABAYASHI	HBP Surgeon	JAPAN
Helmut WEISS	HBP Surgeon	AUSTRIA
Masakazu YAMAMOTO	HBP Surgeon	JAPAN
Shingo YAMASHITA	HBP Surgeon	JAPAN
Takehisa YAZAWA	HBP Surgeon	JAPAN
Thomas ZACHARIAS	HBP Surgeon	FRANCE

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