Published in final edited form as:

Lancet Oncol. 2018 March ; 19(3): e151–e160. doi:10.1016/S1470-2045(18)30098-6.

Consensus statement on mandatory measurements in pancreatic cancer trials (COMM-PACT) for systemic treatment of unresectable disease

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Contributors

HWMvL, MGHvO, MGB, EtV, LBvR, ORB, and JWW conceived the design of this Review. EtV, LBvR, RMAM, JHMvdM, and MJvdP contributed to the collection and assembly of data, and all authors supported the data collection providing suggestions and evidence for certain characteristics. EtV, LBvR, HWMvL, MGHvO, MGB, and ORB did the general data analysis and interpretation, and for the consensus rounds the data interpretation was done by all authors. All authors contributed to writing the manuscript and gave final approval for submission of the manuscript.

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Declaration of interests

JDB reports personal fees from Celgene, Symphogen, Genentech and Roche, Vertex, Janssen Oncology, EMD Serono, Boston Biomedical, and Pharmacyclics, outside the submitted work. SB reports grants and personal fees from Celgene and Roche, outside the submitted work. EVC reports grants from Bayer, Boehringer, Lilly, Novartis, Merck, Amgen, Celgene, and Roche, and had an advisory role for Bayer, Boehringer, Lilly, and Novartis, outside the submitted work. GD reports grants from MSD and Celgene, and personal fees from Bristol-Myers Squibb, Bayer, and Merck, outside the submitted work. DG reports grants from Amgen, Pfizer, Celgene, Bayer, and Sirtex Medical, outside the submitted work. JPN reports grants from Mylan, Clovis Oncology, Ventana Medical Systems, Boehringer Ingelheim, Nucana, Astellas, AstraZeneca, and Taiho Pharmaceutical, outside the submitted work. MR reports grants from Celgene, and had an advisory role for Novocure, Halozyne, Baxalta, Pfizer, Merck, and Novartis, outside the submitted work. JTS reports grants from Celgene, Bristol-Myers Squibb, Novartis, and Boehringer, and had an advisory role for Merrimack, Baxalta, Celgene, and Lilly, outside the submitted work. MGHvO reports grants from Bayer, Lilly, Merck, Roche, and Amgen, outside the submitted work. HWMvL reports grants from Lilly, Nordic, Celgene, Bayer, Merck Serono, MSD, and Roche, and had an advisory role for Lilly, Celgene, and Bayer, outside the submitted work. All other authors declare no competing interests.

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See Online for appendix

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Abstract

Variations in the reporting of potentially confounding variables in studies investigating systemic treatments for unresectable pancreatic cancer pose challenges in drawing accurate comparisons between findings. In this Review, we establish the first international consensus on mandatory baseline and prognostic characteristics in future trials for the treatment of unresectable pancreatic cancer. We did a systematic literature search to find phase 3 trials investigating first-line systemic treatment for locally advanced or metastatic pancreatic cancer to identify baseline characteristics and prognostic variables. We created a structured overview showing the reporting frequencies of baseline characteristics and the prognostic relevance of identified variables. We used a modified Delphi panel of two rounds involving an international panel of 23 leading medical oncologists in the field of pancreatic cancer to develop a consensus on the various variables identified. In total, 39 randomised controlled trials that had data on 15 863 patients were included, of which 32 baseline characteristics and 26 prognostic characteristics were identified. After two consensus rounds, 23 baseline characteristics and 12 prognostic characteristics were designated as mandatory for future pancreatic cancer trials. The CONsensus statement on Mandatory Measurements in unresectable PANcreatic Cancer Trials (COMM-PACT) identifies a mandatory set of baseline and

prognostic characteristics to allow adequate comparison of outcomes between pancreatic cancer studies.

Introduction

Pancreatic cancer has a very poor prognosis and median overall survival is less than 5 months in population-based studies.¹ Approximately 80% of patients with pancreatic cancer present with unresectable disease, which is either due to locally advanced or metastatic disease.

Given the increasing number of studies investigating systemic treatments in patients with unresectable pancreatic cancer, adequate comparisons of outcomes between these studies are crucial and can be used for exploratory analyses that can be hypothesis generating. Interest has been growing in the standardisation of care in various areas of medicine.^{2–4} The Core Outcome Measures in Effectiveness Trials (COMET) initiative was founded to develop multiple core outcome sets, which are guidelines for the minimum amount of outcome data that should be collected, measured, and reported in studies. For example, a guideline for time-to-event outcome definitions in pancreatic cancer trials was developed by the Definition for Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) group on behalf of the COMET initiative. Additionally, the Core Outcome Set–STAndards for Reporting (COS–STAR) informs researchers on how to adequately report the process of developing core outcome sets.^{5–7}

However, even though core outcome sets can facilitate the comparison of studies by standardisation and adequate reporting of outcomes, it is still difficult to compare outcomes across studies if the study reports do not provide sufficient information about the patient population. Until now, reporting population characteristics in baseline tables in prospective clinical studies has often been inconsistent among studies. This inconsistency is also typical for known prognostic characteristics between unresectable pancreatic cancer trials.⁸ Therefore, standardisation of the reporting of potentially confounding characteristics in trials of unresectable pancreatic cancer would allow for the comparison of outcomes across studies and series, and would facilitate communication and evaluation of different treatments. Standardisation of reporting will also help in the development of new models to predict study outcomes and statistical hypotheses, and help to establish evaluation criteria to determine the efficacy of new experimental agents.⁹

The aim of this Review was to establish the first international consensus on mandatory baseline and prognostic characteristic measurements in unresectable pancreatic cancer trials. We used the Delphi technique to systematically obtain expert opinions for this purpose.^{10,11} We aimed to combine expert opinions using evidence from the medical literature, and to develop a scaled grading system for prognostic characteristics that had been identified via a full systematic literature search. The results were then presented to a panel of experts as a part of a modified Delphi process.

Data collection

Search strategy and selection criteria

Adopting the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,¹² we searched the electronic databases MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) for prospective phase 3 randomised controlled trials investigating first-line systemic treatment for unresectable pancreatic cancer, published between Jan 11, 2000, and Jan 11, 2016. We searched medical subject headings (MeSH) in the MEDLINE database and in the main text for “pancreatic cancer” combined with “chemotherapy”, “systemic treatment”, “survival”, “toxicity”, and “quality of life” (appendix pp 2–3). Additionally, meeting abstracts or presentations from the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) and the two largest clinical trial databases (ClinicalTrials.gov and the European Clinical Trials database [EudraCT]) were searched to ensure no studies were missed. In addition, experts who were part of the Delphi panel and who were the principal investigators of randomised controlled trials in the field of advanced pancreatic cancer were asked to suggest studies that might have been missed in our initial literature search. However, members of the expert panel did not suggest any additional studies.

Eligibility criteria for studies to be included were those studies investigating patients aged 18 years or older with histopathologically proven locally advanced or metastatic pancreatic cancer; phase 3 randomised controlled trials investigating systemic treatment (ie, chemotherapy, molecular targeted therapy, or immunotherapy); studies that were published in English; and studies with overall survival as an endpoint. Two authors (EtV and MJvdP) independently screened the titles and abstracts of the search results to find studies that met the eligibility criteria. The full texts of these articles were then screened by EtV and LBvR.

Scaled grading system development

We extracted all reported baseline characteristics from the included studies and extracted all potential prognostic variables that had been analysed in a multivariate Cox regression or logistic regression model. We created a structured overview showing all reported baseline characteristics and how often they had been reported and all investigated potential prognostic characteristics and the proportion of studies and patients for which each factor was identified as an independent prognostic variable for overall survival. A prognostic factor was deemed independent if the multivariable Cox regression or logistic regression analyses had resulted in statistical significance. In this overview, we also included information on whether the prognostic characteristics identified fitted a predefined scaled grading system. This scaled grading system was defined as follows: when a factor had been analysed in a multivariate analysis in three studies or fewer, it was considered an independent predictor of survival in 100% of studies; when a factor had been analysed in four studies, it was considered an independent predictor of survival in 75% or more of the total sample size of the four studies; and, when a factor had been analysed in more than four studies, it was considered an independent predictor of survival in 50% or more of the total sample size of the studies that had analysed it.

The scaled grading system was used to indicate clinically relevant prognostic factors for which a universal definition did not exist. For example, a factor might be called clinically relevant if it was independently prognostic in a multivariable analysis. However, no guidelines seem to exist on the correct sample size to use to make this decision, and how to handle inconsistent results between studies. Criteria used in the scaled grading system were based on a discussion with all experts and an experienced epidemiologist (MGHvO), who all agreed to the predefined scaled grading system. However, a factor was only included in the mandatory set of prognostic variables when it fulfilled the criteria of the graded scaling system and received a majority of votes from the Delphi panel.

Consensus procedure

The experts in the COnsensus statement on Mandatory Measurements in unresectable PAncreatic Cancer Trials (COMM-PACT) group were first authors, corresponding authors, and principal investigators of the trials that were included in our literature search. All individuals were contacted by LBvR and HWMvL to ask whether they wanted to be part of the consensus procedure, which consisted of two rounds using an online survey. In a typical Delphi survey, a group of experts are asked for their opinion on a specific topic and are subsequently re-polled with controlled feedback regarding the polled opinions to encourage consensus between experts.¹³ In our Delphi survey, 24 international experts were approached, of whom 23 (96%) completed both consensus rounds. The full list of experts is shown in the appendix pp 8–10.

In the first round of our Delphi survey, the structured overview of the results was presented, and experts could vote for as many baseline and prognostic variables to eventually be included in the mandatory set as they wanted. The grading system was provided to members of the Delphi panel at this stage of the process to inform them of important baseline and prognostic factors in the medical literature; however, we iterated the point that a factor also needed a majority of votes (>50%) from experts from the consensus rounds to be included in the mandatory set of variables.

After the first round, baseline and prognostic characteristics that received more than 50% of votes from the expert panel were included in the mandatory set. Baseline characteristics with 20–50% of the votes, or with less than 20% of votes but that were present in four or more of the studies, were entered into the second round. Prognostic characteristics with 20–50% of votes, or with less than 20% of votes but which fitted the scaled grading system, were also entered into the second round. Baseline and prognostic variables with less than 20% of votes and that were reported in less than four studies (baseline characteristics) or did not fit the scaled grading system (prognostics characteristics) were excluded from further analysis.

In the second round, the structured overview and the results of the first round were shown to members of the Delphi panel. Additional characteristics suggested by experts and that had not been identified from the literature search in the first round were also put up for voting in the second round. The procedure in the second round was identical to the first. After the second round, all baseline and prognostic characteristics had been included in either the mandatory or the recommended category, or had been excluded from the consensus altogether. Finally, since prognostic characteristics should also be reported in baseline tables,

prognostic characteristics in the mandatory and recommended sets were also added to their corresponding baseline sets—ie, any prognostic characteristic in the mandatory or recommended set of prognostic characteristics was automatically added to the mandatory or recommended set of baseline characteristics.

Findings

Literature review

An overview of the literature search part of our Review is in figure 1. 624 unique references were identified, of which 39 were original studies that contained data from 15 863 patients, ^{14–51} and 11 were separately published subanalyses.^{53–63} Six additional studies were found in the clinical trial registries, of which three ended prematurely, two were completed, and one had an unknown status. With an additional search for these studies in MEDLINE, Embase, CENTRAL, and the ASCO and ESMO conference databases, the reports of these studies could not be retrieved and therefore data could not be extracted. From nine of the 39 original studies, the search gave 11 separately published subanalyses. All studies (including the 39 original randomised trials and all published subanalyses) investigated metastatic pancreatic cancer, or metastatic and locally advanced pancreatic cancer. An overview of the identified studies and number of patients for baseline characteristics is shown in the appendix pp 4–5.

In total, 41 unique baseline characteristics were identified from the literature search, with a further nine added after the first consensus round. The most frequently reported baseline characteristics were age, disease status (locally advanced pancreatic cancer vs metastatic pancreatic cancer), and sex, which were identified in all 39 studies, and then performance status (identified in 38 studies). Multivariable regression analyses were done in 29 (74%) of the 39 randomised controlled trials. A total of 26 unique prognostic characteristics were identified, with a further 11 added after the first consensus round. The five most frequently studied prognostic characteristics were performance status (16 studies), disease status (locally advanced pancreatic cancer vs metastatic pancreatic cancer; 14 studies), sex (12 studies), age (12 studies), and baseline cancer antigen (CA) 19–9 concentration (eight studies). Nine prognostic characteristics met the scaled grading criteria: performance status, disease status, liver metastasis, albumin concentration, CA 19–9 concentration, alkaline phosphatase, pain at baseline, bilirubin concentration, and lactate dehydrogenase (LDH) concentration.

Consensus rounds

Results of the consensus procedure are shown in figure 2 and in the appendix pp 6–7. 32 baseline characteristics and 26 prognostic variables were identified from our literature search. In the first round, 18 baseline characteristics and nine prognostic characteristics received more than 50% of votes and were therefore immediately included in the mandatory set. Six baseline characteristics and ten prognostic variables were excluded from the consensus because they had received less than 20% of the experts' votes and were reported in less than four studies or did not fit the scaled grading system. Eight baseline characteristics obtained 20–50% of the expert votes or obtained less than 20% of the votes

but were reported in four or more randomised controlled trials. Seven prognostic characteristics also obtained 20–50% of expert votes or obtained less than 20% of the votes but fitted the scaled grading criteria. These characteristics therefore proceeded to the second round (appendix pp 6–7).

After the first round, nine additional baseline characteristics and 11 additional prognostic characteristics were suggested by the expert panel and were entered into the second consensus round (appendix pp 6–7). In total, 17 baseline and 18 prognostic characteristics were considered in the second round.

During the second round, two baseline and three prognostic characteristics were voted for by more than 50% of the panel and were automatically included in the mandatory set, along with the other variables that had been identified in round one. 12 baseline characteristics obtained 20–50% of the expert votes or obtained less than 20% of the votes but were reported in four or more randomised controlled trials and were included in the recommended set. Similarly, eight prognostic characteristics also obtained 20–50% of expert votes or obtained less than 20% of the votes but fitted the scaled grading criteria; therefore, these characteristics were also added to the recommended set of variables. LDH concentration, C-reactive protein concentration, and neutrophil-to-lymphocyte ratio were automatically added to the mandatory baseline characteristics set, since these were also in the mandatory prognostic characteristics set. Quality of life physical functioning was also automatically added to the recommended baseline characteristics set, since it was also in the recommended prognostic characteristics set. One baseline characteristic and seven prognostic characteristics were excluded from the consensus after the second round because they obtained less than 20% of votes and were reported in less than four studies or did not fit the scaled grading system. Figure 3 provides an overview of all baseline and prognostic characteristics that were identified from the 39 studies.

Final consensus statements

Panels 1 and 2 show the final consensus statements of the baseline and prognostic characteristics included in the mandatory and recommended sets for inclusion in future trials or outcomes. In total, 23 baseline characteristics were deemed mandatory by the panel to be measured at baseline and to be reported in unresectable pancreatic cancer trials. 12 prognostic characteristics were deemed mandatory to be included in regression analyses in future trials to ensure that differences in the distribution of these characteristics between study groups do not confound the observed treatment effect. Additionally, 12 baseline and eight prognostic characteristics are recommended to be reported in unresectable pancreatic studies since the members of the panel and the evidence from the literature did not rule out their possible clinical value. The prognostic characteristics C-reactive protein concentration, LDH concentration, and neutrophil-to-lymphocyte ratio, which are in the mandatory set, and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-30) score on a physical-functioning subscale, which is in the recommended set, were also added to the corresponding baseline sets to be reported in the baseline tables.

Discussion

The consensus statements from a group of experts in the field of pancreatic cancer provides mandatory and recommended measurements of baseline and prognostic characteristics to be included in trials investigating palliative systemic therapy for unresectable pancreatic cancer. Compliance with the COMM-PACT guidelines on characteristics to be included in future trials and studies should allow better comparisons of outcomes between medical centres and countries, and facilitate new studies in the field of pancreatic cancer. Non-prognostic baseline variables are also included in the consensus statement because, even though they might not be predictive of patient outcomes, they ensure that the cohorts being compared are similar and representative of the broad range of patients that are seen in routine clinical practice.

The mandatory measurements of the consensus findings included 23 baseline and 12 prognostic characteristics. In future randomised controlled trials in unresectable pancreatic cancer, we recommend that these characteristics are all reported in the baseline tables. The mandatory prognostic characteristics should be included in regression analyses to adjust for their effect on treatment outcomes. Alternatively, they could be considered for patient stratification at randomisation.

Most of the prognostic characteristics included in the mandatory set have previously been found to have had a significant association with survival.^{64–66} For some factors that have been included in the mandatory set, few data were available to make an association with survival—ie, LDH concentration was reported in only three studies.^{15,16,38} Moreover, C-reactive protein concentration, neutrophil-to-lymphocyte ratio, and quality of life were reported in only one study,³⁸ and therefore did not fit the scaled grading criteria for prognostic factors. However, most members of the expert panel considered these factors to have prognostic value in clinical practice and so they were included in the mandatory set. LDH concentration, neutrophil-to-lymphocyte ratio, C-reactive protein concentration, and quality of life are characteristics that are rarely used and being increasingly researched, with promising clinical utility in other gastrointestinal malignancies, and, moreover, for some of these factors, prognostic significance was found in smaller retrospective studies of pancreatic cancer.^{8,67–76}

Some factors, such as sex, alkaline phosphatase concentration, or tumour location, have been well studied but were not statistically significant in most of the patients and studies examined. The expert panel confirmed this absence of prognostic significance during the consensus process, so these items were added to the recommended set rather than the mandatory set. Most items that were not included in the mandatory or recommended sets had been investigated in only one study or had not shown statistical prognostic significance in at least one study of the patients and studies examined. Future research into these factors (eg, other laboratory factors or other quality-of-life dimensions), however, could establish whether they have independent and clinically relevant prognostic potential.

The expert opinions of the panel generally matched the identified factors derived from the studies. In many studies, only the statistically significant hazard ratios or odds ratios were

reported, whereas non-significant factors were only mentioned in a table or the text, or not mentioned at all. Therefore, doing a meta-analysis with studies that provided extractable data for calculation of effect sizes only would lead to bias. Hence, we designed our study so that all included randomised trials contributed to the overview. For example, figure 3B shows the number of patients and randomised controlled trials in which a factor was statistically significant or non-significant, regardless of whether a hazard ratio was reported or not. Furthermore, when putting together the list of baseline factors in the consensus statement, we felt that a large meta-analysis was not possible. We used the frequency of reporting of these baseline factors to indicate their importance. The Delphi process was a combined process of quantifying the number of baseline characteristics reported in the baseline tables of the randomised controlled trials included in this analysis, and also measuring the number of prognostic characteristics analysed in the multivariate proportional hazards or logistic regression analyses calculated as those that were statistically significant or not (weighted by sample size) in these trials.

Unresectable pancreatic cancer includes both locally advanced and metastatic pancreatic cancer, which differ in terms of treatment and prognosis. Traditionally, studies of unresectable pancreatic cancer include roughly 20% of patients with locally advanced pancreatic cancer; however, because of the differences in treatment for locally advanced and metastatic pancreatic cancer, they tend to be studied separately.⁷⁷ We included studies that investigated metastatic pancreatic cancer alone or studies that investigated metastatic and locally advanced pancreatic cancer combined (no studies investigated locally advanced pancreatic cancer only), since baseline and prognostic factors were also pooled in these studies. Furthermore, when the expert panel responded to questionnaires for the consensus rounds, both forms of the disease were considered.

Cancer is being increasingly defined by molecular and genetic characteristics, which both play an important role in patient survival and in clinical practice; for example, more attention is being given to *BRCA* or *BRCA*-like mutations, which are associated with an increased incidence of pancreatic cancer and could also be associated with prognosis.^{78–81} Most molecular and genetic factors, however, are not routinely measured in phase 3 randomised controlled trials and were therefore not identified in our systematic Review. Some factors, such as *KRAS* mutations, were identified but did not meet the criteria to be included in either the mandatory or recommended sets since no prognostic value was found for *KRAS* mutations by multivariable analysis in a single included study.⁶⁰ However, notably, *KRAS* mutations were a prognostic factor in one retrospective study.⁸² Although *KRAS* mutations are a promising prognostic characteristic, their routine application into clinical practice has not taken place yet; therefore, the expert panel might not have voted for *KRAS* mutations as useful prognostic characteristics at this time.

Our Review has some limitations. Some characteristics that have recently emerged might have important prognostic relevance but could have been underreported in our study—eg, biomarkers that have received important early clinical evidence but have not yet been studied in randomised controlled trials. This limitation might, however, have been compensated for because of the allowance of suggestions by the expert panel—eg, SMAD-4 (small mothers against decapentaplegic homolog-4). Furthermore, the consensus process was internet-based

and no meeting between members of the expert panel had been held; therefore, experts were not able to discuss the value of characteristics with less than 50% of the votes (eg, geographical region of the randomised trials, or ethnicity of the patients) in a face-to-face meeting. However, our procedure had some associated benefits. Experts could vote independently from each other for all baseline and prognostic characteristics; therefore, decisions were based on their own clinical experience and on an up-to-date overview of the medical literature obtained through our search. Additionally, members of the expert panel saw the responses of the other members after the first consensus round, and they could then make their decisions in the second round independently but with knowledge of the results of the first round. Finally, we acknowledge that few data are available for some of the identified characteristics that were eventually included in either the mandatory or recommended set. However, we believe the method we established was the best available method for our data synthesis. We provided objective data through a systematic literature search combined with objective criteria (ie, the scaled grading system) for potential clinical relevance, to the expert panel to make an evidence-based decision. On the whole, the expert opinion of the panel matched the identified factors derived from the studies.

This Review also has strengths. For the characteristics included in the mandatory set, the expert experience and literature evidence were highly concordant, and the most frequently reported baseline characteristics were also picked by the members of the expert panel to be included in the consensus statement as mandatory measurements. This high concordance was to be expected as the experts who were recruited are very familiar with the medical literature, including the studies reviewed for this analysis. Furthermore, the prognostic relevance of the characteristics that fitted the scaled grading system was confirmed by the majority of experts (more than 50% of the panel), since all the characteristics were included in the mandatory setting except for alkaline phosphatase. Another important strength of this Review is that characteristics with a moderate number of votes (between 20% and 50%), after the first round and by use of the scaled grading system, had an increased chance of proceeding to the next consensus round. In the second round, instead of being excluded from the consensus process, these characteristics were then considered in the recommended category instead of being completely discarded, thereby minimising the risk of losing valuable information. Finally, although many prognostic characteristics of unresectable pancreatic cancer have been studied, a full systematic review, as far as we were aware, had not been done before.⁸

Conclusion

Although unresectable pancreatic cancer is still associated with a poor prognosis, developments in systemic treatments are encouraging. The COMM-PACT guidelines on baseline and prognostic characteristics for pancreatic cancer trials should allow for the valid assessment and comparison of unresectable pancreatic cancer studies and facilitate new studies in this field.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This Review was funded in part by a grant from the Dutch Cancer Society (UVA 2013-5842).

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Panel 1: Consensus statement on mandatory and recommended baseline variables in randomised controlled trials investigating first-line systemic therapy for unresectable pancreatic cancer

Mandatory set

- Age
- Albumin
- Biliary stent
- Bilirubin
- CA 19–9
- C-reactive protein
- Disease status
- Sex
- Histology
- Lactate dehydrogenase
- Liver metastasis
- Neutrophil-to-lymphocyte ratio
- Number of metastatic sites
- Pain at baseline
- Performance status
- Peritoneal metastasis
- Primary tumour location
- Previous chemotherapy or radiotherapy
- Previous surgery
- Pulmonary metastasis
- Time from diagnosis
- Tumour differentiation
- Weight or BMI

Recommended set

- Alkaline phosphatase
- Carcinoembryonic antigen
- Ethnicity
- Geographical region

- Measurable lesion
- N stage
- Previous deep-venous thrombosis or embolus
- QoL–global*
- QoL–physical functioning*
- Synchronous or metachronous metastasis
- T stage
- White blood cell count

CA=cancer antigen. QoL=quality of life. *These factors are relative to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 score.

Panel 2: Consensus statement on mandatory and recommended prognostic variables in randomised controlled trials investigating first-line systemic therapy for unresectable pancreatic cancer

Mandatory set

- Age
- Albumin*
- Bilirubin*
- CA 19–9*
- C-reactive protein
- Disease status*
- Lactate dehydrogenase*
- Liver metastasis*
- Neutrophil-to-lymphocyte ratio
- Number of metastatic sites
- Pain at baseline*
- Performance status*

Recommended set

- Alkaline phosphatase*
- Sex
- Primary tumour location
- Pulmonary metastasis
- Previous deep venous thrombosis or embolus
- QoL–global†
- QoL–physical functioning†
- Synchronous or metachronous metastasis

CA=cancer antigen. QoL=quality of life. *Fulfilled scaled grading criteria of prognostic factors. †These factors are relative to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–C30 score.

Figure 1: Literature search

Using PRISMA guidelines, a flowchart of our literature search used in the identification of baseline and prognostic characteristics that helped to inform our scaled grading system. CENTRAL=Cochrane Central Register of Controlled Trials. ASCO=American Society of Clinical Oncology. ESMO=European Society for Medical Oncology. PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses. RCT=randomised controlled trial.

Figure 2: Consensus strategy

Flow diagram of the procedures followed in the first and second consensus rounds by the expert panel to establish which baseline and prognostic characteristics should be in the mandatory and recommended sets for clinical trial reporting. As prognostic characteristics should be reported also in baseline tables, prognostics characteristics in the mandatory and recommended sets were also added to their corresponding baseline sets; these included C-reactive protein concentration, lactate dehydrogenase concentration, and neutrophil-to-lymphocyte ratio in the mandatory set, and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 score on a physical-functioning subscale in the recommended set.

Figure 3: Identified baseline and prognostic characteristics

(A) Baseline characteristics. The y-axis shows the identified baseline characteristics and the x-axis shows the number of randomised controlled trials in which the characteristic was reported. (B) Prognostic characteristics analysed in multivariate Cox or logistic regression in the randomised controlled trials. The x-axis shows the number of patients, and the number of randomised controlled trials are in parentheses. The bars represent the corresponding number of patients in which the given factor was statistically significant ($p \leq 0.05$) or non-significant ($p > 0.05$) in the multivariate analysis of the randomised controlled trial.

CA=cancer antigen. BMI=body-mass index. BUN=blood-urea-nitrogen concentration. LDH=lactate dehydrogenase. QoL=quality of life. DVT=deep-venous thrombosis. γGT=γ-glutamyltransferase. SMAD-4=small mothers against decapentaplegic homolog-4. *These characteristics fit the scaled grading system.