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Review Article

CLINICAL PRACTICE

Systematic review and consensus definitions for standardised endpoints in perioperative medicine: postoperative cancer outcomes

D. J. Buggy[1,5,*], J. Freeman[1], M. Z. Johnson[1], K. Leslie[2,3], B. Riedel[4], D. I. Sessler[5], A. Kurz[6], V. Gottumukkala[6], T. Short[7], N. Pace[8], P. M. Myles[9], and The StEP-COMPAC Group[10]

[1]Department of Anaesthesia, Mater Misericordiae University Hospital, School of Medicine, University College Dublin, Ireland, [2]Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Melbourne Medical School, University of Melbourne, Melbourne, Australia, [3]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia, [4]Department of Anaesthesia, Perioperative and Pain Medicine, Peter MacCallum Cancer Centre and University of Melbourne, Australia, [5]Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, USA, [6]Department of Anesthesiology and Perioperative Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA, [7]Auckland City Hospital, Auckland, New Zealand, [8]Department of Anesthesiology, University of Utah, Salt Lake City, UT, USA and [9]Department of Anaesthesia and Perioperative Medicine, Alfred Hospital and Monash University, Melbourne, Australia

*Corresponding author. E-mail: donal.buggy@ucd.ie

[10] All members are listed in the web-based supplement.

Abstract

Background: The Standardising Endpoints for Perioperative Medicine group was established to derive an appropriate set of endpoints for use in clinical trials related to anaesthesia and perioperative medicine. Anaesthetic or analgesic technique during cancer surgery with curative intent may influence the risk of recurrence or metastasis. However, given the current equipoise in the existing literature, prospective, randomised, controlled trials are necessary to test this hypothesis. As such, a cancer subgroup was formed to derive endpoints related to research in onco-anaesthesia based on a current evidence base, international consensus and expert guidance.

Methods: We undertook a systematic review to identify measures of oncological outcome used in the oncological, surgical, and wider literature. A multiround Delphi consensus process that included up to 89 clinician–researchers was then used to refine a recommended list of endpoints.

Results: We identified 90 studies in a literature search, which were the basis for a preliminary list of nine outcome measures and their definitions. A further two were added during the Delphi process. Response rates for Delphi rounds one, two, and three were 88% (n=9), 82% (n=73), and 100% (n=10), respectively. A final list of 10 defined endpoints was refined and developed, of which six secured approval by ≥70% of the group: cancer health related quality of life, days

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alive and out of hospital at 90 days, time to tumour progression, disease-free survival, cancer-specific survival, and overall survival (and 5-yr overall survival).
Conclusion: Standardised endpoints in clinical outcomes studies will support benchmarking and pooling (meta-analysis) of trials. It is therefore recommended that one or more of these consensus-derived endpoints should be considered for inclusion in clinical trials evaluating a causal effect of anaesthesia–analgesia technique on oncological outcomes.

Keywords: clinical trials, endpoints; cancer, surgery; surgery, postoperative outcomes; cancer, recurrence

Editor's key points

- Interpreting different clinical trials that address the same research question can be compromised without uniform, consensus endpoints.
- Clinical trials evaluating the effect of anaesthetic-analgesic technique during surgery of curative intent on cancer outcomes are warranted.
- This review outlines the process of identifying a number of endpoints that should be included in the design of such trials.

Cancer is a leading cause of death worldwide accounting for 8.2 million deaths in 2012.[1] While surgical excision is the mainstay of treatment for many tumour types, there is mounting evidence that perioperative factors alter patient susceptibility to cancer metastasis and influence cancer progression. The surgical stress response, type of anaesthesia, and analgesia might all impact cancer outcomes.[2–4] Despite some compelling *in vitro* data and some retrospective clinical studies, the potential effect of different types of anaesthesia on cancer recurrence or metastasis is not proved and large randomised clinical trials are required to guide clinical practice.[2–4] Defining appropriate endpoints for trials of anaesthetic technique on cancer outcomes is important to enable the provision and improvement of high quality clinical care.[5,6]
Standardised endpoints are an integral part of oncological research, yet endpoints often lack consistency and loose definitions are common.[7,8] Previous efforts have been made to establish a formal consensus on cancer trial endpoints, for example survival endpoints in colorectal cancer and the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials).[9,10] Despite these efforts, definitions and endpoints are often constrained by lack of general consensus. Furthermore, many agreed endpoints remain specific to various types of tumour and are not necessarily transferrable to different types of cancer.[11–13]

The Standardising Endpoints for Perioperative Medicine (StEP) initiative aims to formulate set endpoints for use in perioperative trials based on a current evidence base, international consensus and expert guidance.[6] We describe the identification of important, cancer-specific endpoints for use in perioperative randomised, controlled trials after a systematic review and Delphi process.

Methods

Literature search and systematic review

A systematic search of EMBASE, MEDLINE, Web of Knowledge, the Cochrane Library Database and PubMed was performed to identify systematic reviews, trials, or guidance reporting oncological outcome measures. The result of this search was a collection of relevant endpoints suitable for further refinement. Only literature published from January 1, 2005 was included to avoid inclusion of obsolete material. Two authors (M.Z.J. and D.J.B.) independently identified the abstracts and titles to be considered for inclusion. Discrepancies were resolved by consultation between these two researchers.

The intended population for inclusion were adults (age ≥18 yr) undergoing surgery for tumour excision or debulking of abdominal cancers. Exclusion criteria were those reviews including patients younger than 18 yr, where open or laparoscopic surgery was not performed, and reviews where <50 patients were reported. We restricted our search to the six highest ranked anaesthesiology journals (*British Journal of Anaesthesia*, *Anesthesiology*, *Anesthesia and Analgesia*, *Anaesthesia*, *Regional Anesthesia and Pain Medicine*, and *European Journal of Anaesthesiology*), the four highest-ranked journals in surgery (*Annals of Surgery*, *British Journal of Surgery*, *Journal of the American College of Surgeons*, and *JAMA Surgery*) and the four highest ranked journals in general medicine for 2017 (*New England Journal of Medicine*, *Lancet*, *Journal of the American Medical Association*, and *British Medical Journal*) by journal impact factor (8 January 2018. https://www.pubmed.com).

Potentially eligible literature, identified from the references of initially included material but published in other journals, were considered for inclusion if appropriate. A total of 290 potential publications were collated initially. Of these, 85 met the criteria for inclusion. Examination of the reference lists of these publications led to five more publications for inclusion. Therefore, 90 studies were included in this review. The results of this initial systematic review then underwent consensus evaluation by Delphi process.

Delphi process

A Delphi process obtained input and consensus opinion from a cohort of researchers experienced in anaesthesia and perioperative medicine trials.[14,15] A four-step process similar to that described by Myles and colleagues[16] was used in order to develop consensus clinical endpoints. A Steering Committee oversaw the StEP Working Group, which itself consisted of an international cohort of experienced investigators.[6,17]

Step 1: Establishing an initial list of trial endpoints and definitions for consideration

Literature from the initial search (Fig. 1) resulted in a preliminary list of eight outcome measures and their definitions. Two further candidate endpoints were added to the list before Delphi Round 1: return to intended oncological therapy (RIOT) and days alive out of hospital (DAOH) at 90 days. Although not identified on the initial search, these two endpoints were included after canvassing the opinions of the theme subgroup for suggested items for inclusion before the first Delphi round.

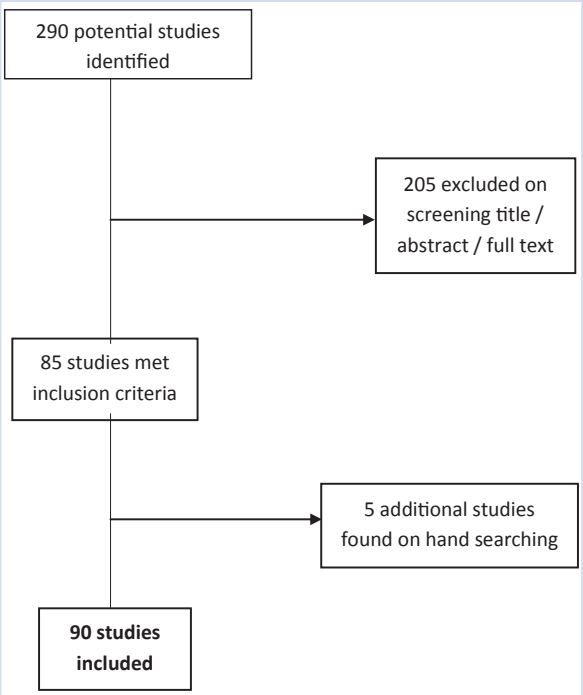

Fig 1. Results of the literature search.

This process was performed to identify novel endpoints to be considered for development that may have been missed by the initial search.

Step 2: Formal rating of recommendations (Delphi round one)

Proposed endpoints and their definitions were distributed to members of the StEP theme cancer subgroup (n=9 in round 1 and n=10 in round 3) and the StEP Steering Committee (n=89). A Delphi questionnaire was used, and committee and subgroup members were asked to score each of the initial items. Items for assessment were rated on a numerical scale of 1–9, where a score of 1–3 was considered 'invalid' or 'not that important' and 7–9 was deemed 'critical for inclusion'. A score of 4–6 was judged 'Important but requires revision'. Participants had the option of selecting 'unsure' if they were uncertain how to score an item, and were invited to suggest other endpoints, definitions, or how existing definitions might be modified. Participants were invited to comment on the proposed endpoints and suggest modifications or to suggest other endpoints. A reminder e-mail was sent to ensure prompt completion of the survey. Both the number of respondents and recommendation assessments were recorded.

Step 3: Delphi round two

The second Delphi round was coordinated by the cancer theme sub-group chair (D.J.B.). Participation in round two was not limited to the theme subgroup committee and the entire StEP Working Group was invited to participate (n=89). The results of the first round were initially made available to the cancer theme subgroup, including the number of participants who scored any particular item and the mean and inter-quartile ranges of the scores assigned. Subgroup members then discussed the findings of round one by email. Those items with a median score of $\geq$7 from round one were retained for consideration in round two. Lower-scoring items could be retained if considered 'critical for inclusion' by any subgroup member. Any item with a median score of $\leq$3 was not retained for further consideration.

Contributors to round two were provided with information on this set of items. This included the number of participants allocating a score of $\geq$7 for any given item in round one and the responses from other Delphi members and round two participants were asked to re-score the items carried forward from round one. As in the other subtheme groups[16] (and in press), 'consensus' was defined as a score of $\geq$7 from 70% of participants.

Stage 4: Development of final recommendations/Delphi round three

The third Delphi round was again coordinated by the subgroup chair (D.J.B.); participation was restricted to cancer theme subgroup members (n=10). A summary of results from Delphi rounds one and two was available to these participants and further discussion via e-mail was encouraged. While it was proposed that any items not scoring a median value of $\geq$7 from round two were to be excluded, all of the initial 10 endpoints were deemed 'critical for inclusion' by at least one participant. If it was suggested that modification to an endpoint was necessary, this was then resolved by the theme subgroup members by e-mail discussion.

The Research Unit of the Department of Anaesthesia and Perioperative Medicine at the Alfred Hospital, Melbourne, Australia, coordinated each Delphi round. The scores of the items for consideration and the number of responding participants were recorded for each round of the Delphi process in an Excel spreadsheet. Participants' responses were anonymised by listing their responses in the database under a coded number, arranged by the study administrator. This was then converted into an SPSS database (IBM Corp. Released 2013. IBM SPSS statistics for Windows, v22. Armonk, NY, USA) in order to calculate the consensus rates, and the median and range scores.

Results

Cancer definition presented at Delphi round one[18]

Cancer, also termed malignancy, is a term for diseases in which abnormal cells divide without control and with the potential to invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of cancer. Carcinoma is a cancer that begins in the skin or in tissues that line or cover internal organs. Sarcoma is a cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukaemia is a cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are cancers that begin in the cells of the immune system. Central nervous system cancers are those that begin in the tissues of the brain and spinal cord.

The 10 cancer-related outcome measures presented in Delphi round three are shown in Table 1. Six of these met the definition of consensus as described in the Methods section. These endpoints and a definition for cancer for use in perioperative clinical trials examining oncological outcome are noted below. Response rates for Delphi rounds one, two, and

Table 1 Results of the Delphi process. R1, round 1 Delphi process, R2, round 2 Delphi process, R3, round 3 Delphi process

Endpoint candidate	R1 *n*=9	R1 *n*=9	R1 *n*=9	R2 *n*=89	R2 *n*=89	R2 *n*=89	R3 *n*=10	R3 *n*=10	R3 *n*=10
	Unsure number	Score median	Score ≥7 (%)	Unsure number, *n* (%)	Score median	Score ≥7 (%)	Unsure number	Score median	Score ≥7 (%)
Cancer definition[18]	0	9 (8–9)	89	0	9 (9–9)	85	0	9 (9–9)	100
Endpoint 1. Overall survival 5 yr	0	9 (7–9)	88	0	9	83	0	8.5 (7–9)	80
Endpoint 2. Cancer health related quality of life	0	9 (8–9)	77	0	8	81	0	9 (8–9)	90
Endpoint 3. Disease free survival	0	8 (6.5–9)	77	0	9	85	0	8 (7–8)	80
Endpoint 4. Time to tumour progression	0	8 (6–9)	67	3 (4)	8	75	0	7.5 (6–9)	70
Endpoint 5. Distant disease-free survival	0	6.5 (5–8)	55	4 (6)	7	71	1 (10)	5 (5–7)	30
Endpoint 6. Time to treatment failure	0	5 (3–8)	33	7 (10)	6	71	2 (20)	5 (3–7)	20
Endpoint 7. Cancer specific survival	0	7 (5–9)	67	2 (3)	6	73	0	6 (5–8)	70
Endpoint 8. Biochemical recurrence	0	7.5 (6–9)	67	0	7	70	0	7 (6–8)	60
Endpoint 9. Return of intended oncological therapy	0	6 (3–7)	33	3 (4)	8	77	1 (10)	6.5 (5–9)	50
Endpoint 10. Days alive out of hospital at 90 days	0	8 (7–9)	77	5 (8)	8 (7–9)	73	1 (10)	8 (7–9)	80

three of the Delphi process were 89% (*n*=8), 82% (*n*=73), and 100% (*n*=10), respectively.

Endpoints and definitions presented at Delphi round three are shown in Table 2. Table 3 presents these endpoints as they might be used in studies of oncological outcomes.

Discussion

Standardised cancer-related endpoints within the context of onco-anaesthesia and perioperative medicine have not been clearly defined. Establishing standardised endpoints for clinical trials evaluating the effect of anaesthesia on cancer progression differs from other areas of anaesthetic research. Aside from the lack of consistency in endpoint definitions in the existing oncology literature,[9,10] different cancers types have variable natural histories[19] and long follow-up times are often required.[20] Moreover, cancer is a complex multisystem disease and multiple treatments are frequently given in parallel (e.g. surgery in the setting of neoadjuvant/adjuvant chemo-radiotherapy and immunotherapy).[13]

To establish standardisation of endpoints and definitions, we performed a systematic review and used a Delphi process to obtain consensus. Our aim was to achieve consensus using international expertise in the study of anaesthesia outcomes with representation from different countries and healthcare systems. Ultimately, the cancer theme subgroup agreed to a consensus definition for cancer (based on the NIH definition)[18] and identified six consensus standardised endpoints for use in perioperative trials examining cancer outcomes.

Consensus endpoints and definitions are as follows:

1. Overall survival: *the time elapsed between randomisation and death of any cause*. Overall survival (OS) has previously been recognised as the 'gold standard' primary outcome in clinical trials[19] and is the most objectively defined endpoint. It is the

Table 2 Endpoints and definitions presented at Delphi round three

Endpoint presented	Definition
Overall survival	The time elapsed between randomisation and death from any cause.
Cancer health-related quality of life	Evaluation of cancer-related quality of life through validated instruments during course of cancer diagnosis and treatment.
Disease free survival	The time elapsed between (surgical) treatment and tumour progression or death from any cause.
Time to tumour progression	The time elapsed between treatment and tumour progression or death from tumour.
Distant disease-free survival	The time elapsed between treatment and confirmed metastatic disease or death from any cause. Excludes local or regional recurrence.
Time to treatment failure	The time elapsed between treatment and second cancer, local or regional recurrence, distant metastases, or death from cancer and treatment-related death.
Cancer specific survival	The time elapsed between treatment and death from specific cancer. Excludes local or regional recurrences, distant metastases and second primary cancer, and death from other causes.
Biochemical recurrence	The time elapsed between treatment and biochemical evidence of tumour progression.
Return of intended oncologic therapy	Time between surgery and commencing (or re-commencing) chemotherapy or radiation therapy after the operation. Expanded return of intended oncological therapy parameters could include: time to initiation of adjuvant therapy, total dose of each adjuvant drug, number of cycles of adjuvant therapy completed, and duration of adjuvant therapy.
Days alive and out of hospital at 90 days	Number of days not in hospital or other nursing facility, counted from day of surgery until 90 days after surgery.

Table 3 Suggested events for endpoints presented at Delphi round 3. OS, overall survival; cancer HRQoL, cancer health-related quality of life; DFS, disease-free survival; TTP, time to tumour progression; DDFS, distant disease-free survival; TTF, time to treatment failure; CSS, cancer specific survival; BCR, biochemical recurrence; RIOT, return of intended oncological therapy; DAOH-90, days alive and out of hospital at 90 days; E, event; I, ignore; C, censor

Event	Endpoint									
	OS	Cancer HRQoL	DFS	TTP	DDFS	TTF	CSS	BCR	RIOT	DAOH-90
Loco-regional recurrence	I	I	E	E	I	E	I	I	I	I
Distant metastasis	I	I	E	E	E	E	I	I	I	I
Second primary, same cancer	I	I	E	I	E	E	I	I	I	I
Second primary, other cancer	I	I	I	I	I	I	I	I	I	I
Death from same cancer	E	C	E	E	E	E	E	C	I	E
Death from other cancer	E	C	E	C	E	C	E	C	I	E
Non-cancer related death	E	C	E	C	E	C	C	C	I	E
Treatment-related death	E	C	E	C	E	E	E	C	I	E
Loss to follow-up	C	C	C	C	C	C	C	C	C	C

only validated 'time to event' endpoint in cancer clinical trials. OS is of direct benefit to patients and can be recorded accurately and unambiguously. Provided that quality of life is not diminished, OS offers the greatest gains from a clinical perspective.

There are some limitations to the use of OS as a primary endpoint. Using OS as the primary endpoint increases the duration and cost of a clinical trial, usually outlasts funding and does not keep pace with the changing landscape of cancer therapies.[20] This is of particular relevance in cancers with good prognosis and for cancers where effective treatments already exist.[13] It should be noted that the endpoint is not necessarily specific to cancer outcome. For instance, if a patient dies in a road traffic accident, OS is affected even though the cause of death is not a result of cancer.

2. Cancer health-related quality of life: *evaluation of cancer-related health related quality of life (HRQoL) using validated instruments during course of cancer diagnosis and treatment*. HRQoL is a patient-centred clinical variable. It is a measure that takes into account the treatment outcome in combination with the patients' physical, social, mental, and overall satisfaction.[21] As an outcome, improved HRQoL has direct benefit to patients. It also confers the ability to conduct studies of shorter duration.[20] There are limitations to using HRQoL questionnaires. Many different, heterogeneous HRQoL questionnaires are available, they are a subjective measure, they can represent incomplete data, and there is a lack of standardisation in analysing results.[22] Despite these limitations, patient-reported outcomes have been used in a significant number of oncology treatment approvals.[23] After e-mail discussion between participants during the Delphi process, the endpoint was modified to specify a 'cancer related QoL instrument' to reflect how this measure describes the patient-centred effect of the cancer and oncological treatment taken together. Several cancer working groups are developing standardised core sets on patient symptoms, and it is essential that similar sets be explored in the perioperative setting after major cancer surgery and considered for inclusion in clinical trials where patient-reported outcomes are measured.

3. Disease-free survival: *the time elapsed between treatment and tumour progression or death from any cause*. In the setting of curative solid tumour surgical treatment, disease-free survival (DFS) is an important endpoint, particularly in the future design of trials testing the hypothesis that anaesthetic technique during primary (curative-intent) cancer surgery might affect DFS. Indeed, DFS at 3 yr has been proposed as a pragmatic endpoint that is likely to have similar sensitivity as DFS at 5 yr and therefore reduce time to trial endpoint and costs.[10,11] Three-yr median DFS seems to have best correlation with OS at 5 yr (but is tumour type and stage dependent). Interim analysis using 2 yr DFS may be an adequate predictor of 5-yr DFS and therefore could help investigators terminate a futile trial early, therefore saving resources. DFS with 1 yr minimum follow-up has been shown to have a 'perfect' negative predictive of effect on 5 yr OS, further allowing trial resources to be reallocated.[10,11]

Progression free survival (PFS) is more appropriately used in the setting of medical oncology, where the term is used to refer to patients with existing recurrence or metastasis, which is controlled like a chronic disease.[24] PFS is a tumour-centred, surrogate endpoint in cancer trials.[10] It has the benefits of being available earlier and more frequently than OS, and treatments initiated after tumour progression do not influence PFS. Although PFS is an attractive endpoint, its use does have limitations, including measurement error and an ingrained exposure to bias and subjectivity.[25] Differences in an observed PFS can be a result of differences in subjective assessment of what constitutes progression and might not reflect clinically significant improvement.

4. Time to tumour progression: *the time elapsed between treatment and tumour progression or death from tumour (or cancer therapy)*. A very similar endpoint to PFS, the time to tumour progression (TTP) can also be used as a potential surrogate endpoint for overall survival.[26] PFS differs from TTP in that it includes deaths as a result of causes other than cancer.[8,26] While the assumption that retarding tumour growth is beneficial is an intuitively attractive one, there is limited definitive evidence that links an improvement in OS with an improvement with progression endpoints.[27]

5. Cancer specific survival: *the time elapsed between treatment and death from specific cancer*. The application of cancer-specific survival (CSS) is most appropriate where a recurrence of the primary disease is an important factor in the cause of death of the study population. In patient cohorts with high tumour burden or staging, OS may reflect CSS with reasonable accuracy but this only occurs if the number of deaths unrelated to cancer is small[28] and studies using CSS as an endpoint may require larger numbers to elucidate significant differences

between groups. CSS is considered a 'net' measure as it excludes competing causes of death other than those attributable to the cancer (and cancer-related therapies).[28] This endpoint has found widespread use in clinical studies, as the cause of death is usually readily available and accurately determined.[29,30]

6. Days alive out of hospital at 90 days: *number of days not in hospital, counted from day of surgery until 90 days after surgery*. Days alive and out of hospital (DAOH), as an endpoint, has the advantage of combining the duration of the index hospital stays, the burden of subsequently required hospital admissions and mortality into one endpoint.[31] When used in a perioperative context, DAOH should be maximised in those patients who rapidly recover without complication, delay in discharge, or loss of function.[32] Using DOAH therefore allows investigators to focus on an outcome which is of reflective of patient values.[32,33] There was widespread approval for inclusion of this endpoint within the subgroup with some discussion as to the optimal timeframe. To date, DOAH has been used in both oncological and non-oncological clinical studies.[34–37] This endpoint, DAOH at 90 days, would be likely to also have direct association with the endpoint RIOT, which is postoperative adjuvant therapies. This endpoint did not achieve the consensus criteria for inclusion. However, several studies, albeit retrospective, suggest that suboptimal RIOT endpoints (e.g. time to initiation of adjuvant therapy, total dose of each adjuvant drug, number of cycles of adjuvant therapy completed, and duration of adjuvant therapy) associate with poorer cancer outcomes, and that postoperative complications are a key driver of reduced RIOT rates.

Limitations to our data could include the absence of surgical and medical oncologists from the group convened, and that the top four clinical oncology journals could reasonably have been included among the journals screened for relevant endpoints. Similarly, our data fields were limited to cancer surgery for abdominal cancers.

Conclusions

Initially, 10 candidate endpoints and definitions were considered by an international group experienced in perioperative clinical trials related to cancer. Using a Delhi process for refinement and further development, six consensus endpoints were established. Standardising endpoints should support uniformity in data analysis and reporting and lead to improved benchmarking in future trials. Our recommendation is that these six endpoints be given preferential consideration when designing clinical trials assessing the impact of perioperative events on longer-term outcomes in cancer.

Authors' contributions

Literature search: J.F., M.Z.J., D.J.B.
Analysis of Delphi responses: J.F.D.J.B.
Identification of candidate endpoints: M.Z.J., D.J.B. K.L., B.R., T.S., D.S., A.K., N.P., P.M.
Manuscript inclusion eligibility confirmation: M.Z.J., K.L., B.R., T.S., D.S., A.K., N.P., P.M., D.J.B.
Participation in the Delphi survey: All authors.
Analysis and co-ordination of responses after each round: D.J.B.
Final manuscript drafting: all authors.

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Declarations of interest

D.J.B. and P.M. are editorial board members and K.L. is an associate board member of the *British Journal of Anaesthesia*. The other authors do not report any conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2018.03.020.

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