EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Design and Analysis of Patient Reported Outcomes and Health-Related Quality of Life Endpoints in Cancer Randomized Controlled Trials

Madeline Pe, PhD
Specialist in Quality of Life
Quality of Life Department
European Organisation for Research and Treatment of Cancer

Why assess PROs and HRQOL in cancer clinical trials?

Why assess PROs and HRQOL in cancer clinical trials?

According to the World Health Organization (WHO), the main goals of cancer diagnosis and treatment programs are to:

- cure
- considerably prolong the life of patients
- ensure the best possible quality of life for cancer survivors.

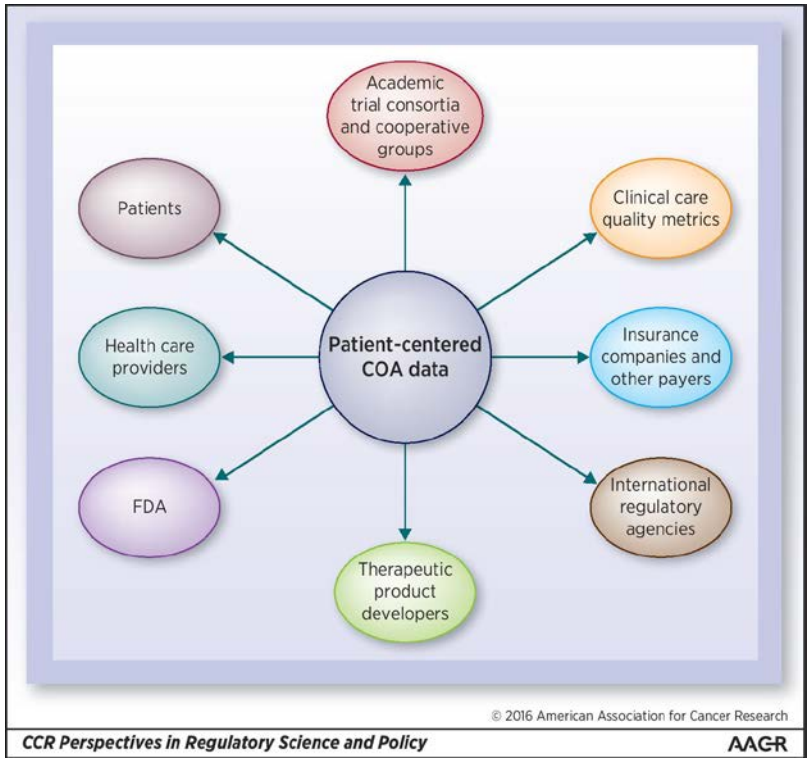
Why assess PROs and HRQOL in cancer clinical trials?

- Supplement survival and tumor response endpoints to gain a better picture of the overall benefit/risk assessment of a new treatment

- Provide future patients a more informed choice about their treatment options

Benefit of PRO and HRQOL assessment is well-acknowledged

Multiple stakeholders are interested in PRO data, whether it is based on a single PRO domain or a more comprehensive assessment of HRQOL



Kluetz et al., 2016 *Clinical Cancer Research; FDA perspective*

Consequence

- Increased collection of PROs, assessing patients' reported symptoms, functioning and HRQOL

- But there were no set standards on how to analyze these data

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bevacizumab plus Radiotherapy–Temozolomide for Newly Diagnosed Glioblastoma

Olivier L. Chinot, M.D., Wolfgang Wick, M.D., Warren Mason, M.D., Roger Henriksson, M.D., Frank Saran, M.D., Ryo Nishikawa, M.D., Antoine F. Carpentier, M.D., Ph.D., Khe Hoang-Xuan, M.D., Ph.D., Petr Kavan, M.D., Ph.D., Dana Cernea, Ph.D., Alba A. Brandes, M.D., Magalie Hilton, M.Sc., Lauren Abrey, M.D., and Timothy Cloughesy, M.D.

ABSTRACT

BACKGROUND

Standard therapy for newly diagnosed glioblastoma is radiotherapy plus temozolomide. In this phase 3 study, we evaluated the effect of the addition of bevacizumab to radiotherapy–temozolomide for the treatment of newly diagnosed glioblastoma.

METHODS

We randomly assigned patients with supratentorial glioblastoma to receive intravenous bevacizumab (10 mg per kilogram of body weight every 2 weeks) or placebo, plus radiotherapy (2 Gy 5 days a week; maximum, 60 Gy) and oral temozolomide (75 mg per square meter of body-surface area per day) for 6 weeks. After a 28-day treatment break, maintenance bevacizumab (10 mg per kilogram intravenously every 2 weeks) or placebo, plus temozolomide (150 to 200 mg per square meter per day for 5 days), was continued for six 4-week cycles, followed by bevacizumab monotherapy (15 mg per kilogram intravenously every 3 weeks) or placebo until the disease progressed or unacceptable toxic effects developed. The coprimary end points were investigator-assessed progression-free survival and overall survival.

RESULTS

A total of 458 patients were assigned to the bevacizumab group, and 463 patients to the placebo group. The median progression-free survival was longer in the bevacizumab group than in the placebo group (10.6 months vs. 6.2 months; stratified hazard ratio for progression or death, 0.64; 95% confidence interval [CI], 0.55 to 0.74; P<0.001). The benefit with respect to progression-free survival was observed across subgroups. Overall survival did not differ significantly between groups (stratified hazard ratio for death, 0.88; 95% CI, 0.76 to 1.02; P=0.10). The respective overall sur-

From Aix-Marseille University, Assistance Publique–Hôpitaux de Marseille, Service de Neuro-Oncologie, Centre Hospitaliere Universitaire Timone, Marseille (O.L.C.), UFR de Santé, Médecine et Biologie Humaine, Bobigny (A.F.C.), and Assistance Publique–Hôpitaux de Paris (AP–HP), Hôpital Avicenne, Service de Neurologie, Université Paris 13 (A.F.C.), and AP–HP, Université Pierre-et-Marie-Curie, Group Hospitalier Pitié-Salpêtrière (K.H.-X.), Paris — all in France; University Hospital of Heidelberg, Department of Neurooncology, and German Cancer Consortium, German Cancer Research Center, Heidelberg, Germany (W.W.); Princess Margaret Hospital, Toronto (W.M.), and McGill University, Montreal (P.K.) — both in Canada; Regional Cancer Center, Stockholm Gotland, Karolinska, Stockholm, and the Department of Radiation Sciences and Oncology, Umeå University, Umeå — both in Sweden (R.H.); the Royal Marsden National Health Service Foundation Trust, Sutton, Surrey, United Kingdom (F.S.); Saitama Medical University, Saitama, Japan (R.N.); Oncology Institute "Ion Chiricuta," Cluj-Napoca, Romania (D.C.); Medical Oncology Department, Azienda Unità

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 20, 2014 VOL. 370 NO. 8

A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma

Mark R. Gilbert, M.D., James J. Dignam, Ph.D., Terri S. Armstrong, Ph.D., A.N.P.-B.C., Jeffrey S. Wefel, Ph.D., Deborah T. Blumenthal, M.D., Michael A. Vogelbaum, M.D., Ph.D., Howard Colman, M.D., Ph.D., Arnab Chakravarti, M.D., Stephanie Pugh, Ph.D., Minhee Won, M.A., Robert Jeraj, Ph.D., Paul D. Brown, M.D., Kurt A. Jaeckle, M.D., David Schiff, M.D., Volker W. Stieber, M.D., David G. Brachman, M.D., Maria Werner-Wasik, M.D., Ivo W. Tremont-Lukats, M.D., Erik P. Sulman, M.D., Kenneth D. Aldape, M.D., Walter J. Curran, Jr., M.D., and Minesh P. Mehta, M.D.

ABSTRACT

BACKGROUND

Concurrent treatment with temozolomide and radiotherapy followed by maintenance temozolomide is the standard of care for patients with newly diagnosed glioblastoma. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor A, is currently approved for recurrent glioblastoma. Whether the addition of bevacizumab would improve survival among patients with newly diagnosed glioblastoma is not known.

METHODS

In this randomized, double-blind, placebo-controlled trial, we treated adults who had centrally confirmed glioblastoma with radiotherapy (60 Gy) and daily temozolomide. Treatment with bevacizumab or placebo began during week 4 of radiotherapy and was continued for up to 12 cycles of maintenance chemotherapy. At disease progression, the assigned treatment was revealed, and bevacizumab therapy could be initiated or continued. The trial was designed to detect a 25% reduction in the risk of death and a 30% reduction in the risk of progression or death, the two coprimary end points, with the addition of bevacizumab.

RESULTS

A total of 978 patients were registered, and 637 underwent randomization. There was no significant difference in the duration of overall survival between the bevacizumab

From the University of Texas M.D. Anderson Cancer Center (M.R.G., T.S.A., J.S.W., P.D.B., I.W.T.-L., E.P.S., K.D.A.) and the University of Texas Health Science Center School of Nursing (T.S.A.), Houston; American College of Radiology (J.J.D., S.P., M.W.) and Thomas Jefferson University (M.W.-W.) — both in Philadelphia; the University of Chicago, Chicago (J.J.D.); Tel-Aviv Medical Center, Tel Aviv, Israel (D.T.B.); Cleveland Clinic, Cleveland (M.A.V.); the University of Utah, Salt Lake City (H.C.); Ohio State University, Columbus (A.C.); University of Wisconsin, Madison (R.J.); Mayo Clinic, Jacksonville, FL (K.A.J.); University of Virginia, Charlottesville (D.S.); Southeast Cancer Control Consortium, Winston-Salem, NC (V.W.S.); Barrow Neurologic Institute, Phoenix, AZ (D.G.B.); Emory University, Atlanta (W.J.C.); and the University of Maryland, Baltimore (M.P.M.). Address reprint requests to Dr. Gilbert at the Department of Neuro-Oncology, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Unit 431, Houston

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Bevacizumab in glioblastoma

	RTOG 0825 (Gilbert et al NEJM, 2014)	AVAglio (Chinot et al NEJM, 2014)
Population	Newly diagnosed glioblastoma with central histological confirmation	
Treatment	TMZ+RT+placebo vs TMZ+RT+Bev	
Sample size	309 vs 312	463 vs 458
Efficacy	OS: 16.1 vs 15.7 mths (HR=1.13 [0.93-1.37]; p=0.11) PFS: 7.3 vs 10.7 mths (HR=0.79 [0.66-0.94]; p=0.004)	OS: 16.7 vs 16.8 mths (HR=0.88 [0.76-1.02]; p=0.10) PFS: 6.2 vs 10.6 mths (HR=0.64 [0.55-0.74]; p<0.001)
HRQoL	**"Longitudinal evaluation also revealed greater deterioration in the bevacizumab group…"**	**"In the prespecified primary analysis, deterioration-free survival was significantly longer among patients in the bevacizumab group than among those in the placebo group …"**

Slide from Conrad Cooms MSc

EDITORIAL

CORRESPONDENCE

Bev

THIS WEEK'S LETTERS

TO THE EDITOR: P
for cancer live no
clinical benefits
tween similar stu
for glioblastoma,
gy Group (RTOG)
et al. (Feb. 20 issu
toma (AVAglio) tr
leagues in the sam
and their finding
though both trial
survival and simi
mab, AVAglio, th
ceutical company,
of-life outcomes,
sponsored by th
showed decrease
claimed that thei
plained," in part,
about quality of li
they provided no q
assertion. We are

2048

J Med 2014;370:709-22.
3. Drazen JM. Open data.
4. Fine HA. Bevacizumab in
N Engl J Med 2014;370:764-
5. Ross JS, Krumholz HM.
ence through data sharing
2013;309:1355-6.

THIS WEEK'S LETTERS

Glioblaston
lethal tumo
vival of onl
aggressive
apeutic tai
characteris
phase 2 tr
monoclona
endothelial
with recurr
showed dra
on magneti
casionally,
with a recu
treatment e
bevacizuma
tion (FDA)
glioblaston
concern sui
bevacizuma
of response
much of th
function of
tion rather
highly infil
mas treatec

VOLUME 34 · NUMBER 3 · JANUARY 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Similar Trials With Differing Outcomes: Reconciliation in Glioblastoma

TO THE EDITOR: Taphoorn et al[1] report a health-related quality of life (HRQOL) analysis of the randomized prospective trial AVAglio (Avastin in Glioblastoma), a clinical study that compared standard of care (SOC; radiation and concurrent and adjuvant temozolomide) with or without bevacizumab (BEV) for newly diagnosed glioblastoma (GBM).[1,2] The authors conclude that, in patients treated on the experimental arm with BEV in which a progression-free survival (PFS) but not an overall survival (OS) benefit was seen, the HRQOL outcome (ie, maintenance of the baseline score) was similar to that of patients in the SOC arm. On the basis of this analysis, the AVAglio investigators posited that a stable HRQOL until disease progression (the primary end point of the study) is clinically relevant in patients with newly diagnosed GBM. Furthermore, because PFS was prolonged in patients treated with BEV + SOC compared with SOC alone, an argument can be made for a clinical benefit in patients treated with BEV + SOC, notwithstanding the inability of the trial to demonstrate an OS advantage. Several comments seem apropos.

The study used the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30; a 30-item questionnaire) and the EORTC Quality of Life Questionnaire BN20 (QLQ-BN20; a 20-item questionnaire) instruments, in which five preselected scales (believed to be most relevant in GBM) were used for analysis. A raw score was calculated from a given scale and then was transformed as a standardized raw score of 0 to 100. Baseline scores were computed and compared, and scores were obtained at predetermined time points during the conduct of the trial. A change in 10 points from baseline was considered clinically meaningful. At the time of disease progression, no additional HRQOL assessments were made, so the analysis was confined to the time without disease progression. Two methods of determining the validity of the findings were used. Both methods were defined by a 10-point decrement in HRQOL compared with baseline; in one, progressive disease or death was used as a deterioration event. Not evident in the analysis was how baseline HRQOL in patients compared with age-matched controls. In essentially all of the BEV to the first-line therapy setting in the treatment of patients with GBM.

By comparison, the parallel Radiation Therapy Oncology Group (RTOG) study RTOG 0825, which used a similar though slightly different trial design, came to different conclusions about the benefit of BEV added to the SOC.[5] RTOG 0825 was unable to show a statistically significant difference in either PFS or OS in the BEV arm, and data also suggested deterioration in a composite score (net clinical benefit) that included both patient-reported outcome tools and neurocognition. Net clinical benefit, an outcome not mandated by protocol but used in 80% of all study patients, comprised the EORTC QLC-C30 and -BN20 instruments as used in AVAglio. In addition, RTOG 0825 used a neurocognitive function battery (arguably the most important functional test) and a brain tumor symptom index, the MD Anderson Symptom Inventory-Brain Tumor, for computation of net clinical benefit. Similar to AVAglio, baseline scores were compared with those obtained during treatment. The end point differed, however, in that RTOG 0825 compared scores at a prespecified end point of 46 weeks postsurgery and in patients free of progressive disease. Across all domains, HRQOL, neurocognitive function and symptom index, patients who received BEV, and patients who were free of disease progression at 46 weeks performed less well than patients who received SOC only. The challenge is how to reconcile these differing conclusions between AVAglio and RTOG 0825. There are distinct methodological and statistical differences; for example, PFS was not statistically improved in RTOG 0825, in part because of the statistical weighting of the coprimary end points of the study (PFS and OS). Because PFS, OS, and net clinical benefit did not improve in the BEV arm, the authors of RTOG 0825 concluded that there was no benefit to up-front BEV in newly diagnosed GBM and suggested that the current use of BEV in GBM be confined to patients with recurrent GBM. The cost of adjuvant BEV in conjunction with the inability to improve OS, in large part because of the effectiveness of BEV as salvage therapy, would suggest that the current use of BEV in GBM remain unchanged.[6,7]

Marc C. Chamberlain
University of Washington, Seattle, WA

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Disclosures provided by the authors are available with this article at www.jco.org

differences in data acquisition, analytic methods, and extent of surgical resection could have influenced these data, the true reason for the difference remains an enigma. This discrepancy is neither trivial nor academic, because if bevacizumab is associated with an increase in and maintenance of quality of life and performance status, then a strong argument can be made for its use as part of the initial treatment of glioblastoma regardless of its effect on survival. By contrast, if bevacizumab is associated with worsening neurocognitive function, then its use as part of initial therapy cannot be widely advocated, especially in light of its questionable effects on survival.

So where do we go from here? First, and most immediately, the investigators of the RTOG 0825 and AVAglio trials need to share their raw data with each other and with independent investigators (including the FDA) to try to resolve the question of the true effects of bevacizumab on quality of life and neurocognitive function. Future efforts should focus on identifying imaging markers and biomarkers that may be predictive of a response to bevacizumab in an individual patient.[10] In addition, new and robust imaging and clinical end points need to be identified and incorporated into future clinical trials of gliomas, given the complex effects of anti-VEGF agents on the images obtained with the use of routine MRI and the questionable usefulness of our current patient-reported outcomes, as exemplified by the RTOG 0825 and AVAglio trials. Future trials of bevacizumab in glioblastoma will also need to explore its activity in combination with newer agents that inhibit glioma invasion (e.g., c-Met inhibitors), given the increased tumor invasiveness seen with bevacizumab at the time of progression.[6]

Finally, it is worth noting that despite its limitations, bevacizumab remains the single most important therapeutic agent for glioblastoma since temozolomide. Ongoing and future trials will better define how and when it should be used in this population of patients for whom so few treatment options currently exist.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the New York University (NYU) Cancer Institute, NYU Langone Medical Center, New York.

1. Jain RK, di Tomaso E, Duda DG, Loeffler JS, Sorensen AG, Batchelor TT. Angiogenesis in brain tumours. Nat Rev Neurosci 2007;8:610-22.
2. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009;27:4733-40.
3. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol 2009; 27:740-5.
4. Cohen MH, Shen YL, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. Oncologist 2009;14:1131-8.
5. LaViolette PS, Cohen AD, Prah MA, et al. Vascular change measured with independent component analysis of dynamic susceptibility contrast MRI predicts bevacizumab response in high-grade glioma. Neuro Oncol 2013;15:442-50.
6. Lu KV, Chang JP, Parachoniak CA, et al. VEGF inhibits tumor cell invasion and mesenchymal transition through a MET/VEGFR2 complex. Cancer Cell 2012;22:21-35.
7. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy–temozolomide for newly diagnosed glioblastoma. N Engl J Med 2014;370:709-22.
8. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014;370:699-708.
9. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
10. Harris RJ, Cloughesy TF, Pope WB, et al. 18F-FDOPA and 18F-FLT positron emission tomography parametric response maps predict response in recurrent malignant gliomas treated with bevacizumab. Neuro Oncol 2012;14:1079-89.

DOI: 10.1056/NEJMe1313309

Why it matters for clinical practice

Conclusion about usefulness of HRQOL to assess clinical benefit of new therapies

Conclusions from various stakeholders…

- PRO and HRQOL measures and assessments are unreliable.
- Findings from PROs and HRQOL are not robust.
- It is difficult to draw conclusions about PROs and HRQOL when evaluating cancer treatments.

But…

it is also possible that different design and statistical analysis decisions led to different results

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Bevacizumab in glioblastoma*

	RTOG 0825 (Gilbert et al NEJM, 2014)	AVAglio (Chinot et al NEJM, 2014)
Research hypothesis	Broad: differential acute effects [between arms] on HRQOL	Broad: to compare HRQOL between treatment arms
Endpoint	Between group difference at 46 weeks (~10 months)	DFS: time to >/10 point deterioration from baseline without improvement; disease progression; death *(Result: ~4 months – ~8 months)*
Statistical Method	Linear mixed model	Time to event analysis
Analysis population	mITT: Only patients free of disease at 46 weeks (20% “at risk” patients)	ITT (All patients)
Clinical relevance	Between group difference (not specified)	Within-individual deterioration (>/10 points deterioration from baseline)

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

In a nutshell:

What is the issue?	**No standardization in the use and analysis of PRO and HRQOL data** from cancer clinical trials.
Why is this a problem?	Lack of standardization leads to variation in analysis methodology causing inefficient resource use, fragmented reporting and interpretational barriers.
What is the impact on PRO and HRQoL field?	This could undermine the credibility of the PRO and HRQOL field since it can lead to **differences in interpretation of the findings depending on how the data is analyzed**.
What is the proposed solution?	To develop, by consensus, and recommend **international standards for the analysis of PRO and HRQOL data** from cancer clinical trials.

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

SISAQOL initiative was born

Collaborative work coordinated by the EORTC

Academic Researchers / Statisticians / Clinicians	Regulatory Bodies	Medical Institutes	Industry Representatives
Australia Austria Belgium Canada Denmark France Germany Netherlands Sweden UK USA	FDA (USA) EMA (Europe) Health Canada (Canada) Institute for Quality and Efficiency in Health Care (Germany)	MD Anderson Mayo Clinic (USA) National Cancer Institute (USA) EORTC (Belgium)	Adelphi Boehringer-Ingelheim Genentech

Academic / Learned Societies

International Society for Quality of Life Research (ISOQOL)
Consolidated Standards of Reporting Trials (CONSORT-PRO)
International Society for Pharmaeconomics and Outcomes Research (ISPOR)
Multinational Association of Supportive Care in Cancer (MASCC)

Journal	Lancet Oncology	Patient Representative	International Brain Tumour Alliance

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

The SISAQOL Question

- If we want to draw conclusions about PROs and HRQOL in cancer clinical trials, are we rigorous on how we analyze PRO and HRQOL data?
- Is there a need to standardize the analyses of HRQOL and other PRO data?
- If yes, can we develop guidelines and recommendations for this?

The SISAQOL Question

- **If we want to draw conclusions about PROs and HRQOL in cancer clinical trials, are we rigorous on how we analyze PRO and HRQOL data?**
- Is there a need to standardize the analyses of HRQOL and other PRO data?
- If yes, can we develop guidelines and recommendations for this?

Evidence from systematic reviews

Metastatic breast cancer review (RCT= 66)

- 88% of the RCTs did not report a specific hypothesis
- At least 10 different analyses methods
  - 23% did not report their statistical method!
- 58% of the RCTs did not report the clinical relevance of their findings
- 73% did not report how they handled missing data
- …

Pe, et al., for the SISAQOL Consortium. *The Lancet Oncology. In press.*

The SISAQOL Question

- If we want to draw conclusions about PROs and HRQOL in cancer clinical trials, are we rigorous on how we analyze PRO and HRQOL data**?**
- **Is there a need to standardize the analyses of HRQOL and other PRO data?**
- If yes, can we develop guidelines and recommendations for this?

Patients' view

"Cancer patients and their families are not only concerned about a cure, but also about the symptoms (e.g. pain, fatigue) and other physical and emotional consequences that come along with the disease and treatment, impacting the daily life of the patient…"

STANDARDIZING ANALYSIS OF PATIENT REPORTED OUTCOMES RESEARCH

Patient Reported Outcomes (PROs) have become a standard part of clinical trials, but the way the data from PROs is analyzed can affect trial results. To address this problem, the European Organization for Research and Treatment of Cancer (EORTC) built a multi-stakeholder coalition to make recommendations on standardizing these processes. Kathy Oliver of the International Brain Tumour Alliance (IBTA) and Andrew Bottomley and Madeline Pe from the EORTC explain why a standard approach is needed and how advocacy involvement has helped.

Patient Reported Outcor
major tool in understanc
its treatments on patient
patients, physicians and
the relative impact of dif
patient's functioning, syr
standard PRO tools are
but at the end of a trial,
analyze and interpret thi
those at the EORTC start
yet, no international stan
the results from these di

"We have conducted hu
the years," says Andrew
and Head of the Quality
"When we publish the re

Peer rev

Working together to foster better patient-centred cancer care

"Setting International Standards in Analysing Patient-Reported Outcomes and Quality Of Life Endpoints Data" (SISAQOL)

Kathy Oliver, International Brain Tumour Alliance and Carmen Peuters, EORTC on behalf of the SISAQOL Consortium*

*The members of the Consortium are named in the reference.

Above: Attendees of the SISAQOL Consortium meeting held in Amsterdam in January 2017

A patient's health-related quality of life during treatment and in the long-term is important. Cancer patients and their families are not only concerned about a cure, but also about the symptoms (e.g. pain, fatigue) and other physical and emotional consequences that come along with the disease and treatment, impacting the daily life of the patient. It is therefore essential that these health aspects are taken into account when evaluating any new therapies. Questionnaires to measure health-related quality of life are increasingly being used throughout cancer research. Patients devote their time to completing these questionnaires, but often it is unclear how the responses are analysed and reported. Thanks to the input from and collaboration with patients, the Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) project might offer a solution.

SISAQOL

The Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) initiative has been established to create consistency in the analysis and reporting of patient-reported data in cancer clinical trials. An international, multidisciplinary Consortium was assembled by the European Organisation for Research and Treatment of Cancer (EORTC). Not only were leading statisticians and researchers from various disciplines including psychology and medicine involved, but also key individuals from various international oncological and medical societies; advisory and regulatory bodies; academic societies; the bio-pharmaceutical industry; cancer institutes; and, crucially, patient advocacy organisations, including brain tumour patient advocates. They are now all working together to develop guidelines for the analysis and interpretation of health-related quality of life and other patient-reported outcome data in cancer research.

What are health-related quality of life and other patient-reported outcomes?

A patient-reported outcome refers to any report about a patient's health condition that comes directly from the patient, without the interpretation of the patient's response by anyone

Brain Tumour

Clinician's view

As an oncologist, when I sit with patients to discuss starting a new chemotherapy regimen, their first questions are often "How will it make me feel?" and "How did patients like me feel with this treatment?"

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

AUGUST 1, 2013

Toward Patient-Centered Drug Development in Oncology

Ethan Basch, M.D.

As an oncologist, when I sit with patients to discuss starting a new chemotherapy regimen, their first questions are often "How will it make me feel?" and "How did patients like me feel with this treatment?" Regrettably, this information is generally missing from U.S. drug labels and from published reports of clinical trials — the two information sources most commonly available to people trying to understand the clinical effects of cancer drugs.

In 2011, 15 hematology–oncology drugs were approved by the U.S. Food and Drug Administration (FDA). In only one case — that of ruxolitinib for the management of myelofibrosis — was symptom information included in the portion of the label that manufacturers can legally use for marketing purposes. In fact, ruxolitinib was the first cancer therapeutic in more than a decade for which symptom information was included in a U.S. drug label.

Cancer-drug labels stand in sharp contrast to labels for other types of drugs, about 25% of which list the drugs' effects on patients' symptoms or functioning.[1] That disparity is surprising, given how common symptoms and functional impairment are in patients with cancer and how toxic oncology drugs can be.

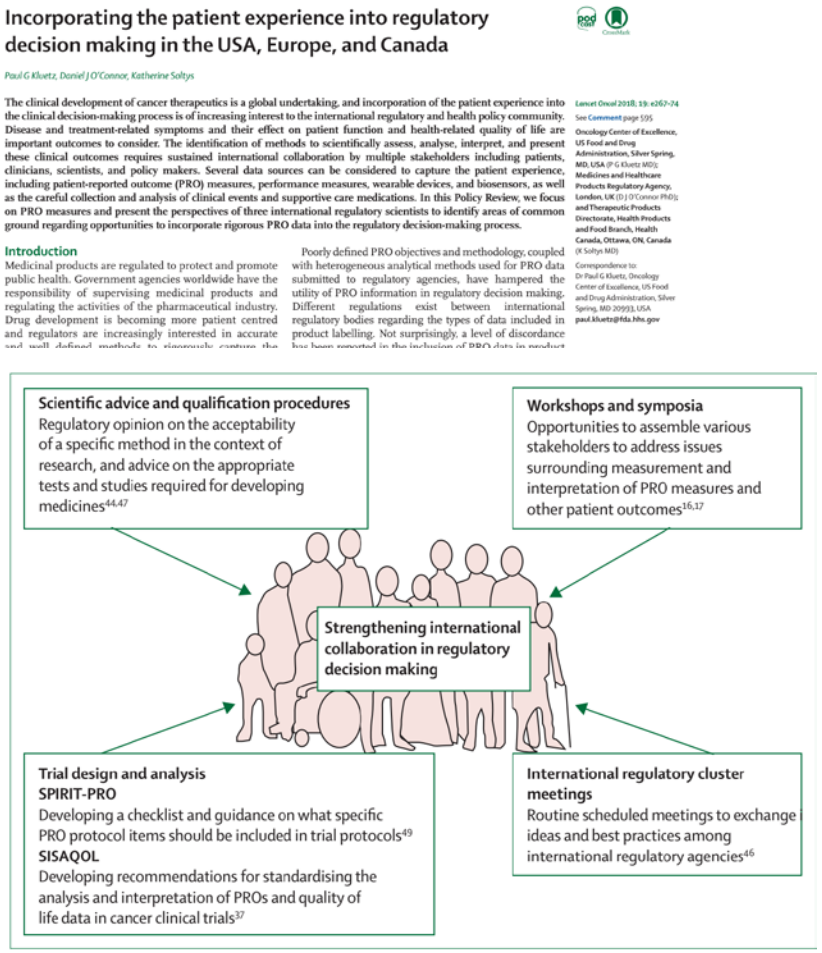
The FDA has taken several recent steps toward encouraging inclusion of the patient perspective in drug development. It issued highly influential guidance on the use of patient-reported outcomes (PROs) in drug development,[2] collaborated with the Critical Path Institute and industry to form the PRO Consortium with the aim of developing robust symptom-measurement tools, and obtained support from Congress in the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA) to expand its internal expertise on the methodology of measuring PROs. (Unfortunately, allocated PDUFA funds have been withheld, which substantially impairs the FDA's ability to implement planned patient-centered programs.)

These FDA efforts are evident in the ruxolitinib label and in the label for abiraterone acetate, approved this year for metastatic prostate cancer, which describes beneficial delays in time to the development of pain and the need for opioid use. Yet in preapproval trials in patients with cancer, symptom or functional-status evaluations that meet the FDA's standards remain rare.

Some experts have argued that the FDA has raised the methodologic bar too high, whereas others accuse the pharmaceutical industry of paying too little attention to patients' experiences. The bottom line is that both regulators and industry continue to prioritize survival-based end points rather

Regulators' view

"Drug development is becoming more **patient-centered** and regulators are increasingly interested in accurate and well-defined methods to rigorously capture the patients' perspective throughout the drug development process"



Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada

Paul G Kluetz, Daniel J O'Connor, Katherine Soltys

The clinical development of cancer therapeutics is a global undertaking, and incorporation of the patient experience into the clinical decision-making process is of increasing interest to the international regulatory and health policy community. Disease and treatment-related symptoms and their effect on patient function and health-related quality of life are important outcomes to consider. The identification of methods to scientifically assess, analyse, interpret, and present these clinical outcomes requires sustained international collaboration by multiple stakeholders including patients, clinicians, scientists, and policy makers. Several data sources can be considered to capture the patient experience, including patient-reported outcome (PRO) measures, performance measures, wearable devices, and biosensors, as well as the careful collection and analysis of clinical events and supportive care medications. In this Policy Review, we focus on PRO measures and present the perspectives of three international regulatory scientists to identify areas of common ground regarding opportunities to incorporate rigorous PRO data into the regulatory decision-making process.

Lancet Oncol 2018; 19: e267–74

See Comment page 595

Oncology Center of Excellence, US Food and Drug Administration, Silver Spring, MD, USA (P G Kluetz MD); Medicines and Healthcare Products Regulatory Agency, London, UK (D J O'Connor PhD); and Therapeutic Products Directorate, Health Products and Food Branch, Health Canada, Ottawa, ON, Canada (K Soltys MD)

Correspondence to: Dr Paul G Kluetz, Oncology Center of Excellence, US Food and Drug Administration, Silver Spring, MD 20993, USA paul.kluetz@fda.hhs.gov

Introduction

Medicinal products are regulated to protect and promote public health. Government agencies worldwide have the responsibility of supervising medicinal products and regulating the activities of the pharmaceutical industry. Drug development is becoming more patient centred and regulators are increasingly interested in accurate and well-defined methods to rigorously capture the

Poorly defined PRO objectives and methodology, coupled with heterogeneous analytical methods used for PRO data submitted to regulatory agencies, have hampered the utility of PRO information in regulatory decision making. Different regulations exist between international regulatory bodies regarding the types of data included in product labelling. Not surprisingly, a level of discordance

Figure: **Framework for strengthening international collaboration in regulatory decision making**
PRO=patient-reported outcomes.

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Experts' view

There is wide support for SISAQOL and a need to standardize PRO and HRQOL analysis in cancer clinical trials on a global scale.

THE LANCET
Oncology

Online First Current Issue All Issues Multimedia Information for Authors

All Content Search Advanced Search

< Previous Article Volume 17, No. 11, e510–e514, November 2016

Personal View

Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards

Dr Andrew Bottomley, PhD, Madeline Pe, PhD, Jeff Sloan, PhD, Ethan Basch, MD, Franck Bonnetain, PhD, Melanie Calvert, PhD, Alicyn Campbell, APh, Charles Cleeland, PhD, Kim Cocks, PhD, Laurence Collette, PhD, Amylou C Dueck, PhD, Nancy Devlin, PhD, Hans-Henning Flechtner, MD, Carolyn Gotay, PhD, Eva Greimel, PhD, Ingolf Griebsch, PhD, Mogens Groenvold, MD, Jean-Francois Hamel, PhD, Madeleine King, PhD, Paul G Kluetz, MD, Michael Koller, PhD, Daniel C Malone, PhD, Francesca Martinelli, MSc, Sandra A Mitchell, PhD, Carol M Moinpour, PhD, Jammbe Musoro, PhD, Daniel O'Connor, MBChB, Kathy Oliver, BA, Elisabeth Piault-Louis, PharmD, Martine Piccart, MD, Francisco L Pimentel, MD, Chantal Quinten, MSc, Jaap C Reijneveld, MD, Christoph Schürmann, PhD, Ashley Wilder Smith, PhD, Katherine M Soltys, MD, Martin J B Taphoorn, MD, Galina Velikova, MD, Corneel Coens, MSc for the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) consortium

Published: 18 October 2016

Altmetric 17

The SISAQOL Question

- If we want to draw conclusions about PROs and HRQOL in cancer clinical trials, are we rigorous on how we analyze PRO and HRQOL data**?**
- Is there a need to standardize the analyses of HRQOL and other PRO data?
- **If yes, can we develop guidelines and recommendations for this?**

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

How can we standardize PRO and HRQOL analysis in cancer RCTs?

A hypothetical situation

A common HRQOL and PRO research objective (hypothesis):

We want to examine whether Treatment A is better than Treatment B in improving *physical functioning* [*or pre-specify a different PRO domain; or multiple relevant domains for HRQOL*].

What statistical method will be used to test this hypothesis?

S1	Time to first deterioration	Treatment A is worse than Treatment B
S2	"Global picture": Overall means across time	No difference between treatments
S3	Specific time point: end of treatment	Treatment A is better than Treatment B

With such findings, we might be tempted to say:

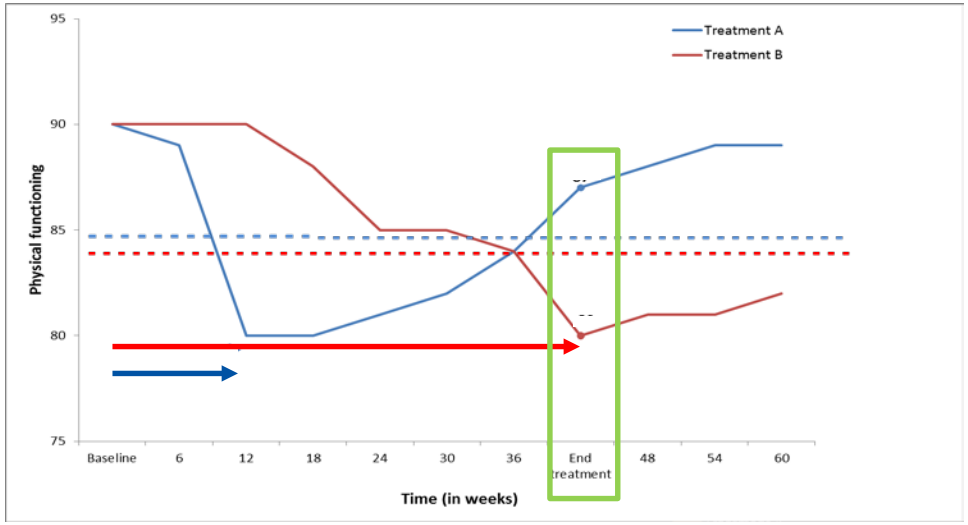
- HRQOL and PROs are confusing and not reliable.
- We cannot trust the findings from HRQOL and PRO data.

This is not true…

A hypothetical situation

S1	Time to first deterioration	Treatment A is worse than Treatment B
S2	"Global picture": Overall means across time	No difference between treatments
S3	Specific time point: end of treatment	Treatment A is better than Treatment B

It is possible that the data looked like this:



Based on the research objective that they received, none of these researchers would be wrong.

The statistical methods used may all assess "improvement" but in different ways.

A solution

There is nothing wrong with:

- the quality of the data that is provided by the patients, or
- the statistical methods used by the researchers

Rather:

Each statistical method focuses on a different aspect of the data and responds to a different research objective.

A solution:

A need for more well-defined research objectives that can be matched with appropriate statistical methods.

It is not enough to say **"improved"** physical functioning [*or any PRO domain; or multiple relevant domains for HRQOL*]

Important parts of a PRO research objective

- **Primary PRO domains of interest**
  - Specific PRO domains (symptoms, functioning, etc)? Multiple PRO domains that capture patients' HRQOL?
  - Use a validated questionnaire

- **Time frame of interest**
  - Until end on treatment? Long-term follow-up? First three months from randomization (acute effects)?

- **Identify analysis population**
  - ITT population? Patients while on treatment?

- … see SPIRIT PRO guidelines for more details

Specify *a-priori* PRO domains, population and time frame of interest

Calvert et al., 2018 JAMA

What analytical method to use?

- What kind of change and/or effect is expected *[for the pre-specified PRO domains within the time frame of interest for the identified population]*?
  - Reminder: For example, “improved” is not enough. Different kinds of “improvements” can be assessed for PROs. This needs to be more specific.
- SISAQOL on-going work: Matching these specific PRO research objectives with appropriate statistical methods

	Draw conclusions on treatment efficacy / clinical benefit	
Within-treatment arms assumption *(longitudinal design: applies to both short-term and long-term)*	*Between treatment arms objective*	
	Superiority	*Equivalence / Non-inferiority*
1. **Improvement**/worsening (event)	-	
a. Time to event	- Cox proportional Hazards - Log rank test	
b. Proportion of patients with event at time *t*	- Chi-square test - Fisher's exact test - Cochrane-Mantel Haenszel test	
c. Intensity of event at time *t*	- (Generalized) Linear mixed model (time as discrete: specific time point) - (Generalized) Linear mixed model (time as continuous) - Generalized estimating equation - Linear regression - ANOVA - T-test - Wilcoxon ranks test	
2. ...		

Recommending Statistical Methods

Statistical features that were agreed to be essential and/or highly desirable for PRO analysis in RCTs

Essential

- Perform a statistical test between two samples
- Be clinically relevant

Highly desirable

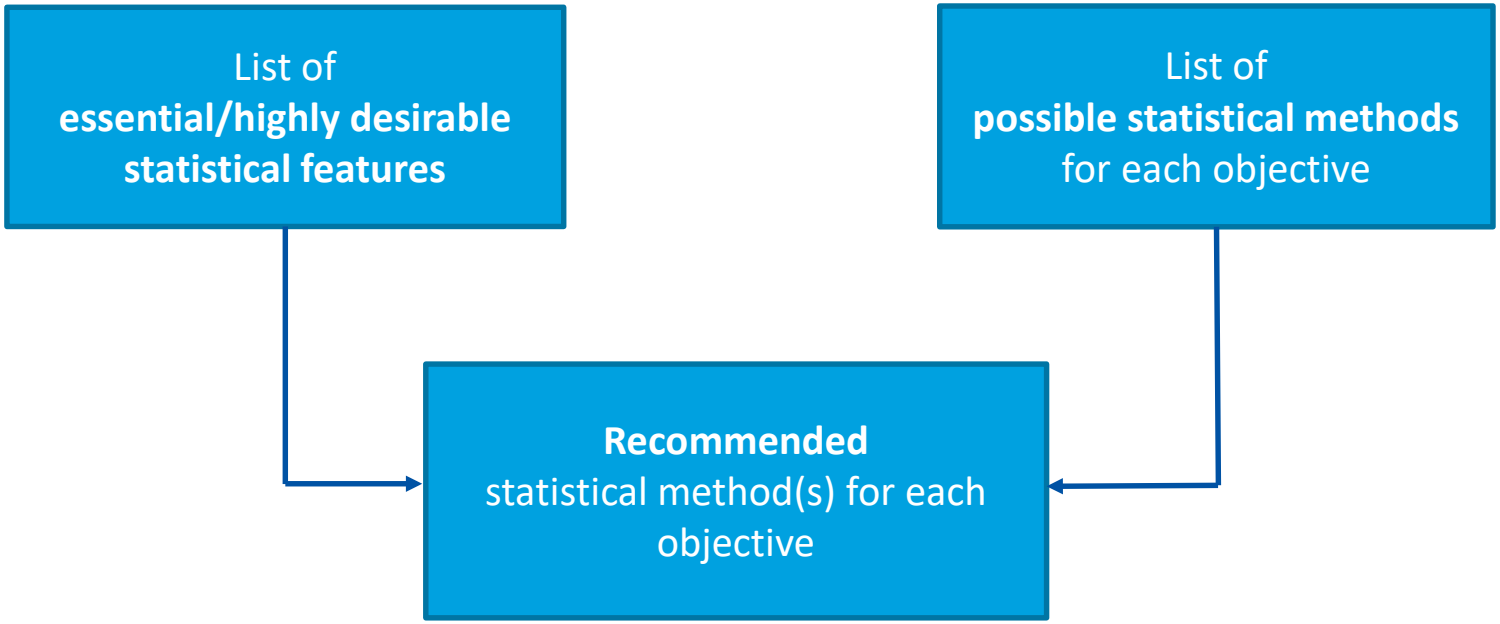
- Adjust for covariates, including baseline PRO
- Allow for incomplete data
- Allow for correlations over time

Clinical Relevance

- Definition:
  - Produce results on the size, certainty and direction of the estimation and precision of the treatment effect that have a direct link with the clinical relevance classification of the instrument.
- Rationale:
  - Essential for proper interpretation of the results.
- Statistical significance ≠ Clinical relevance
- Different kinds of clinical relevance
  - Change within an individual (responder) ≠ mean change within a treatment arm ≠ difference between treatment arms

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Recommending Statistical Methods



Missing data

What about missing data?

What is missing PRO data?

"Missing data" is almost always an inherent part of PRO analysis

Essential

- Perform a statistical test between two samples
- Be clinically relevant

Highly desirable

- Adjust for covariates, including baseline PRO
- Allow for incomplete data
- Allow for correlations over time

Appropriate PRO method would be robust to missing data (least restrictive assumptions)

What is missing PRO data?

Regulatory documents (EMA, FDA) ICH E9 (2017):

- *Data that would be meaningful for the analysis of a given estimand (target of estimation) but were not collected.*

Little et al. (2012), NEJM:

- *Values that are not available and would be meaningful for analysis if they were observed.*

What is "meaningful for analysis"?

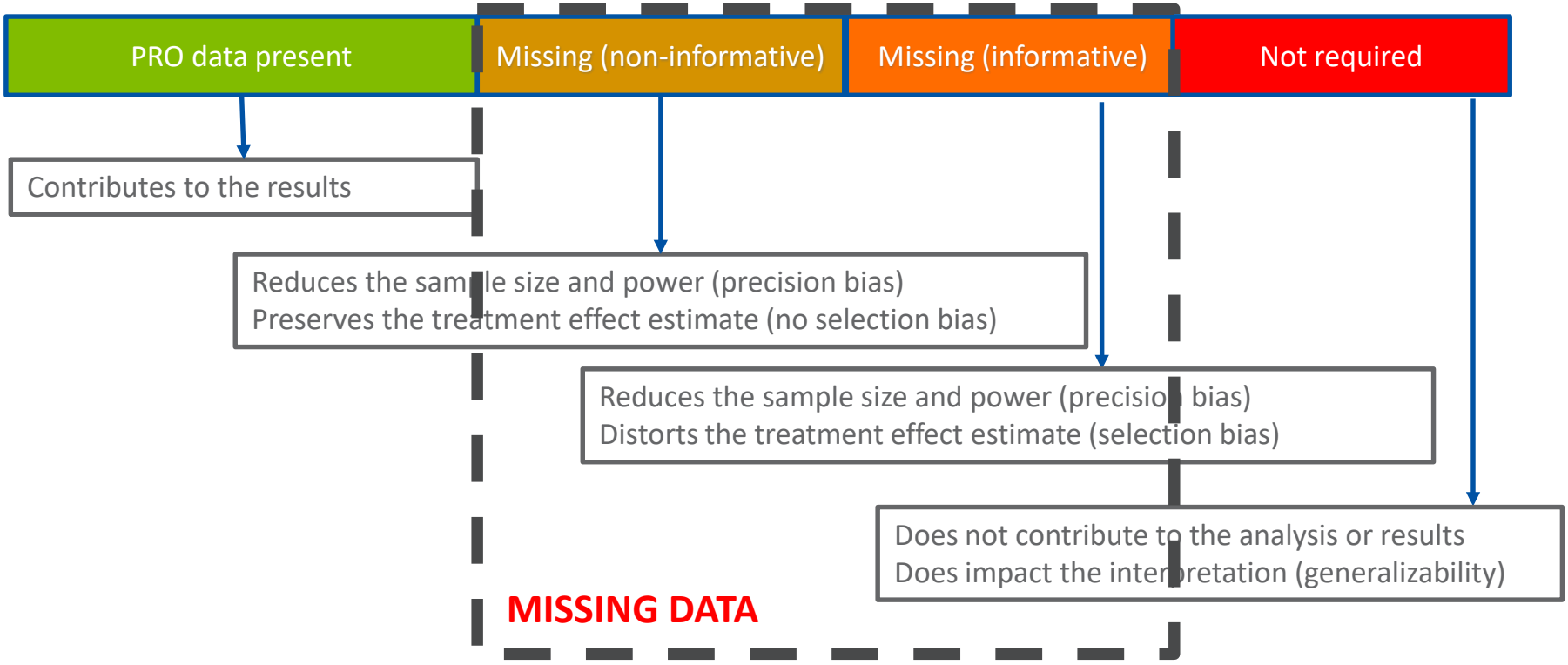
- Measures of quality of life are usually not meaningful for patients who have died and hence would not be considered as missing data under this definition (Little et al., 2012, NEJM)

Slide from Lien Dorme MSc

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

What is missing PRO data?

For each PRO assessment time, data for all enrolled patients breaks down to:



Slide from Corneel Coens MSc

Handling missing data

Two critical points:

- There is no foolproof way to analyze trial data with substantial amounts of missing data.
- No analysis method recovers the potential for robust treatment comparisons derived from follow-up of all randomized patients (Little et al., 2012)

Little et al., 2012, *New England Journal of Medicine*

Handling missing data

First line “solution”: Avoid missing data

- PROs need to be fully integrated into the design and conduct of study (protocol)
- Balance between clinically informative and feasible assessment schedule
- Minimize patient burden
- Rigorous collection of good quality PRO data

Mercieca-Bebber et al., 2016 *BMJ Open;*
Bell & Fairclough, 2013, *Statistical Methods in Medical Research*

Handling missing data

Second line “solution” : statistical approaches

1. Evaluate the **amount** and kind of missing data

- What is a “substantial” amount of missing data? – an open question
  - Definition of “substantial” will depend on the kind of missing data
  - Missing data is often a mixture of informative and non-informative missing data

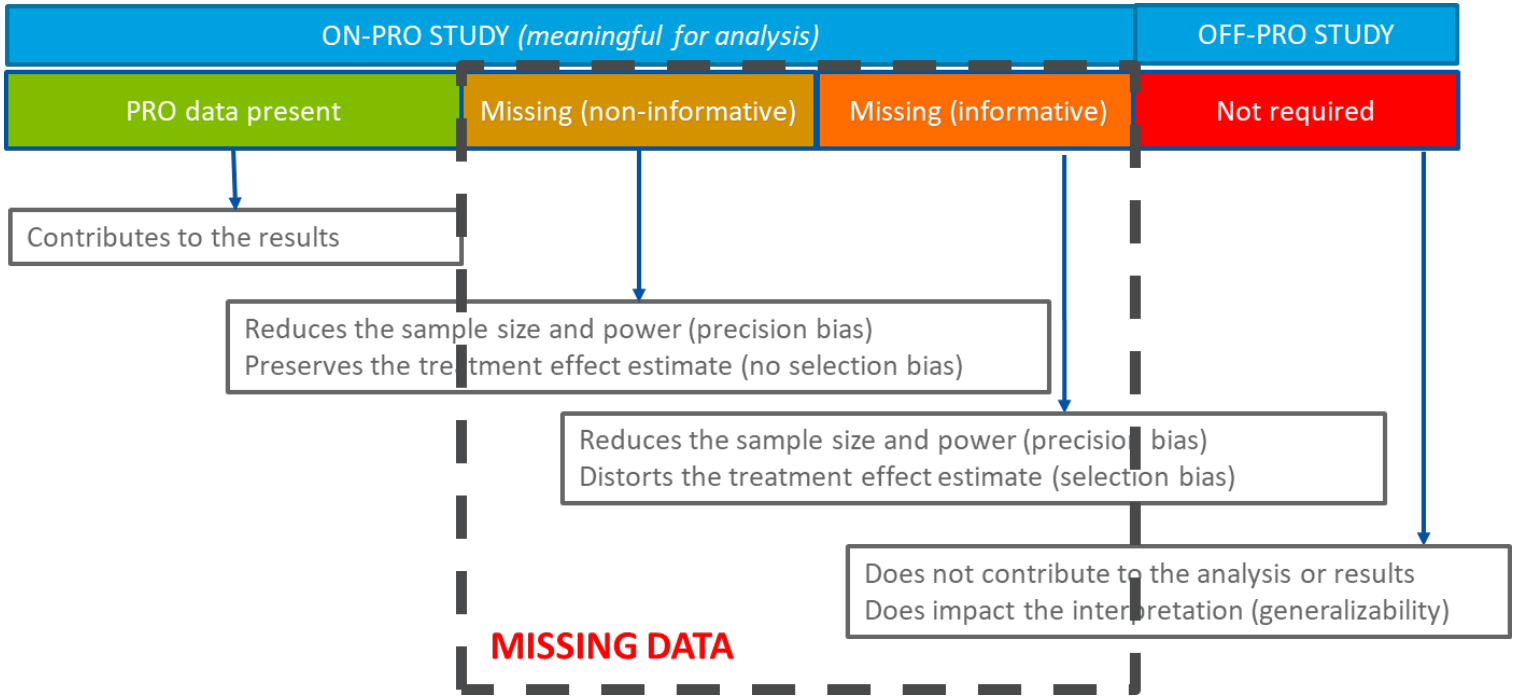
No statistical method will be able to “fix” a substantial amount of missing data

Mazza et al. *on behalf of SISAQOL missing data working group* (2018) – to be presented in ISOQOL 2018

Handling missing data

Second line “solution” : statistical approaches

1. Evaluate the amount and **kind** of missing data



Handling missing data

Second line "solution" : statistical approaches

1. Evaluate the kind and amount of missing data

- Missing completely at random (MCAR):
  - Probability of data missing is **unrelated to the patient's outcome**
  - For example: staff forgot to give questionnaire

- Missing at random (MAR):
  - Probability of data missing **depends only on past observed data**
  - For example: patient was too sick the last visit and doctor tells the patient not to respond to the current assessment

- Missing not at random (MNAR):
  - Probability of data missing **depends on the value of the missing outcome itself**
  - For example: patient was usually feeling well, but on the day of assessment, patient was too ill to fill out the form

Missing (non-informative)

Missing (informative)

Bell & Fairclough, 2013, *Statistical Methods in Medical Research*

Handling missing data

Second line "solution" : statistical approaches

2. Primary statistical method is robust to missing data

- Primary analysis is based on MAR assumption
- Missing data in cancer RCTs are only rarely MCAR

3. Conduct a sensitivity analysis

- Not possible to differentiate between MAR vs MNAR
- Different clinically plausible models that use different assumptions and examine whether estimates change

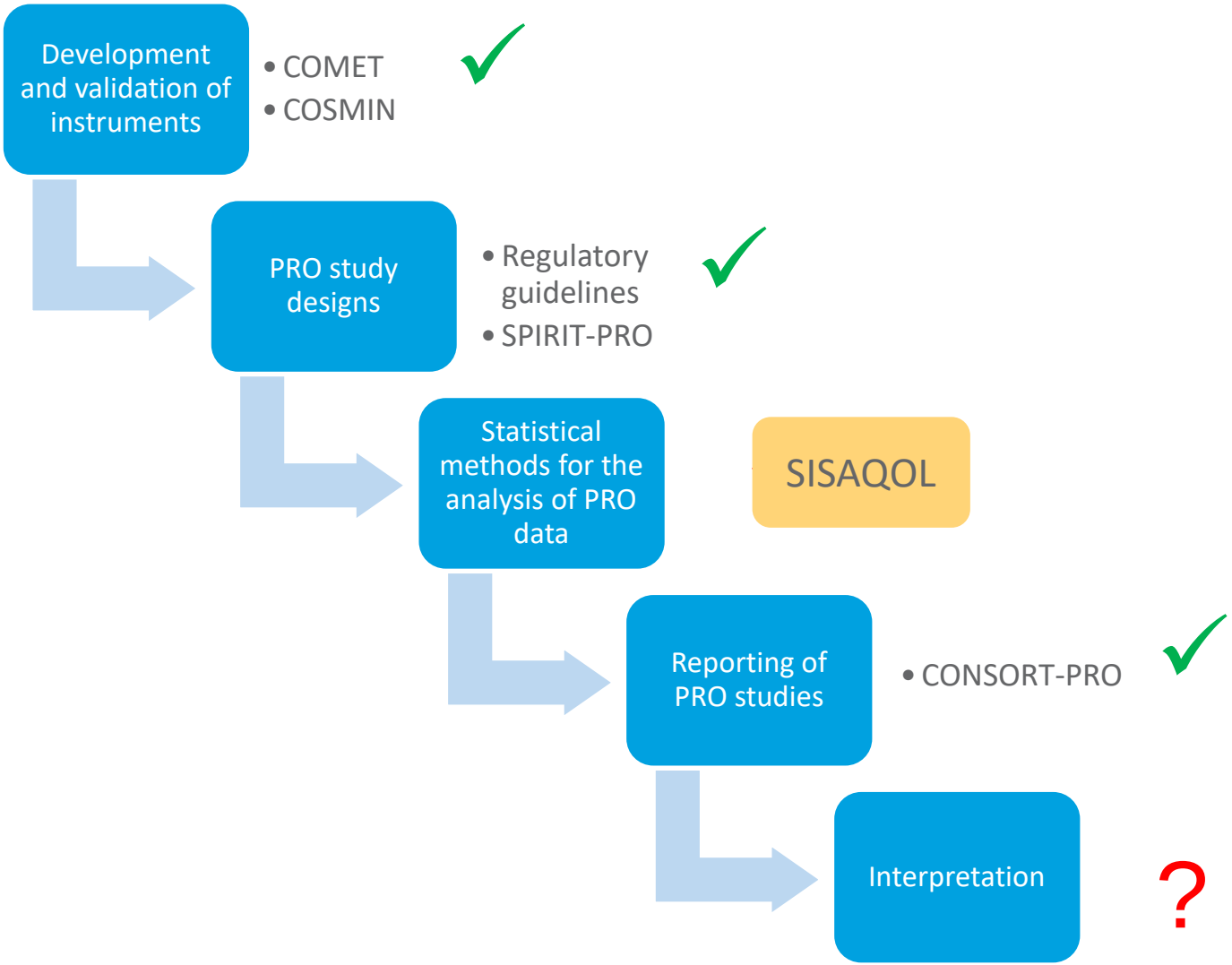
Collect reasons for missing data

- Useful for evaluating kind of missing data and sensitivity analysis

Bell & Fairclough, 2013, *Statistical Methods in Medical Research*

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Conclusion



Slide from Corneel Coens MSc

Conclusion

- There is a shift towards patient-centered care and patient-centered drug development programs.
- Increased importance of PROs and HRQOL led to increased awareness of a need for better standards in assessing PROs in clinical trials
- SISAQOL aims to address the need for a standardization of PRO and HRQOL analyses.
- PRO objective and interpretation remains crucial
    - Statistical ‘magic’ is no salvage trick.

Acknowledgements

- Corneel Coens
- Lien Dorme
- Andrew Bottomley
- SISAQOL Consortium

Ethan Basch	Amylou Dueck	Daniel C Malone	Chantal Quinten
Andrew Bottomley	Hans-Henning Flechtner	Francesca Martinelli	Jaap C Reijneveld
Melanie Calvert	Carolyn Gotay	Sandra A Mitchell	Christoph Schürmann
Alicyn Campbell	Eva Greimel	Jammbe Z Musoro	Jeff Sloan
Charles Cleeland	Ingolf Griebsch	Daniel O'Connor	Ashley Wilder Smith
Kim Cocks	Mogens Gronvold	Kathy Oliver	Kathy Soltys
Corneel Coens	Jean-Francois Hamel	Madeline Pe	Rajeshwari Sridhara
Laurence Collette	Laura Lee Johnson	Elisabeth Piault-Louis	Martin Taphoorn
David Collingridge	Madeleine King	Martine Piccart	Galina Velikova
Nance Devlin	Paul Kluetz	Francisco Pimentel	
Lien Dorme	Michael Koller		

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Thank you