

# Q-RECIST: Development of a response criteria for longitudinal health-related quality of life data in oncology clinical trials

Dr Amélie ANOTA

Methodology and Quality of Life in Oncology Unit

# Collaborators



- **Health Outcomes Unit, GIMEMA:** Pr Fabio EFFICACE

- **EORTC QoL department :** Corneel COENS



- **MAYO Clinic :** Pr Jeff SLOAN



***Coordination by the UMQVC***



***Grant obtained from the EORTC for 2 years***

# Background

Numerous calls have been made in the literature to **standardize** the way **cancer clinical trials** are **conducted** and **reported** in terms of HRQoL

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 SPECIAL COMMUNICATION

## Reporting of Patient-Reported Outcomes in Randomized Trials

The CONSORT PRO Extension

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Melanie Calvert, PhD

Jane Blazeby, MD

Douglas G. Altman, DSc

Dennis A. Revicki, PhD

David Moher, PhD

Michael D. Brundage, MD  
for the CONSORT PRO Group

The CONSORT (Consolidated Standards of Reporting Trials) Statement aims to improve the reporting of randomized controlled trials (RCTs); however, it lacks guidance on the reporting of patient-reported outcomes (PROs), which are often inadequately reported in trials, thus limiting the value of these data. In this article, we describe the development of the CONSORT PRO extension based on the methodological framework for guideline development proposed by the Enhancing the Quality and Transparency of Health Research (EQATOR) Network. Five CONSORT PRO checklist items are recom-

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*JAMA. 2013;309(8):814-822*

**Table 1.** Information for Reporting Randomized Controlled Trials With Patient reported Outcomes

Section/Topic	Item	CONSORT 2010 Statement Checklist Item	PRO-Specific Extensions Are Prefaced by the letter <i>P</i>
<b>Title and Abstract</b>			
	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) <sup>3</sup>	P1b: The PRO should be identified in the abstract as a primary or secondary outcome
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	Including background and rationale for PRO assessment
	2b	Specific objectives or hypotheses	P2b: The PRO hypothesis should be stated and relevant domains identified, if applicable
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial), including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	Not PRO-specific, unless the PROs were used in eligibility or stratification criteria
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	P6a: Evidence of PRO instrument validity and reliability should be provided or cited if available including the person completing the PRO and methods of data collection (paper, telephone, electronic, other)
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	Not required for PRO unless it is a primary study outcome
	7b	When applicable, explanation of any interim analyses and stopping guidelines	

# ISOQOL, EORTC point of view

ISOQOL and other bodies are undertaking activities to try to standardize how randomized clinical trials (RCTs) with HRQoL are drafted

Review

Qual Life Res (2013) 22:1161–1175  
DOI 10.1007/s11136-012-0252-1

**Health-related quality of life in small-cell lung cancer: a systematic review on reporting of methods and clinical issues in randomised controlled trials**



*Efstathios Zikos, Irina Ghislain, Corneel Coens, Divine E Ediebah, Elizabeth Sloan, Chantal Quinten, Michael Koller, Jan P van Meerbeeck, Hans-Henning Flechtner, Roger Stupp, Athanasios Pallis, Agnes Czimbalmos, Mirjam A G Sprangers, Andrew Bottomley*

J Neurooncol (2012) 108:221–226  
DOI 10.1007/s11060-012-0819-2

METHODS AND CLINICAL TOOLS FOR OUTCOME ASSESSMENTS

**Methodological issues in designing and reporting health-related quality of life in cancer clinical trials: the challenge of brain cancer studies**

Fabio Efficace · Martin Taphoorn

**Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards**

Michael Brundage · Jane Blazeby · Dennis Revicki · Brenda Bass · Henrica de Vet · Helen Duffy · Fabio Efficace · Madeleine King · Cindy L. K. Lam · David Moher · Jane Scott · Jeff Sloan · Claire Snyder · Susan Yount · Melanie Calvert

# Still needing standardization

- Regarding the analysis of longitudinal HRQoL data from cancer clinical trials
- Limitations regarding
  - Comparisons of HRQoL results between trials
  - Variation in analyses/reporting
  - Difference in the interpretation of the results
  - Mainly statistically significance not integrating the MCID except in the TTD approach



Journal of Clinical Epidemiology 72 (2016) 1–3

EDITORIAL



Limitation to use HRQoL  
as decision criteria in oncology

The way in which effects are analyzed and communicated can  
make a difference for decision making

# Methodology for longitudinal analysis

Mainly 2 statistical approaches are used in oncology RCTs:

## The **linear mixed model**

- Most used method
- Assess the change of HRQoL level over time
- $\neq$  effects: arm, time, treatment by time interaction
- Normality assumptions rarely checked
- Sometimes wrong interpretation between arm and time by treatment coefficients
- Could be difficult to interpret for clinicians
- Often interpreted in a statistical point of view only

# Methodology for longitudinal analysis

## The **time to deterioration** (TTD) approach

- Proposed since a decade, more and more used in phase III RCTs
- Based on survival analysis (time to event)
- Very attractive for clinicians (median of deterioration, HR, Kaplan-Meier curves, ..)



Required a definition of the event : the deterioration



The clinical relevance of the results is ensured since the MCID is integrated in the definition



# Direct consequences: illustration



The NEW ENGLAND  
JOURNAL of MEDICINE

2014

- 2 phase III RCTs have been conducted in glioblastoma patients
- Treatment compared :Temozolomide +/- Bevacizumab
- In both clinical trials :
  - Co-primary endpoint : PFS + OS
  - HRQoL was a secondary endpoint assessed by the QLQ-C30 and BN20 brain cancer module
  - Positive effect of bevacizumab on PFS
  - But no impact on OS



Need to assess the impact of treatment on the HRQoL in order to ensure the clinical benefit for the patients

# Direct consequences: illustration



A Randomized Trial of  
for Newly Diagnosed

Mark R. Gilbert, M.D., James J. Dignam, Ph.D., Terri  
Deborah T. Blumenthal, M.D., Michael A. Vogelbaum, M.D.,  
Arnab Chakravarti, M.D., Stephanie Pugh, Ph.D., Minhee Won, M.D.,  
Kurt A. Jaeckle, M.D., David Schiff, M.D., Volker W. Stieglitz, M.D.,  
Maria Werner-Wasik, M.D., Ivo W. Tremont-Lukats, M.D., Erik P. W.  
Walter J. Curran, Jr., M.D., and Minesh P. Mehta, M.D.

HRQoL (Health-Related Quality of Life) in the Bevacizumab  
(and model)

Bevacizumab plus Radiotherapy-Temozolomide  
for Newly Diagnosed Glioblastoma

Olivier L. Chinot, M.D., Wolfgang Wick, M.D., Warren M.  
Roger Henriksson, M.D., Frank Saran, M.D., Ryo Nishida, M.D.,  
Antoine F. Carpentier, M.D., Ph.D., Khe Hoang, M.D.,  
Petr Kavan, M.D., Ph.D., Dana Cernea, Ph.D.,  
Magalie Hilton, M.Sc., Lauren Abrey, M.D.

better in the Bevacizumab group  
(measured progression as an event)



the marketing  
of the Bevacizumab

Same HRQoL questionnaires but since  $\neq$  methods have been used  
to analyze HRQoL data, results cannot be directly compared

# Challenges of the longitudinal analysis

Since HRQoL is assessed by questionnaires completed by the patients and it is a **subjective** endpoint, it can be affected by:

- The occurrence of **missing data**



Can be informative of the patient's health status and HRQoL level

- The occurrence of a potential **response shift** effect



Choice of the reference score in the longitudinal analysis

# Clinical relevance of the results

**Objective:** to confirm the superiority of weekly docetaxel and cisplatin over docetaxel monotherapy in elderly patients with advanced NSCLC

- Primary endpoint
- HRQoL secondary endpoint: the change of the FACT-L at baseline, C2 and C3

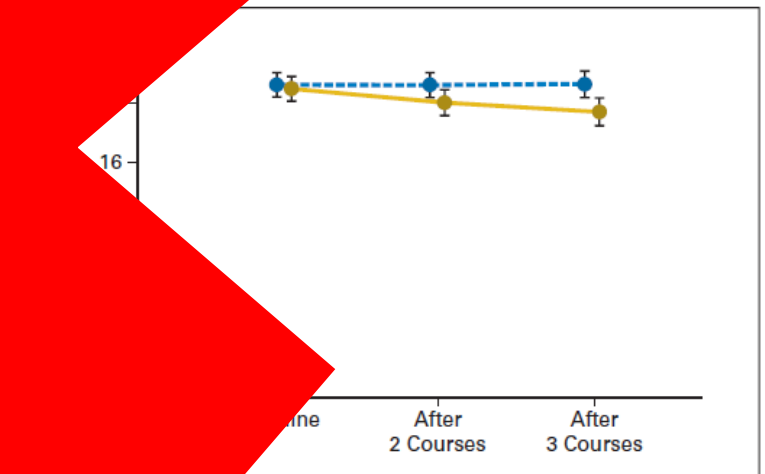
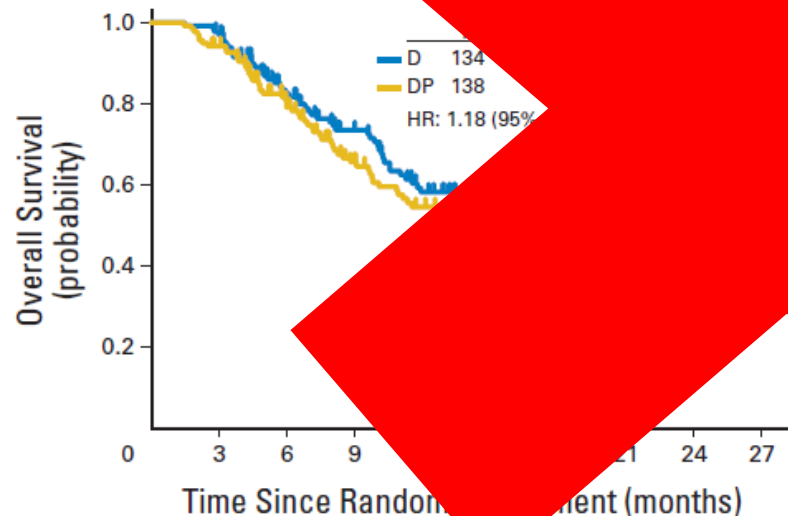
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Trial Comparing Weekly Docetaxel Plus Cisplatin Versus Docetaxel Monotherapy Every 3 Weeks in Elderly Patients With Advanced Non–Small-Cell Lung Cancer: The Intergroup Trial JCOG0803/WJOG4307L

Tetsuya Abe, Koji Takeda, Yuichiro Ohe, Shinzoh Kudoh, Yukito Ichinose, Hiroaki Okamoto, Nobuyuki Yamamoto, Hiroshige Yoshioka, Koichi Minato, Toshiyuki Sawa, Yasuo Iwamoto, Hideo Saka, Junki Mizusawa, Taro Shibata, Shinichiro Nakamura, Masahiko Ando, Akira Yokoyama, Kazuhiko Nakagawa, Nagahiro Saijo, and Tomohide Tamura

See accompanying editorial doi: 10.1200/JCO.2014.59.5033



Assessments were performed according to the seven-item Functional Assessment of Cancer Therapy–Lung (FACT-L). Dots and error bars indicate the least squares mean total scores and 95% CI, respectively. Higher scores indicate a better quality of life. D, docetaxel; DP, docetaxel plus cisplatin.

ence. Although the mean total score remained near its baseline value in the docetaxel arm, it declined gradually in the DP arm, changing in a statistically significant manner between baseline and cycle 3 ( $P < .01$ ; Fig 3).

Clinically meaningful change ?  
Not enough measurement time

# Clinical relevance of the results

The MCID remained few used to interpret the results

		PRO end-point n (%)		Total n (%)
		Primary 22 (33%)	Secondary 44 (67%)	
<b>Interpretation</b>				
Are PRO interpreted? (Not only re-stated) <sup>a</sup>	No	7 (31.82)	29 (65.91)	36 (54.55)
	Yes	15 (68.18)	15 (34.09)	30 (45.45)
The clinical significance of the PRO findings should be discussed	No	14 (63.64)	35 (79.55)	49 (74.24)
	Yes	8 (36.36)	9 (20.45)	17 (25.76)
Methodology used to assess clinical significance (in case this was addressed) <sup>a</sup>	Anchor based	1 (4.55)	3 (6.82)	4 (6.06)
	Distribution based	6 (27.27)	6 (13.64)	12 (18.18)
	Both	1 (4.55)	0 (0)	1 (1.52)

European Journal of Cancer 56 (2016) 144–161



Review

Patient-reported outcomes in head and neck and thyroid cancer randomised controlled trials: A systematic review of completeness of reporting and impact on interpretation<sup>☆</sup>



Rebecca L. Mercieca-Bebber<sup>a,b,\*</sup>, Alessandro Perreca<sup>c</sup>,  
 Madeleine King<sup>a,b</sup>, Andrew Macann<sup>d</sup>, Katie Whale<sup>e</sup>, Salvatore Soldati<sup>c</sup>,  
 Marc Jacobs<sup>f,g</sup>, Fabio Efficace<sup>c</sup>

# Clinical relevance of the results

## The MCID remained few used to interpret the results

**Table 2** The 13 keys parameters for statistical HRQoL analysis assessed as “yes” if the authors specified the parameter, “not clear” it was not clear and “no” if the authors didn’t specify the parameter

	Yes, n (%)	Not clear, n (%)	No, n (%)
Targeted dimensions	13 (48.1)	0	14 (51.9)
HRQoL hypothesis	2 (7.4)	0	25 (92.6)
Procedure to control the type I error	1 (3.7)	1 (3.7)	25 (92.6)
Minimal clinically important difference	9 (33.3)	1 (3.7)	17 (63)
Study population	3 (11.1)	3 (11.1)	21 (77.8)
Number of HRQoL data at subsequent time points	7 (25.9)	6 (22.2)	14 (51.9)
HRQoL scores at baseline for each group and each dimension	6 (22.2)	2 (7.4)	19 (70.4)
Profile of missing data at baseline	1 (3.7)	2 (7.4)	24 (88.9)
Statistical approaches for dealing with missing data	5 (18.5)	0	22 (81.5)
Statistical approach for HRQoL analysis	14 (51.9)	1 (3.7)	12 (44.4)
MCID taken into account in the statistical analysis	7 (25.9)	2 (7.4)	18 (66.7)
Multivariate analysis	1 (3.7)	0	26 (96.4)

Fiteri et al. BMC Cancer (2016) 16:122  
DOI 10.1186/s12885-016-2152-1

BMC Cancer

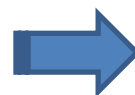
RESEARCH ARTICLE

Open Access



Methodology of health-related quality of life analysis in phase III advanced non-small-cell lung cancer clinical trials: a critical review

Frédéric Fiteri<sup>1,2,4\*</sup>, Amélie Anota<sup>1,2,3</sup>, Virginie Westeel<sup>5</sup> and Franck Bonnetain<sup>1,2,3,6</sup>



MID project of the EORTC  
On MID determination

# Influence of time windows

Annals of Oncology

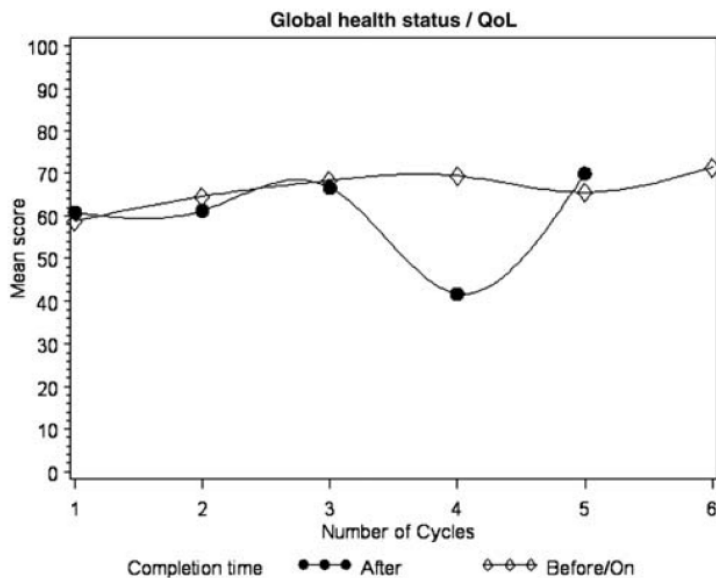
original articles

Annals of Oncology 24: 231–237, 2013  
doi:10.1093/annonc/mds220  
Published online 30 August 2012

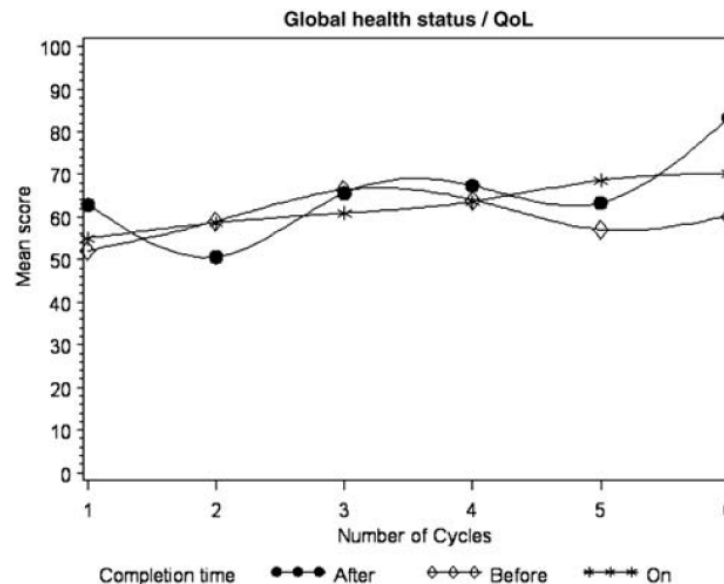
## Effect of completion-time windows in the analysis of health-related quality of life outcomes in cancer patients

D. E. Ediebah<sup>1\*</sup>, C. Coens<sup>1</sup>, J. T. Maringwa<sup>2</sup>, C. Quinten<sup>1</sup>, E. Zikos<sup>1</sup>, J. Ringash<sup>3</sup>, M. King<sup>4</sup>, C. Gotay<sup>5</sup>, H.-H. Flechtner<sup>6</sup>, J. Schmucker von Koch<sup>7</sup>, J. Weis<sup>8</sup>, E. F. Smit<sup>9</sup>, C.-H. Köhne<sup>10</sup> & A. Bottomley<sup>1</sup> on behalf of the Gastro-Intestinal Tract Cancer Cooperative Group, Lung Cancer Cooperative Group, Quality of Life Department and Patient Reported Outcome and Behavioural Evidence (PROBE)

## 3 closed EORTC RCTs in NSCLC and CRC Impact of time windows (before, on, and after CT) on HRQoL results over time



**Figure 2.** Raw mean profiles for the global health status/QoL scale for trial 2 by 'before-or-on' and 'after'.

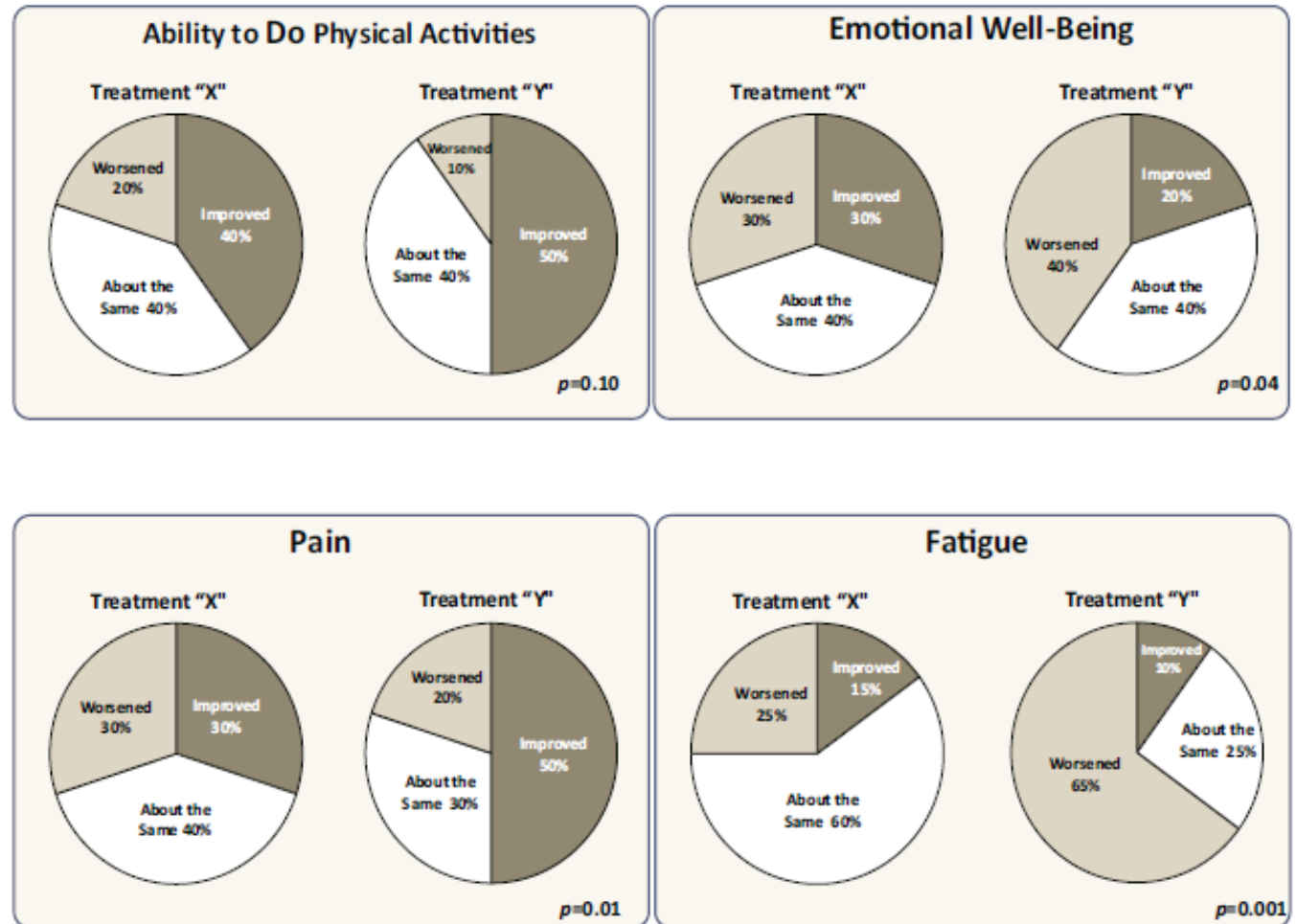


**Figure 3.** Raw mean profiles for the global health status/QoL scale for trial 3 by 'before', 'on' and 'after'.

## A Pie Charts

Status of 100 patients 9 months after starting treatment

**Fig. 4** Examples of format illustrating the proportions of patients changed at 9 months (compared to baseline). **a** Pie chart format. **b** Bar chart format.





# In summary

The heterogeneity of the longitudinal analysis of HRQoL is mainly based on :

- ✓ the statistical methods used to analyse longitudinal HRQoL data
- ✓ the choice of the MCID to interpret the results in a clinically meaningful way
- ✓ the time windows between HRQoL measures
- ✓ the frequency and the timing of assessments
- ✓ handling of missing data, ....

Published Ahead of Print on April 18, 2016 as 10.1200/JCO.2014.56.7974  
The latest version is at <http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2014.56.7974>

JOURNAL OF CLINICAL ONCOLOGY

STATISTICS IN BRIEF

Statistical Challenges in the Analysis of Health-Related  
Quality of Life in Cancer Clinical Trials

*Franck Bonnetain, Frédéric Fiteni, Fabio Efficace, and Amélie Anota*



Need for standardization

# SISAQOL project

International project on the standardization of the analysis of QoL data in oncology RCTs

Personal View

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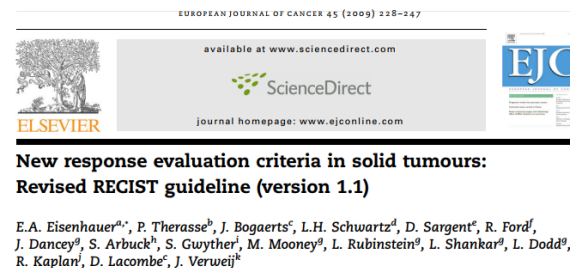
## Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards



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

# RECIST criteria

By contrast, a standardization of the measurement of tumor parameters such as tumor response was already proposed and successfully implemented with the **RECIST criteria**



Same process for HRQoL longitudinal data ?

# Rational

- We do not claim to propose a standardized HRQoL analysis approach applicable to all cancer clinical trials.
- To devise a consensus on an easy metric that can summarize the longitudinal HRQoL information of a patient into simple response/deterioration type criteria
- Such a RECIST-like metric could then be analyzed and reported according to the requirements of the trial but allows a degree of standardization and interpretation across trials

# Rational

- Construction of such a summary statistic would simplify the design, analysis and reporting of HRQoL in cancer clinical trials.
- It should be reliable yet sensitive enough to pick up clinical relevant treatment effects.  
This implies that the MCID of the HRQoL scales must be reflected in this criteria.
- In addition, issues common to HRQoL evaluation in RCTs must also be addressed such as missing data, response shift and floor/ceiling effects.

# Time to QoL score deterioration as a modality of longitudinal analyses in oncology trials

## Methodological development and implementation in R, STATA and SAS statistical software

Qual Life Res  
DOI 10.1007/s11136-013-0583-6

QUANTITATIVE METHODS SPECIAL SECTION

**Time to health-related quality of life score deterioration  
as a modality of longitudinal analysis for health-related quality  
of life studies in oncology: do we need RECIST for quality of life  
to achieve standardization?**

Amélie Anota · Zeinab Hamidou · Sophie Paget-Bailly ·  
Benoist Chibaudel · Caroline Bascoul-Mollevi · Pascal Auquier ·  
Virginie Westeel · Frederic Fiteni · Christophe Borg · Franck Bonnetain

Accepted: 12 November 2013  
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*Journal of Statistical Software*

April 2017, Volume 77, Issue 12.

doi:10.18637/jss.v077.i12

**QoLR: An R Package for the Longitudinal Analysis  
of Health-Related Quality of Life in Oncology**

Amélie Anota  
University Hospital of Besançon

Marion Savina  
Bergonie Institute of Bordeaux

Caroline Bascoul-Mollevi  
Cancer Institute of Montpellier

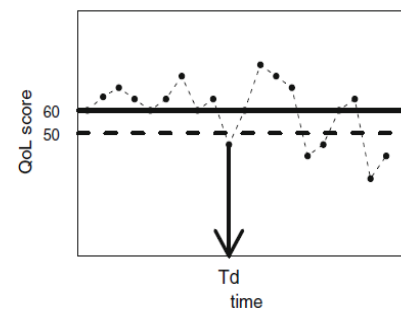
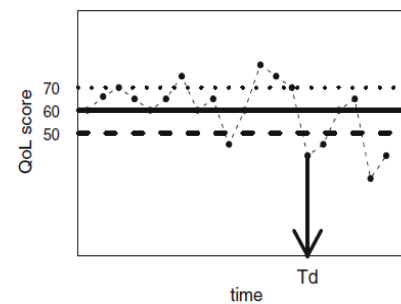
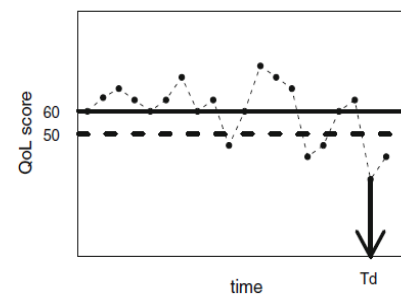
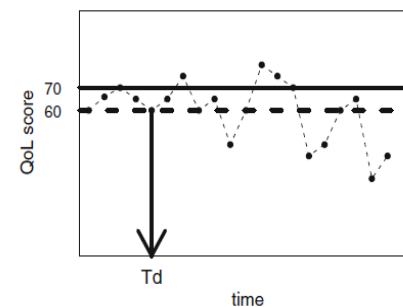
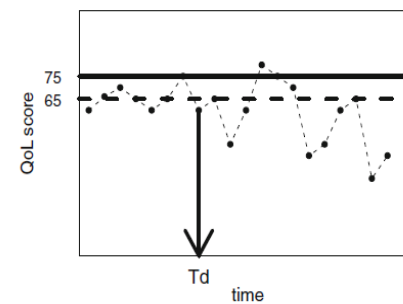
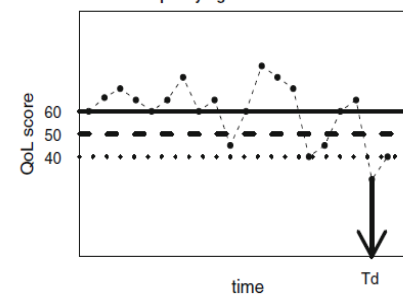
Franck Bonnetain  
University Hospital of Besançon

- **STATA programs**

Bascoul-Mollevi C. et al. Longitudinal Health-related quality of life analysis in oncology with time to event approaches: the STATA program qlqc30\_TTD. Submitted to *Computer Methods and Programs in Biomedicine*

**Table 1** Summary of the different definitions of time to deterioration (TTD) and time until definitive HRQoL score deterioration (TUDD) investigated

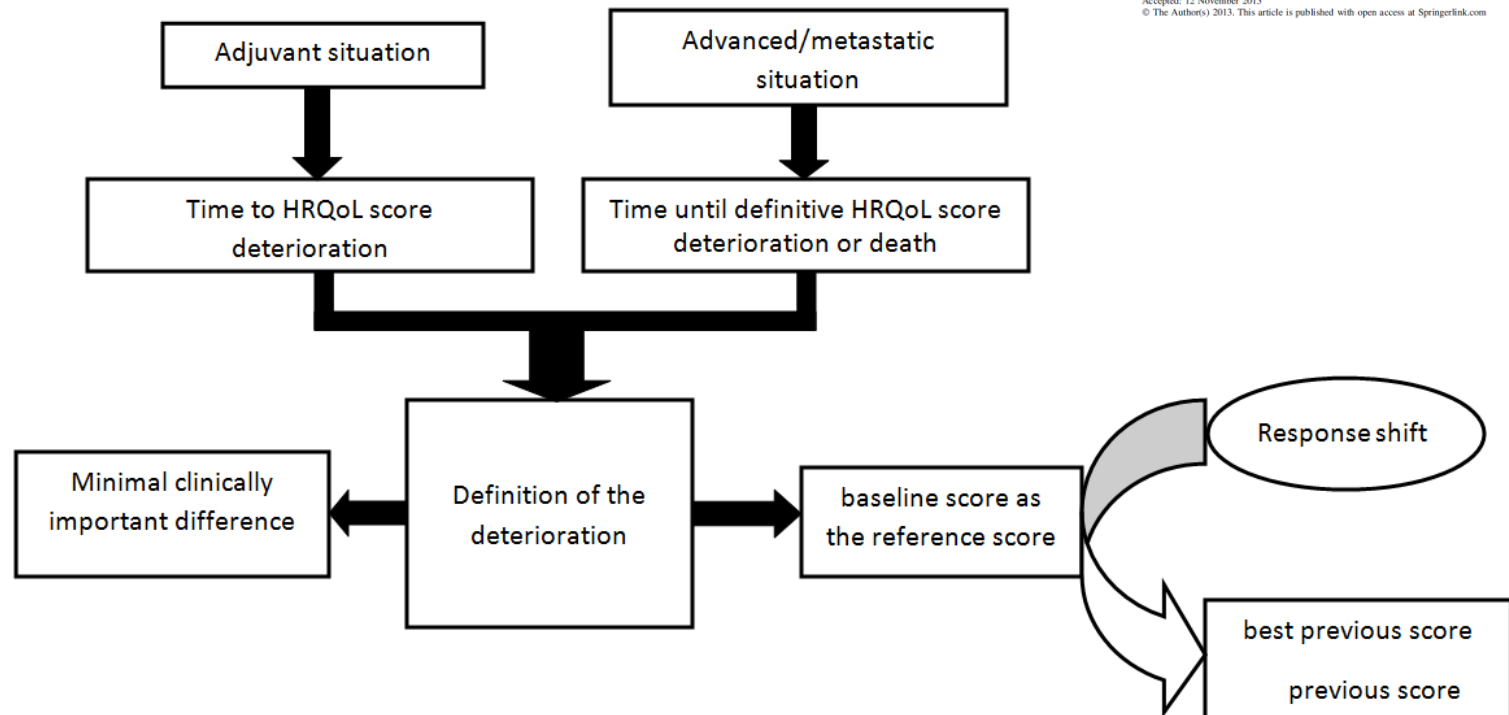
To be considered as events	Reference score			Definitive as compared to		Death	Patients with no baseline	Patients with no follow-up	
	Baseline	Best previous score	Previous score	Reference score					Score qualifying the deterioration
				MCID+ <sup>a</sup>	MCID− <sup>b</sup>				
TTD									
1	X								
2	X						X	X	
3	X					X			
4	X					X	X	X	
5		X							
6		X					X	X	
7		X				X			
8		X				X	X	X	
9			X						
10			X				X	X	
11			X			X			
12			X			X	X	X	
TUDD									
1	X			X					
2	X			X			X	X	
3	X			X		X			
4	X			X		X	X	X	
5	X				X				
6	X				X		X	X	
7	X				X	X			
8	X				X	X	X	X	
9	X					X			
10	X					X	X	X	
11	X					X			
12	X					X	X	X	
13		X		X					
14		X		X			X	X	
15		X		X		X			
16		X		X		X	X	X	
17		X			X				
18		X			X		X	X	
19		X			X	X			
20		X			X	X	X	X	
21		X				X			
22		X				X	X	X	
23		X				X			
24		X				X	X	X	
25			X	X					
26			X	X			X	X	
27			X	X		X			
28			X	X		X	X	X	
29			X		X				
30			X		X		X	X	
31			X		X	X			

**a** TTD as compared to the baseline score**b** TUDD as compared to the baseline score with no further impro as compared to the baseline score**c** TUDD as compared to the baseline score deterioration observed at all times following time of the deterioration**d** TTD as compared to the best previous score**e** TTD as compared to the previous score**f** TUDD as compared to the baseline score with no further impro as compared to the score qualifying the deterioration

# Time to health-related quality of life score deterioration as a modality of longitudinal analysis for health-related quality of life studies in oncology: do we need RECIST for quality of life to achieve standardization?

Amélie Anota · Zeinab Hamidou · Sophie Paget-Bailly ·  
Benoist Chibaudel · Caroline Basoul-Molle · Pascal Auquier ·  
Virginie Westeel · Frédéric Fiteni · Christophe Borg · Franck Bonnetain

Accepted: 12 November 2013  
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Definition should be adapted to the cancer situation:

- "Reversible HRQoL" score deterioration for adjuvant situation
- "Absorbing state" for advanced setting



RESEARCH

Open Access

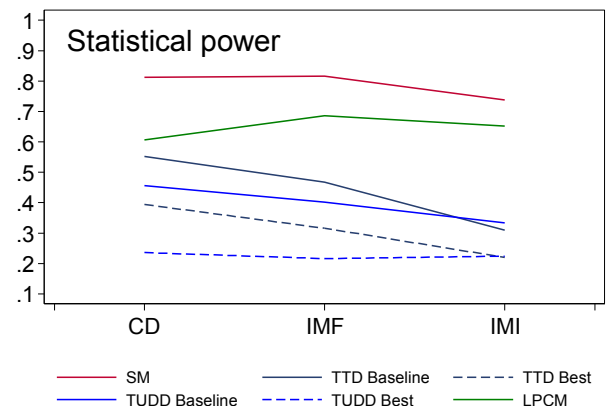
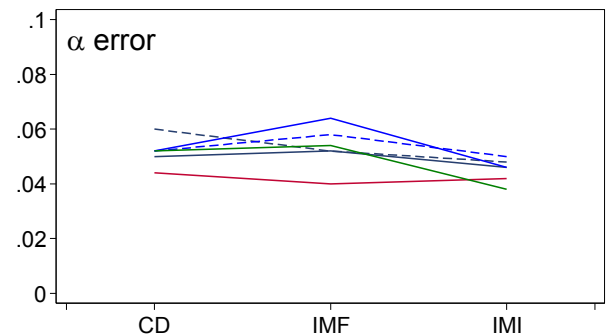
# Comparison of three longitudinal analysis models for the health-related quality of life in oncology: a simulation study

Amélie Anota<sup>1,2\*</sup>, Antoine Barbieri<sup>3,4</sup>, Marion Savina<sup>5,6</sup>, Alhousseiny Pam<sup>2</sup>, Sophie Gourgou-Bourgade<sup>3</sup>, Franck Bonnetain<sup>1,2</sup> and Caroline Bascoul-Mollevi<sup>3</sup>

## Ability of these models to detect a treatment by time interaction

- Type 1 error rate
- Statistical power

4 items / 5 measures



# TUDD proposed in pancreatic cancer

EUROPEAN JOURNAL OF CANCER XXX (2010) XXX-XXX



available at www.sciencedirect.com

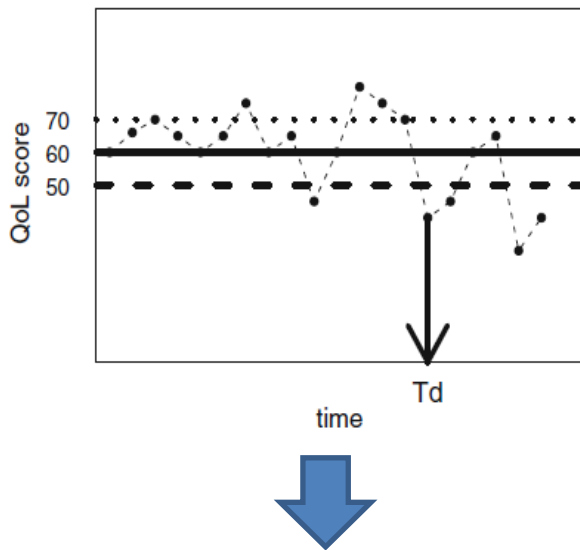
ScienceDirect

journal homepage: www.elsevier.com



**Time until definitive quality of life score deterioration as a means of longitudinal analysis for treatment trials in patients with metastatic pancreatic adenocarcinoma**

Franck Bonnetain <sup>a,g</sup>, Laetitia Dahan <sup>b,d</sup>, Emilie Maillard <sup>a</sup>, Marc Ychou <sup>c</sup>, Emmanuel Mitry <sup>d</sup>, Pascal Hammel <sup>e</sup>, Jean-Louis Legoux <sup>f</sup>, Philippe Rougier <sup>d</sup>, Laurent Bedenne <sup>a,h</sup>, Jean-François Seitz <sup>b,h</sup>



- Composite definition including death
- Validated using sorrogacy approach

**Table 3 – Quality of time until definitive deterioration (TUDD) ( $\geq 5$  points or 10 points) definition according to surrogacy for OS.**

Global health	Physical functioning	Emotional functioning	Pain	Fatigue
Hazard ratio [95% CI] (p value)				
TUDD ≥5 points				
Effect of treatment on TUDD				
HR(trt) = 0.74 [0.40; 1.38] (p = 0.35)	HR(trt) = 1.03 [0.62; 1.72] (p = 0.90)	HR(trt) = 1.49 [0.81; 2.74] (p = 0.20)	HR(trt) = 1.50 [0.78; 2.89] (p = 0.22)	HR(trt) = 0.94 [0.54; 1.63] (p = 0.81)
Effect of TUDD on OS				
HR(TUDD) = 2.15 [1.48; 3.12] (p < 0.0001)	HR(TUDD) = 1.81 [1.30; 2.50] (p = 0.0004)	HR(TUDD) = 1.97 [1.37; 2.83] (p = 0.0003)	HR(TUDD) = 2.79 [1.92; 4.06] (p < 0.0001)	HR(TUDD) = 1.91 [1.35; 2.71] (p = 0.0003)
Effect of TUDD on OS adjusted on treatment				
HR(trt) = 1.03 [0.77; 1.37] (p = 0.84)	HR(trt) = 0.95 [0.71; 1.26] (p = 0.71)	HR(trt) = 0.94 [0.70; 1.25] (p = 0.65)	HR(trt) = 0.96 [0.72; 1.28] (p = 0.78)	HR(trt) = 0.97 [0.73; 1.29] (p = 0.83)
HR(TUDD) = 2.16 [1.48; 3.15] (p < 0.0001)	HR(TUDD) = 1.81 [1.31; 2.51] (p = 0.0004)	HR(TUDD) = 1.98 [1.38; 2.86] (p = 0.0002)	HR(TUDD) = 2.79 [1.92; 4.07] (p < 0.0001)	HR(TUDD) = 1.91 [1.35; 2.71] (p = 0.0003)
Freedman's proportion explained PTE				
2.00	−0.80	−1.72	−0.37	−0.003
TUDD ≥10 points				
Effect of treatment on TUDD				
HR(trt) = 0.64 [0.31; 1.35] (p = 0.24)	HR(trt) = 1.12 [0.63; 1.99] (p = 0.70)	HR(trt) = 1.48 [0.74; 2.92] (p = 0.27)	HR(trt) = 1.50 [0.78; 2.89] (p = 0.22)	HR(trt) = 0.94 [0.54; 1.63] (p = 0.81)
Effect of TUDD on OS				
HR(TUDD) = 2.72 [1.79; 4.14] (p < 0.0001)	HR(TUDD) = 2.13 [1.50; 3.01] (p < 0.0001)	HR(TUDD) = 3.00 [2.02; 4.46] (p < 0.0001)	HR(TUDD) = 2.79 [1.92; 4.06] (p < 0.0001)	HR(TUDD) = 1.91 [1.35; 2.71] (p = 0.0003)
Effect of TUDD on OS adjusted on treatment				
HR(trt) = 1.05 [0.78; 1.39] (p = 0.76)	HR(trt) = 0.96 [0.73; 1.28] (p = 0.80)	HR(trt) = 0.92 [0.69; 1.22] (p = 0.54)	HR(trt) = 0.96 [0.72; 1.28] (p = 0.78)	HR(trt) = 0.97 [0.73; 1.29] (p = 0.83)
HR(TUDD) = 2.75 [1.80; 4.20] (p < 0.0001)	HR(TUDD) = 2.13 [1.50; 3.02] (p < 0.0001)	HR(TUDD) = 3.04 [2.05; 4.53] (p < 0.0001)	HR(TUDD) = 2.79 [1.92; 4.07] (p < 0.0001)	HR(TUDD) = 1.91 [1.35; 2.71] (p = 0.0003)
Freedman's proportion explained PTE				
2.46	−0.24	−1.92	−0.37	−0.003

# Objectives of the Q-RECIST project

- To define response/deterioration criteria for longitudinal QLQ-C30 +/- specific localization questionnaires data in cancer clinical trials
- Recommendations on the longitudinal statistical analysis to do and reporting of the results in a clinical meaningful way
  - ⇒ 4 work packages

# Work package 1

Literature review about the guidelines and the methodology on HRQoL longitudinal analyses in oncology randomized clinical trials (RCTs)

- ① methodological papers related to analysis of longitudinal HRQoL;
- ② guidelines by regulatory agencies or clinical societies on HRQoL in RCTs;
- ③ reporting of the results in RCTs using HRQoL;
- ④ and MCID.



This literature review will serve to elaborate questionnaire for consensus.

# WP 2: The consensus methodology

Objective: to determine what we have to do to achieve to a consensus or some guidelines on the longitudinal analysis in oncology clinical trials.

Different steps:

- 1 creation of an international and representative experts group
- 2 elaboration of the questionnaire to collect experts' opinions by steering committee
- 3 scoring of the questionnaires and analysis of the experts' opinions
- 4 and diffusion of the recommendations according to cancer sites and therapeutic settings

European Journal of Cancer (2013) 49, 769–781



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Protocol of the Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) project: Formal consensus method for the development of guidelines for standardised time-to-event endpoints' definitions in cancer clinical trials

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# Work package 3

Application and validation of the response criteria on both existing and simulated RCT data

- The Q-RECIST definitions retained will be tested on several databases from EORTC or other cooperative groups and according to several statistical approaches for the longitudinal analysis.
- Simulations studies will be investigated where lack of real data exists or where specific scenarios under varying assumptions need to be assessed

## A useful Q-RECIST metric should fulfill the requirements of PRO instruments:

- Appropriateness: is the Q-RECIST outcome reflecting the questions which it seeks to address?
- Acceptability: is Q-RECIST acceptable to patients and clinical researchers?
- Feasibility: is Q-RECIST easy to calculate and process?
- Interpretability: how interpretable are the Q-RECIST categories?
- Precision: how precise are the Q-RECIST categories?
- Reliability: does the algorithm produce results that are reproducible and consistent?
- Validity: do Q-RECIST categories measure what it claims to measure?
- Responsiveness: do Q-RECIST categories detect changes over time that matter to patients?
- Sensitivity: do Q-RECIST categories discriminate between distinct (groups of) patients?

# WP 4: Validating clinically relevant treatment differences

Ultimate aim : to apply Q-RECIST as a standardized endpoint in RCTs to evaluate interventions.

In order for Q-RECIST to be of added value, the relation to efficacy outcomes and toxicity outcomes needs to be established



Guidelines for evaluating treatment benefit using Q-RECIST in combination with survival and toxicity differences are therefore needed

We need to:

- establish that a Q-RECIST treatment effect is a robust measurement of true change
- express the treatment effect in a manner that is a clear indication of what benefit is experienced by what percentage of patients



# Perspectives

- Standardization/ guidelines
- Q-RECIST will enables an:
  - easier understanding of the results
  - easier determination of the sample size
- To promote and to allow use of HRQoL as co-primary endpoints in oncology RCTs

Perspective

EXPERT  
REVIEWS

## Health-related quality-of-life as co-primary endpoint in randomized clinical trials in oncology

*Expert Rev. Anticancer Ther. Early online, 1-7 (2015)*

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Overall survival (OS) has been considered as the most relevant primary endpoint but trials using OS often require large numbers of patients and long-term follow-up. Therefore composite endpoints, which are assessed earlier, are frequently used as primary endpoint but suffer from important limitations specially a lack of validation as surrogate of OS. Therefore, Health-related quality of life (HRQoL) could be considered as an outcome to judge efficacy of a treatment. An alternative approach would be to combine HRQoL with composite endpoints as co-primary endpoint to ensure a clinical benefit for patients of a new therapy. The decision rules of such design, the procedure to control the Type I error and the determination of