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The tale of two trials: improving the use of PROs and HRQoL in cancer clinical research

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Conflicts of interest

None to declare

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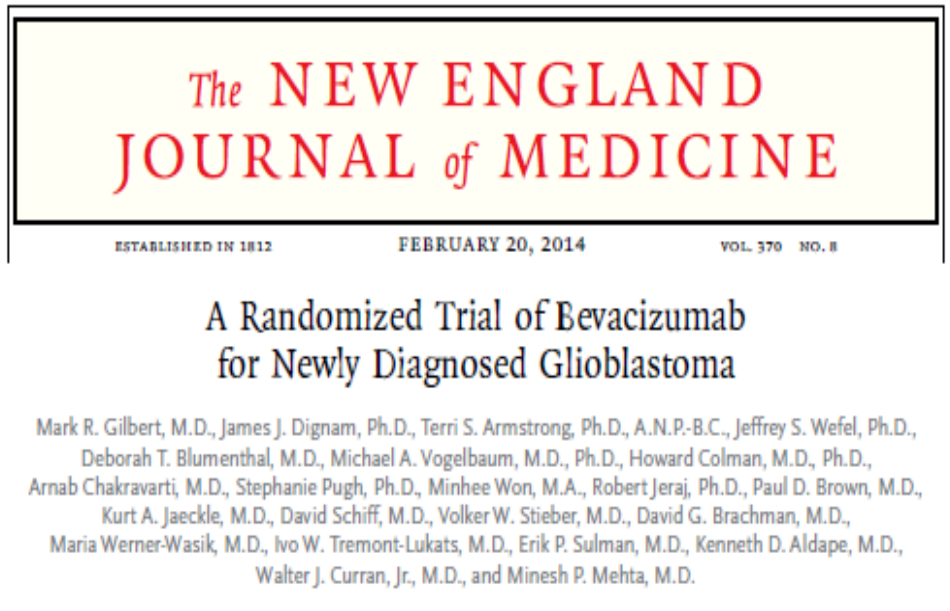
The tale of two tumor trials.....



The NEW ENGLAND JOURNAL of MEDICINE

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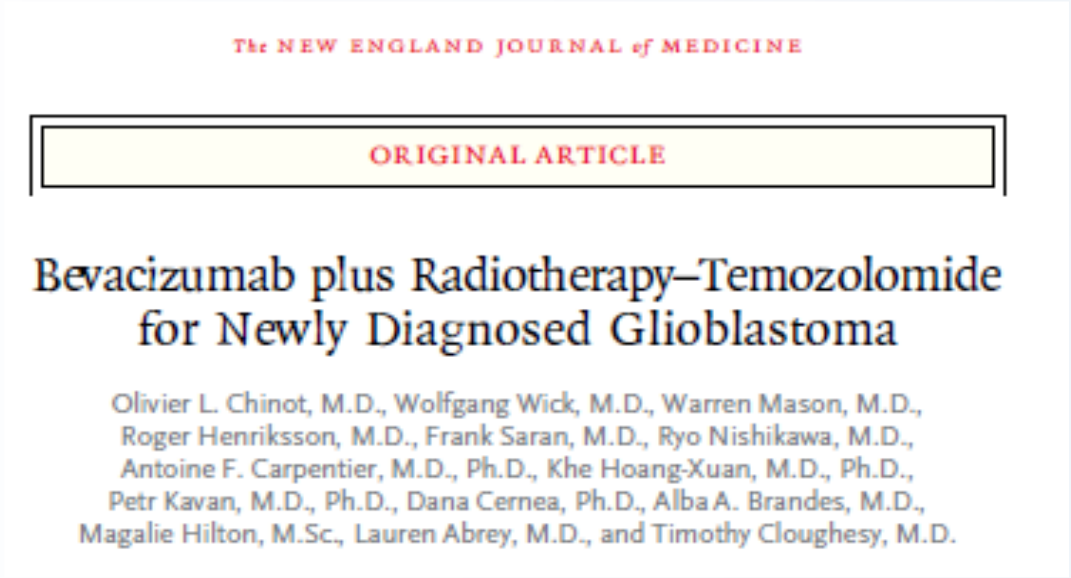
A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma

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.



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.

Gilbert *et al* N Engl J Med 2014; Chinot *et al* N Engl J Med 2014

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The tale of two tumor trials…..

	NEJM, 2014a (Gilbert et al)	NEJM, 2014b (Chinot et al)
Population	Newly diagnosed glioblastoma with central histological confirmation	
Treatment	Placebo vs new treatment	
Sample size	309 vs 312	463 vs 458
Overall survival (OS)	No benefit in OS 16.1 vs 15.7 months (HR=1.13 [0.93-1.37]; p=0.11)	No benefit in OS 16.7 vs 16.8 months (HR=0.88 [0.76-1.02]; p=0.10)
Progression Free Survival (PFS)	Benefit in PFS 7.3 vs 10.7 mths (HR=0.79 [0.66-0.94]; p=0.004)	Benefit in PFS 6.2 vs 10.6 mths (HR=0.64 [0.55-0.74]; p<0.001)
Health-related quality of life (HRQOL)	**Worsening in HRQOL** "Longitudinal evaluation also revealed *greater deterioration* in the [new treatment]…"	**Benefit in HRQOL** "…*deterioration-free survival was significantly longer among patients* in the [new treatment] than among those in the placebo group …"

Courtesy of Madeline Pe

What went wrong?

What went wrong?

Where they assessing the same **patient population**?

Were they assessing the same **HRQOL areas** at the **same time points**?

Were they assessing the same **endpoints?**

Were the same **populations of patients** included in the analysis?

Courtesy of Madeline Pe

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The tale of two tumor trials…..

	NEJM, 2014a	NEJM, 2014b
Patient population	Adult newly-diagnosed histologically confirmed GBM, KPS ≥ 70	Adult newly-diagnosed histologically confirmed supratentorial GBM, WHO ≤ 2, no prior therapy

Courtesy of Madeline Pe

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Patient population – selection bias

METHODS

PATIENTS

Patients 18 to 70 years of age with newly diagnosed and histologically confirmed glioblastoma (World Health Organization [WHO] grade IV astrocytoma) were eligible for the study. Eligible patients had a WHO performance status of 2 or less and adequate hematologic, renal, and hepatic function (absolute neutrophil count, ≥1500 per cubic millimeter; platelet count, ≥100,000 per cubic millimeter; serum creatinine level, ≤1.5 times the upper limit of normal in the laboratory where it was measured; total serum bilirubin level, ≤1.5 times the upper limit of normal; and liver-function values, <3 times the upper limit of normal for the laboratory). Patients who were receiving corticosteroids had to receive a stable or decreasing dose for at least 14 days before randomization. All patients provided written informed consent, and the study was approved by the ethics committees of the participating centers.

Stupp *et al.* N Engl J Med 2005

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Patient population – cultural differences

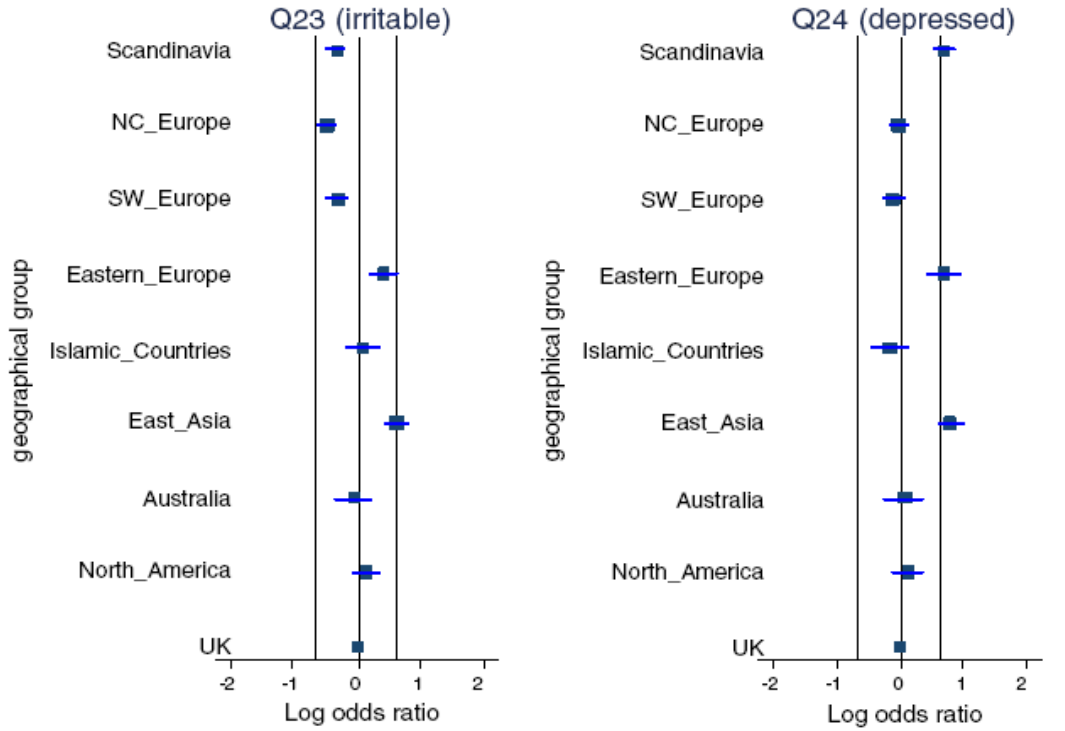

Figure 2. Emotional functioning (EF).

Scott *et al.* Qual Life Res 2007

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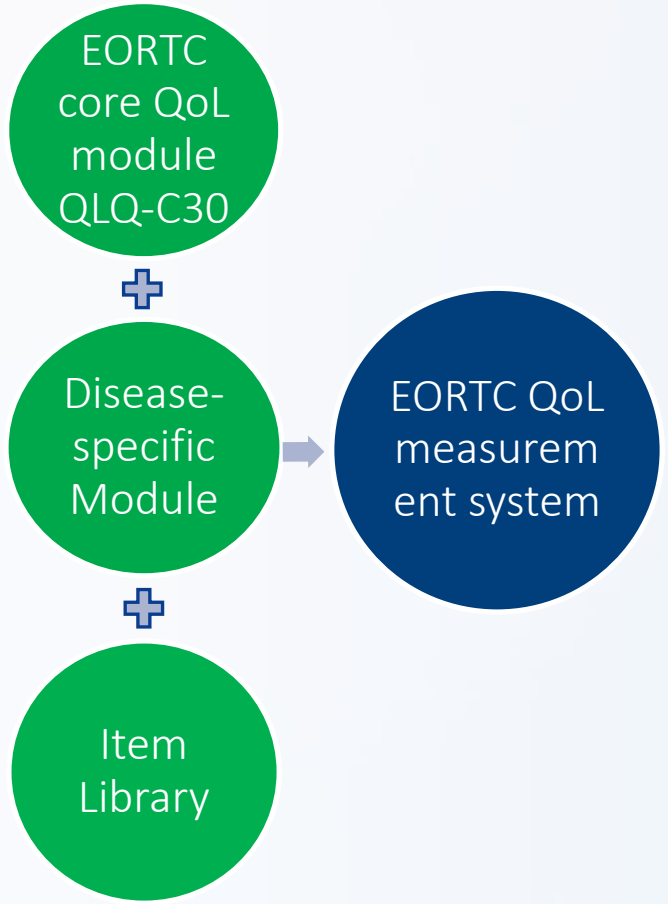
EORTC QLG measurement vision

Free-of-charge for academic users

Royalties for commercial users



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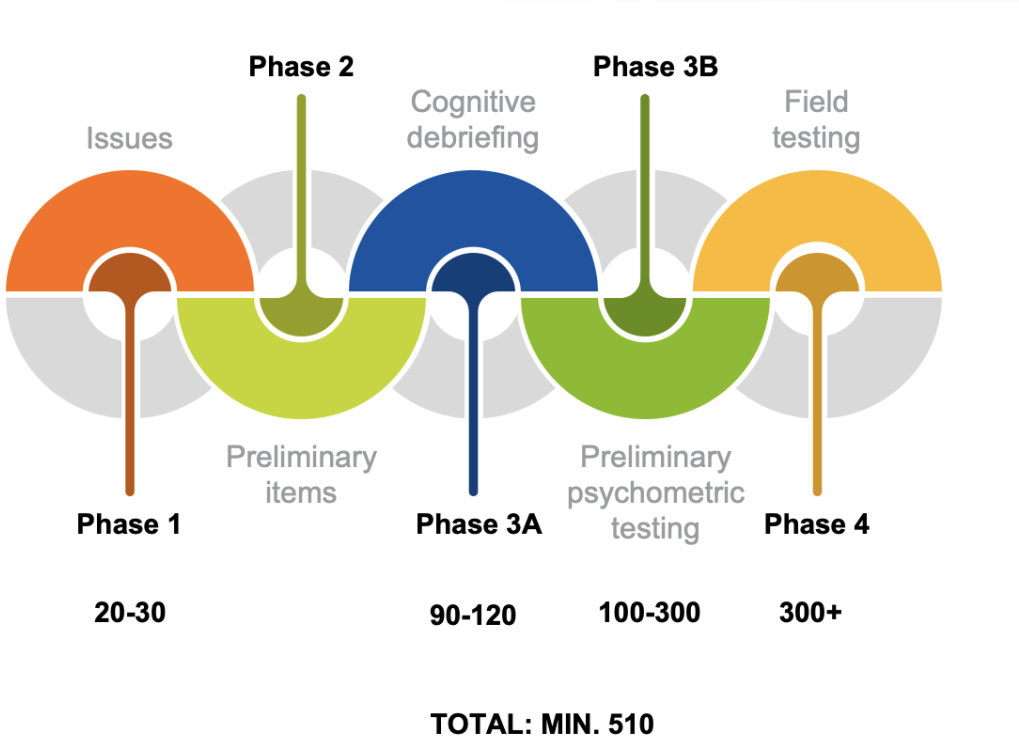
The patients' voice …



Courtesy of Dagmara Kulis; EORTC Module Development Guidelines. 5th Edition. Brussels: 2021.

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The tale of two tumor trials…..

	NEJM, 2014a	NEJM, 2014b
HRQOL measure	EORTC QLQ-C30 & QLQ-BN20	
HRQOL areas	Cognitive functioning, motor dysfunction, communication deficit	Global health status, physical functioning, social functioning, motor dysfunction, and communication deficit

Conclusions about HRQOL were not necessarily based on the same HRQOL areas.

Courtesy of Madeline Pe

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Timing of PRO assessments…..

Health-related quality of life in patients with high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study

Jaap C Reijneveld, Martin J B Taphoorn, Corneel Coens, Jacoline E C Bromberg, Warren P Mason, Khê Hoang-Xuan, Gail Ryan, Mohamed Ben Hassel, Roelien H Enting, Alba A Brandes, Antje Wick, Olivier Chinot, Michele Reni, Guy Kantor, Brian Thiessen, Martin Klein, Eugenie Verger, Christian Borchers, Peter Hau, Michael Back, Anja Smits, Vassilis Golfinopoulos, Thierry Gorlia, Andrew Bottomley, Roger Stupp, Brigitta G Baumert

Summary

Background Temozolomide chemotherapy versus radiotherapy in patients with a high-risk low-grade glioma has been shown to have no significant effect on progression-free survival. If these treatments have a different effect on health-related quality of life (HRQOL), it might affect the choice of therapy. We postulated that temozolomide compromises HRQOL and global cognitive functioning to a lesser extent than does radiotherapy.

Methods We did a prospective, phase 3, randomised controlled trial at 78 medical centres and large hospitals in 19 countries. We enrolled adult patients (aged ≥18 years) with histologically confirmed diffuse (WHO grade II) astrocytoma, oligodendroglioma, or mixed oligoastrocytoma, with a WHO performance status of 2 or lower, without previous chemotherapy or radiotherapy, who needed active treatment other than surgery. We randomly assigned eligible patients (1:1) using a minimisation technique, stratified by WHO performance status (0–1 *vs* 2), age (<40 years *vs* ≥40 years), presence of contrast enhancement on MRI, chromosome 1p status (deleted *vs* non-deleted *vs* indeterminate), and the treating medical centre, to receive either radiotherapy (50·4 Gy in 28 fractions of 1·8 Gy for 5 days per week up to 6·5 weeks) or temozolomide chemotherapy (75 mg/m² daily, for 21 of 28 days [one cycle] for 12 cycles). The primary endpoint was progression-free survival (results published separately); here, we report the results for two key secondary endpoints: HRQOL (assessed using the European Organisation for Research and Treatment of Cancer's [EORTC] QLQ-C30 [version 3] and the EORTC Brain Cancer Module [QLQ-BN20]) and global cognitive functioning (assessed using the Mini-Mental State Examination [MMSE]). We did analyses on the intention-to-treat population. This study is closed and is registered at EudraCT, number 2004-002714-11, and at ClinicalTrials.gov, number NCT00182819.

Findings Between Dec 6, 2005, and Dec 21, 2012, we randomly assigned 477 eligible patients to either radiotherapy (n=240) or temozolomide chemotherapy (n=237). The difference in HRQOL between the two treatment groups was not significant during the 36 months' follow-up (mean between group difference [averaged over all timepoints] 0·06, 95% CI −4·64 to 4·75, p=0·98). At baseline, 32 (13%) of 239 patients who received radiotherapy and 32 (14%) of 236 patients who received temozolomide chemotherapy had impaired cognitive function, according to the MMSE scores. After randomisation, five (8%) of 63 patients who received radiotherapy and three (6%) of 54 patients who received temozolomide chemotherapy and who could be followed up for 36 months had impaired cognitive function, according to the MMSE scores. No significant difference was recorded between the groups for the change in MMSE scores during the 36 months of follow-up.

Interpretation The effect of temozolomide chemotherapy or radiotherapy on HRQOL or global cognitive functioning did not differ in patients with low-grade glioma. These results do not support the choice of temozolomide alone over radiotherapy alone in patients with high-risk low-grade glioma.

Funding Merck Sharp & Dohme-Merck & Co, National Cancer Institute, Swiss Cancer League, National Institute for Health Research, Cancer Research UK, Canadian Cancer Society Research Institute, National Health and Medical Research Council, European Organisation for Research and Treatment of Cancer Cancer Research Fund.

Reijneveld *et al.* Lancet Oncol 2016

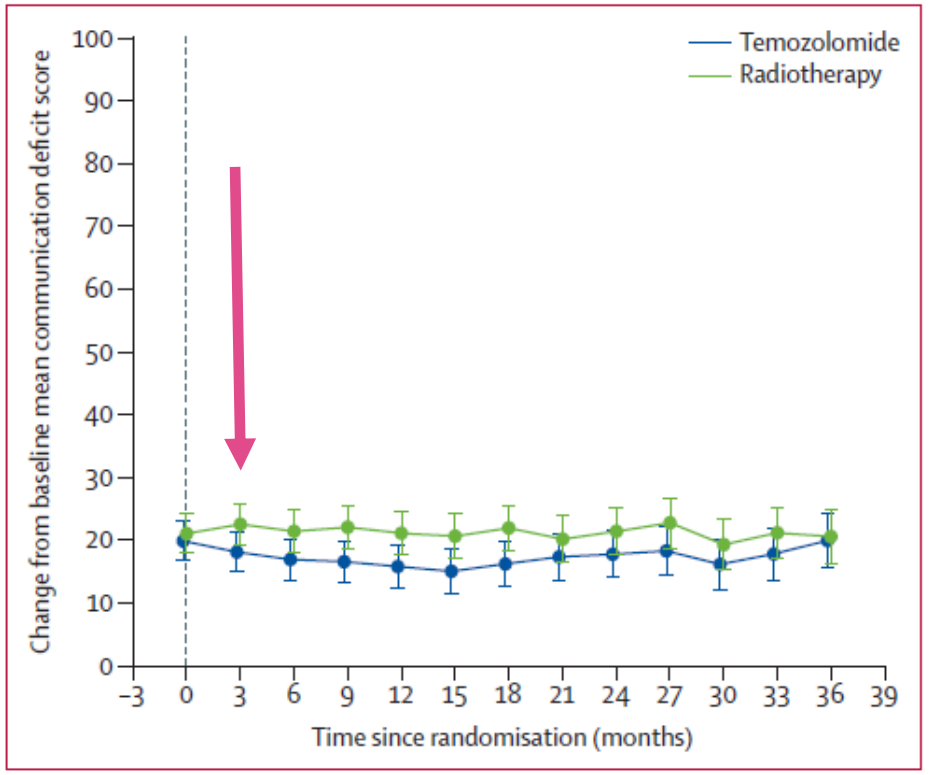

Figure 2: **Changes from baseline in communication deficit scores**
Error bars are SDs. 0 months is the baseline. A higher communication deficit score means more symptoms.

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What went wrong?

Where they assessing the same **patient population**?

Were they assessing the same **HRQOL areas** at the **same time points**?

Were they assessing the same endpoints?

Were the same **populations of patients** included in the analysis?

Courtesy of Madeline Pe

The tale of two tumor trials…..

	NEJM, 2014a	NEJM, 2014b
Endpoints	Change in HRQOL scores at 46 weeks *(~10 months)*	Time to >/10 point worsening from pre-treatment scores without improvement OR disease progression OR death *(Result: ~4 months to ~8 months)*

Conclusions about HRQOL were not based on the same endpoint.

The two trials were responding to different aspects of the data.

Courtesy of Madeline Pe & Mees Egeler

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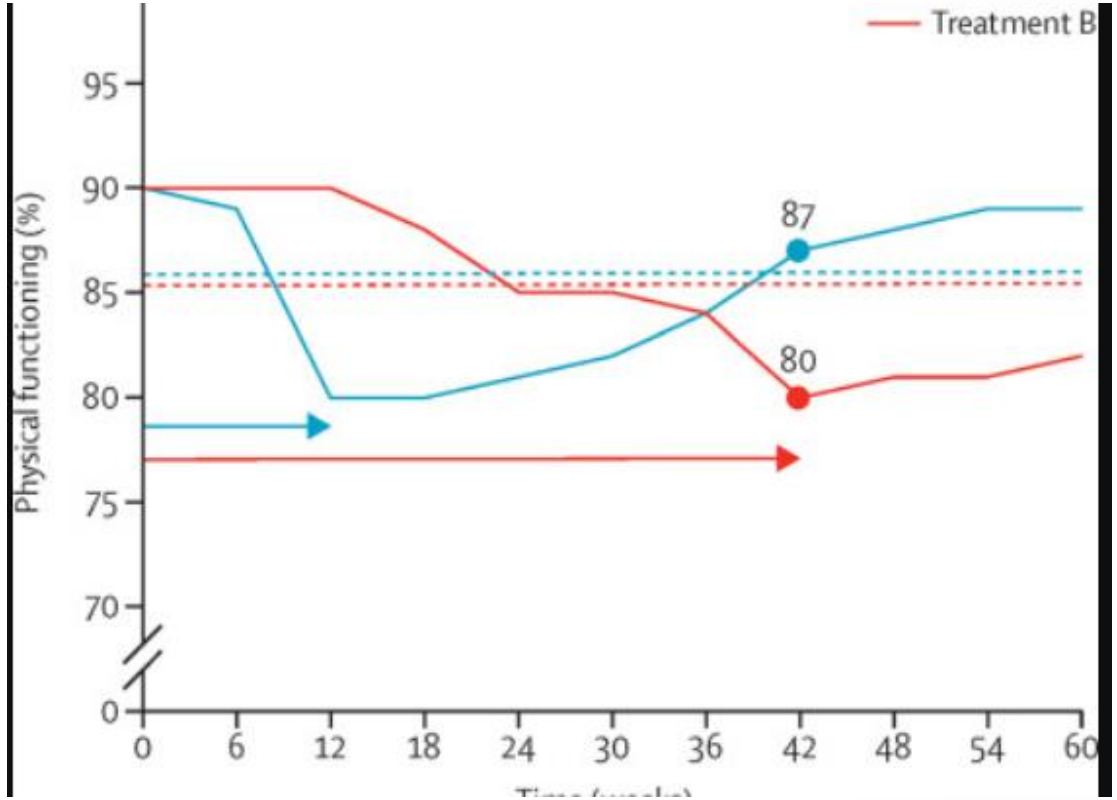
Assessing the same endpoints?



Based on the chosen analysis, the results would show that:

1. The time to deterioration analysis would favor treatment B (12 weeks vs 42 weeks)
2. The overall analysis would not favor either treatment
3. Examining differences at the end of treatment would favor treatment A.

Courtesy of Madeline Pe & Mees Egeler

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The tale of two tumor trials…..

	NEJM, 2014a	NEJM, 2014b
Endpoints	Change in HRQOL scores at 46 weeks *(~10 months)*	Time to >/10 point worsening from pre-treatment scores without improvement OR disease progression OR death *(Result: ~4 months to ~8 months)*
	What if a patient's **disease progresses** and the patient does not respond to the questionnaire at week 46?	What if a patient's **disease progresses** and the patient dropped out of treatment before a >/10 point worsening is recorded?
	Ignored = not included in the analyses*	disease progression = >/10 point worsening of HRQOL scores

Missing data

Handling of missing data

Courtesy of Madeline Pe

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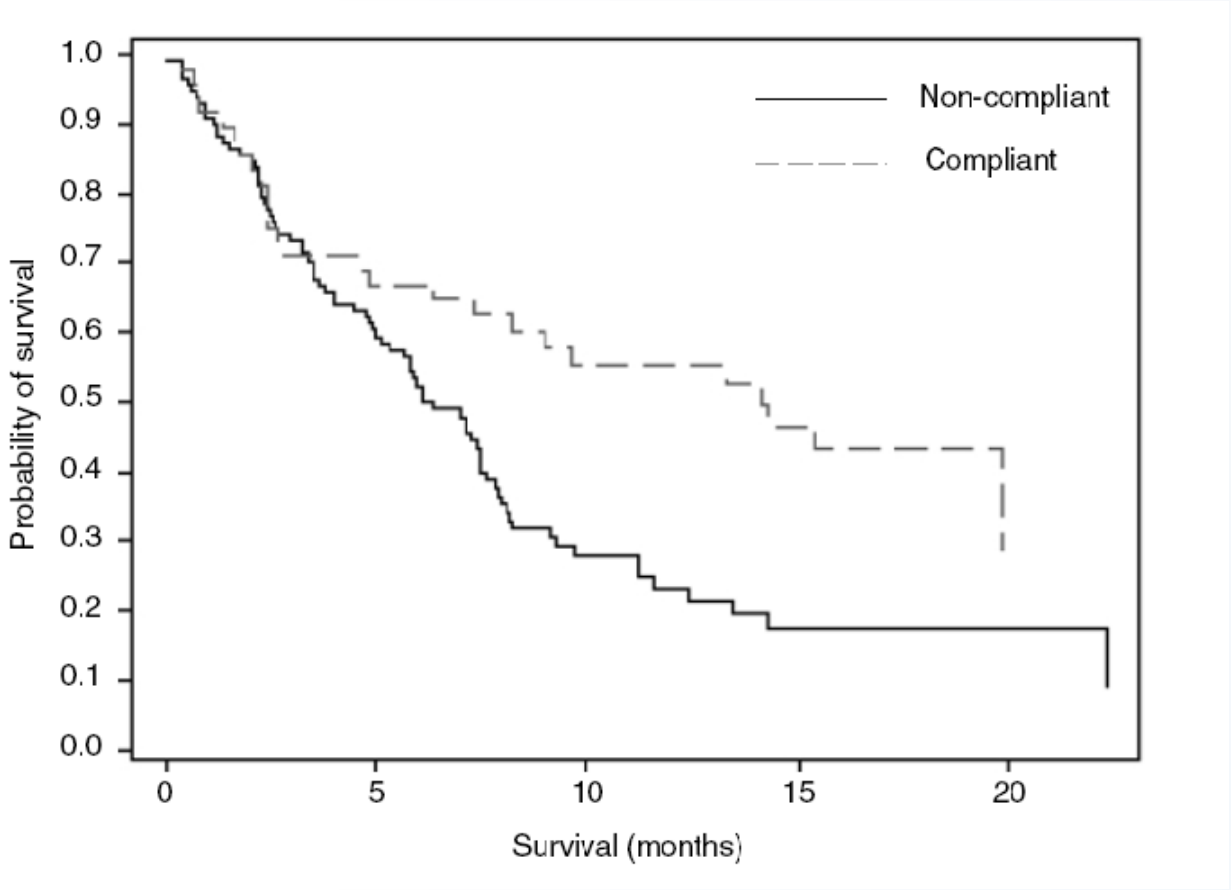
Compliance – patient level



Taphoorn *et al.* Lancet Oncol 2005; Walker *et al.* J Neuro Oncol 2005

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Compliance – institutional level

Institutions with good QOL compliance have better survival outcomes.

HRQOL compliance is not independent from clinical care of HRQOL

Greimel *et al.* Gynecol Oncol 2013

The tale of two tumor trials…..

	NEJM, 2014a	NEJM, 2014b
Analysis population	Only patients alive and free of disease at 46 weeks	All patients included in the trial

The patient population included in the analyses differed between the two trials.

Courtesy of Madeline Pe

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The HRQOL results of the two trials are not directly comparable…

but they looked like they were…

Courtesy of Madeline Pe

Solutions

How can we make things better?

Where they assessing the same **patient population**?

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EORTC Quality of Life Group

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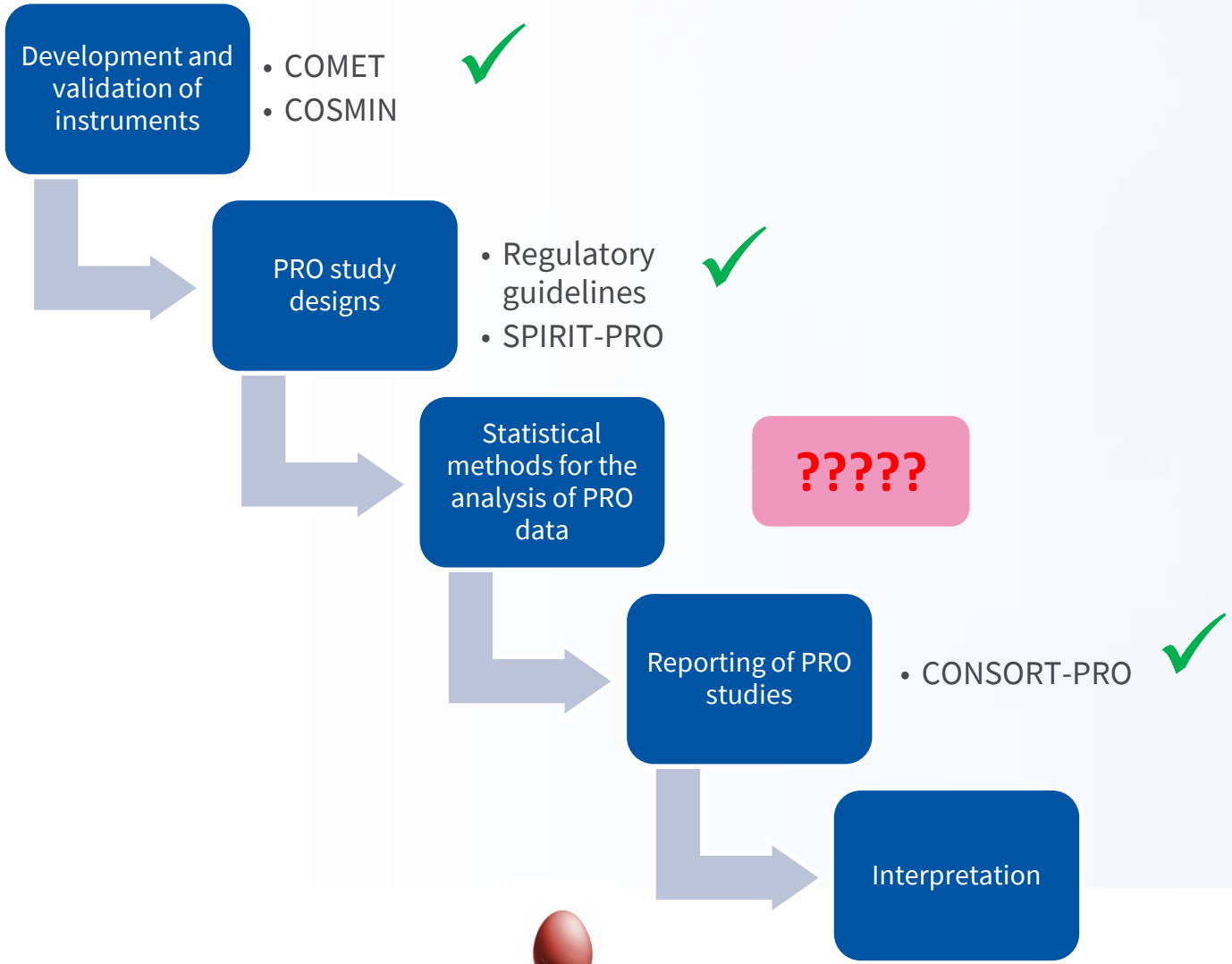
Courtesy of Madeline Pe

Something was missing..



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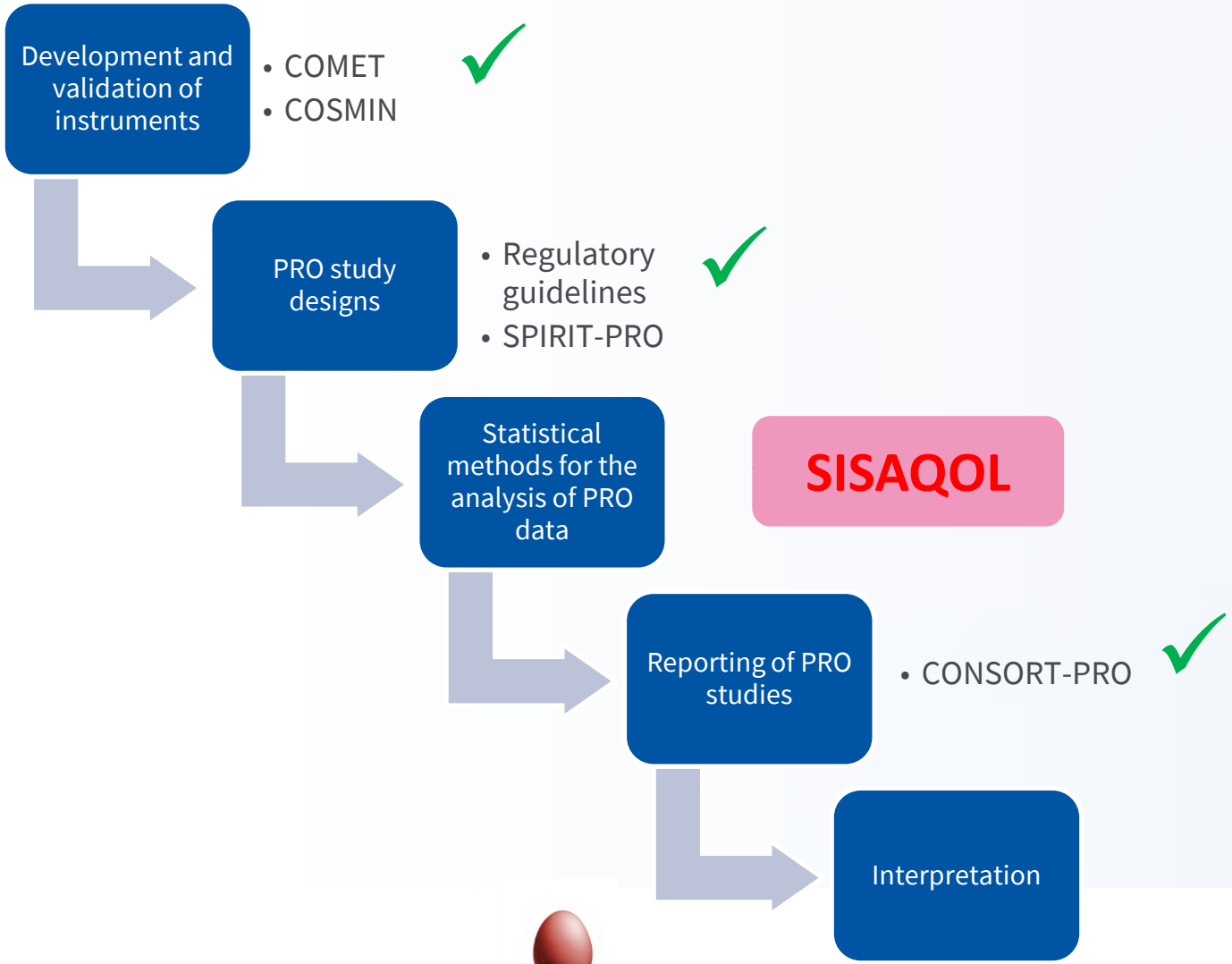
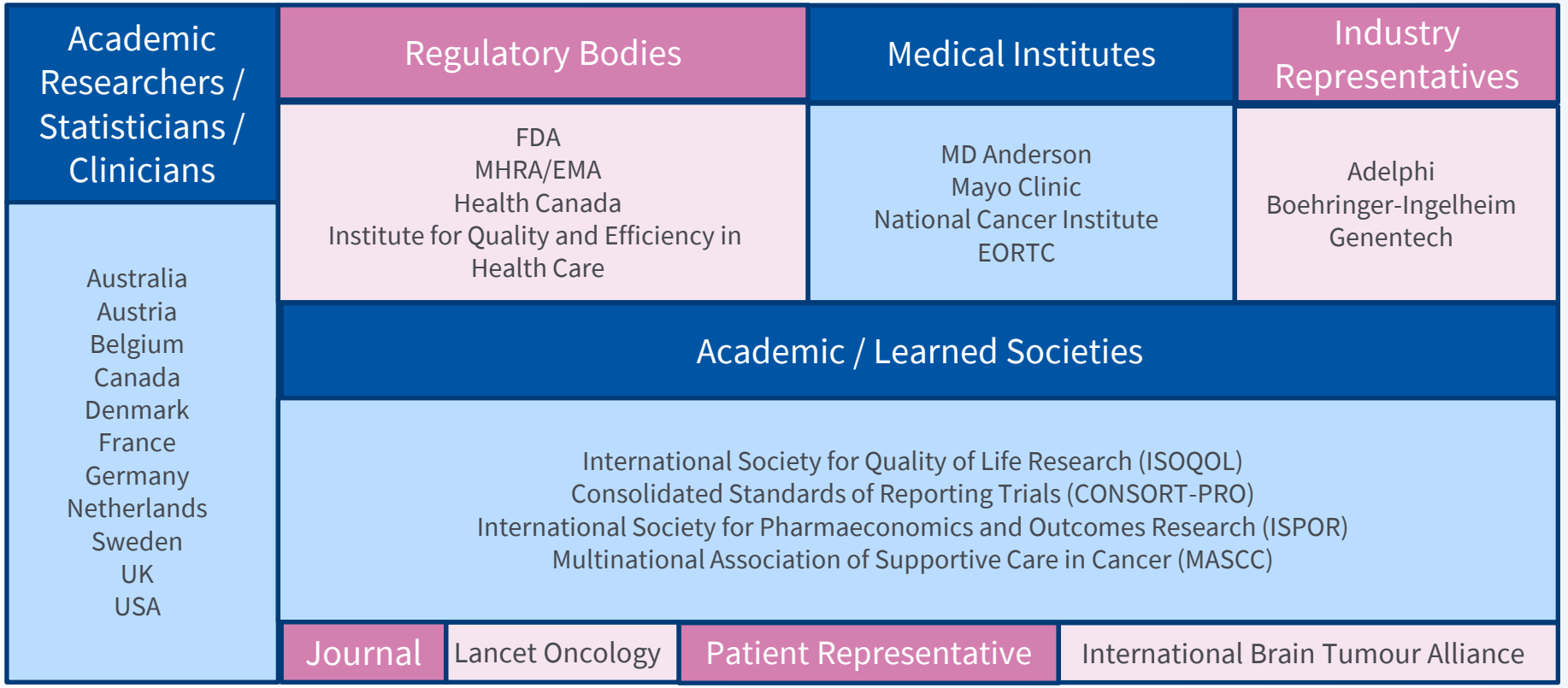


Courtesy of Madeline Pe

Setting International StandArds in QOL Research (SISAQOL) Consortium



Courtesy of Madeline Pe

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Take home messages

The EORTC QOL Group has an extensive portfolio of QOL measures (and continuously updates and further improves them)

We do not only build ‘planes’, but also teach how to fly with them

The next challenge will be to assess how our patient-reported outcomes (PRO) and health-related quality of life (HRQoL) data inform regulatory decisions

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THANK YOU