Endpoints (ICH E9)

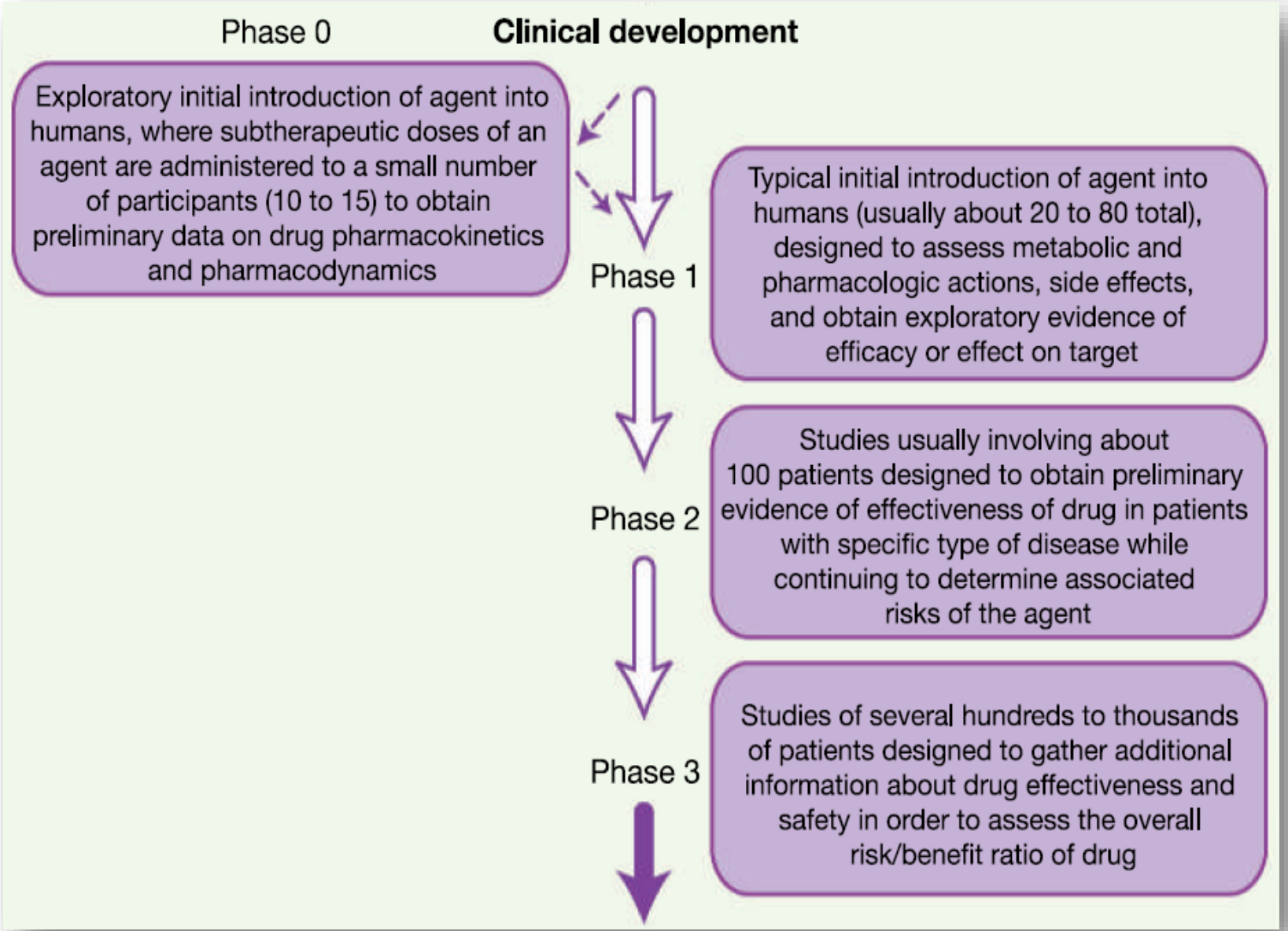
- The primary variable ('target' variable, primary endpoint)
- Capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial
- A reliable and validated variable measuring some clinically relevant and important treatment benefit in the patient population

International Conference for Harmonization (ICH). Efficacy Guidelines. ICH Topic E 9, Statistical Principles for Clinical Trials

What makes a good endpoint?

Characteristic	Meaning
Relevant	Clinically important/useful
Quantifiable	Measured on an appropriate scale
Valid	Measures the intended effect
Objective	Interpreted the same by all observers
Reliable	Same effect yields consistent measurements
Sensitive	Responds to small changes in the effect
Specific	Unaffected by extraneous influences
Precise	Small variability
Other	Tradition, cost, time, missing data

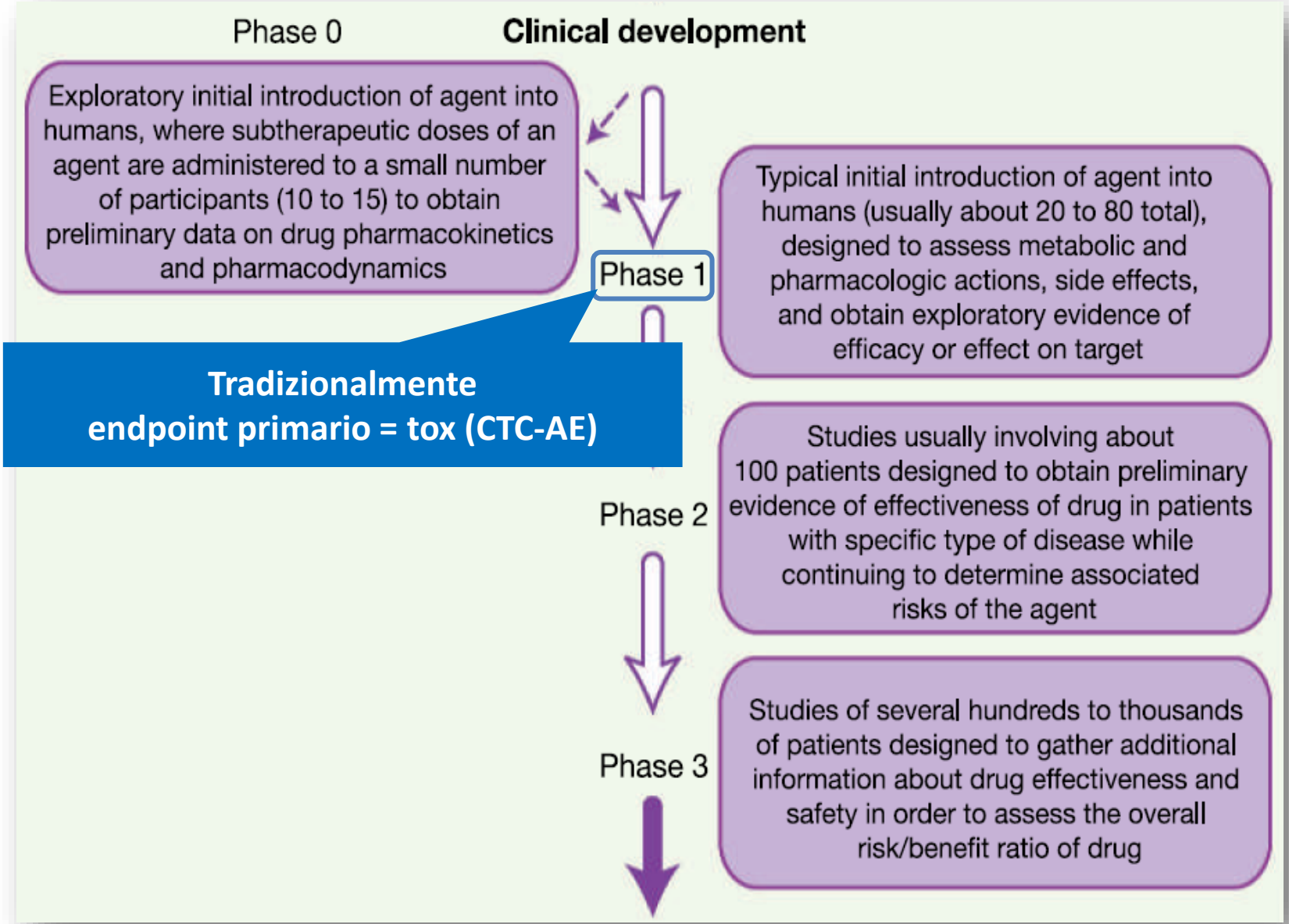
S. Piantadosi (2005)



Clin Cancer Res; 16(6) March 15, 2010

VARIABILE DI RISPOSTA

- di tipo **quantitativo**
  - assume uno spettro continuo di valori e viene misurata in riferimento a una scala a intervalli costanti.
- di tipo **qualitativo**
  - esprime categorie di risposta del tipo successo / insuccesso (di un trattamento somministrato).
- del tipo "**tempo a evento**"
  - rappresenta il tempo trascorso fino al verificarsi (o meno) di un evento.



Clin Cancer Res; 16(6) March 15, 2010

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Issues with Novel Targeted Non-Cytotoxics

- Dose-Toxicity and Dose-Effect relationships: may not be parallel
- May not cause regression of established tumours
- Thus, for newer agents:
  - phase I trials: endpoint should be ????
  - phase II trials: endpoint should be ????

National Cancer Institute Of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe Des Essais Cliniques

E. Eisenhauer, ESMO 2002

EFFICACY AND SAFETY OF A SPECIFIC INHIBITOR OF THE BCR-ABL TYROSINE KINASE IN CHRONIC MYELOID LEUKEMIA

BRIAN J. DRUKER, M.D., MOSHE TALPAZ, M.D., DEBRA J. RESTA, R.N., BIN PENG, PH.D., ELISABETH BUCHDUNGER, PH.D., JOHN M. FORD, M.D., NICHOLAS B. LYDON, PH.D., HAGOP KANTARJIAN, M.D., RENAUD CAPDEVILLE, M.D., SAYURI OHNO-JONES, B.S., AND CHARLES L. SAWYERS, M.D.

N Engl J Med, Vol. 344, No. 14 · April 5, 2001

ADVERSE EVENT	25–140 mg (N=14)		200–300 mg (N=23)		350–500 mg (N=18)		600–1000 mg (N=28)		TOTAL (N=83)
	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADES 1–4
	% of patients								no. (%)
Nausea	21	0	30	0	50	0	59	0	36 (43)
Myalgias	21	0	52	0	33	6	28	14	34 (41)
Edema	21	0	22	0	33	0	55	7	32 (39)
Diarrhea	14	0	4	0	33	0	38	3	21 (25)
Fatigue	14	0	22	0	11	0	24	3	17 (20)
Rash	7	0	17	0	11	0	28	3	16 (19)
Dyspepsia	14	0	13	0	28	0	17	0	15 (18)
Vomiting	0	0	13	0	11	0	34	0	15 (18)
Thrombocytopenia	0	0	4	0	11	6	7	24	13 (16)
Neutropenia	0	0	9	4	6	6	0	24	12 (14)
Arthralgias	0	0	4	0	6	0	28	3	11 (13)

STI571 was generally well tolerated, and a maximal tolerated dose was not identified.

A Practical Approach: Phase I Design Non-Cytotoxics

- Continue to limit dose using toxicity.
- Explore alternative endpoints as part of trial including:
  - Target inhibition
  - Blood levels
- Final dose decision may be based on a composite of these.
- Further exploration of dose effects may need (randomized) phase II designs.

National Cancer Institute Of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe Des Essais Cliniques

E. Eisenhauer, ESMO 2002

Table 1. Overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions*

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

*CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease. *See* text for more details.

cal initial introduction of agent into
ans (usually about 20 to 80 total),
signed to assess metabolic and
rmacologic actions, side effects,
d obtain exploratory evidence of
efficacy or effect on target

Studies usually involving about
100 patients designed to obtain preliminary
evidence of effectiveness of drug in patients
with specific type of disease while
continuing to determine associated
risks of the agent

Phase 2

Tradizionalmente
endpoint primario = risposta (RECIST)

Phase 3

Studies of several hundreds to thousands
of patients designed to gather additional
information about drug effectiveness and
safety in order to assess the overall
risk/benefit ratio of drug

Clin Cancer Res; 16(6) March 15, 2010

Issues with Novel Targeted Non-Cytotoxics

- Dose-Toxicity and Dose-Effect relationships: may not be parallel
- May not cause regression of established tumours
- Thus, for newer agents:
  - phase I trials: endpoint should be ????
  - phase II trials: endpoint should be ????

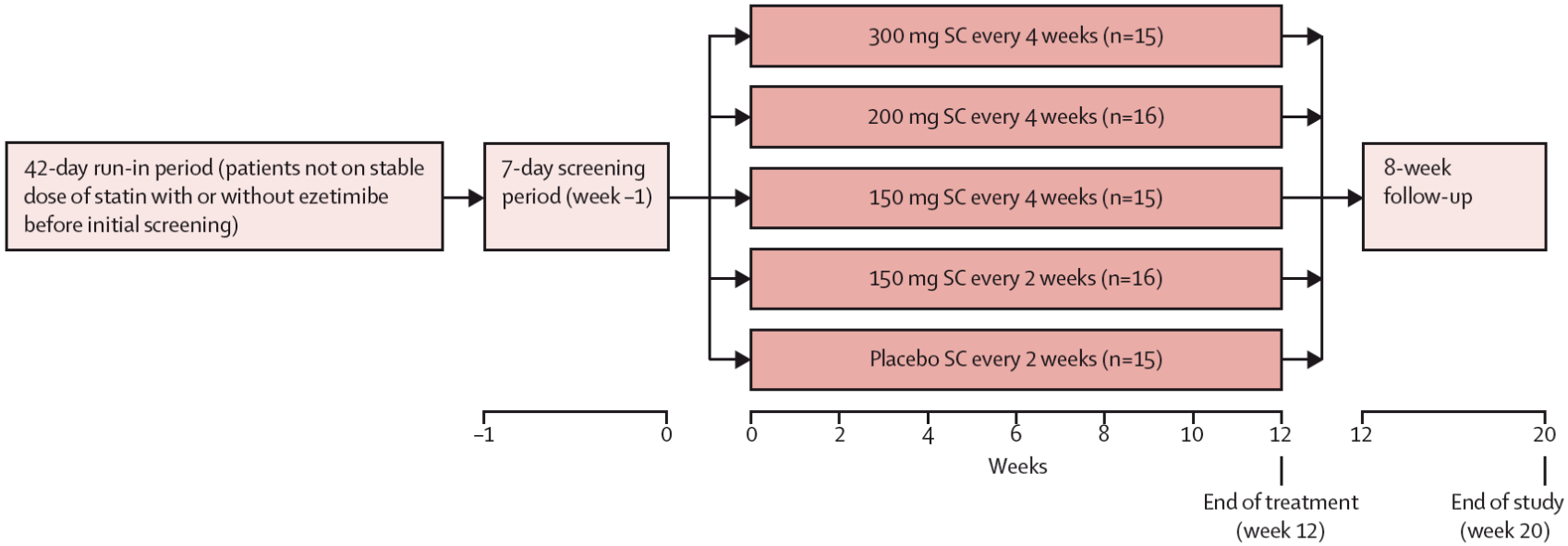
National Cancer Institute Of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe Des Essais Cliniques

E. Eisenhauer, ESMO 2002

Effect of a monoclonal antibody to PCSK9, REGN727/ SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial

Evan A Stein, Dan Gipe, Jean Bergeron, Daniel Gaudet, Robert Weiss, Robert Dufour, Richard Wu, Robert Pordy

Lancet 2012; 380: 29–36



The primary efficacy endpoint was the mean percent change in calculated LDL-C from baseline (mean week –1 and week 0 values) to week 12.

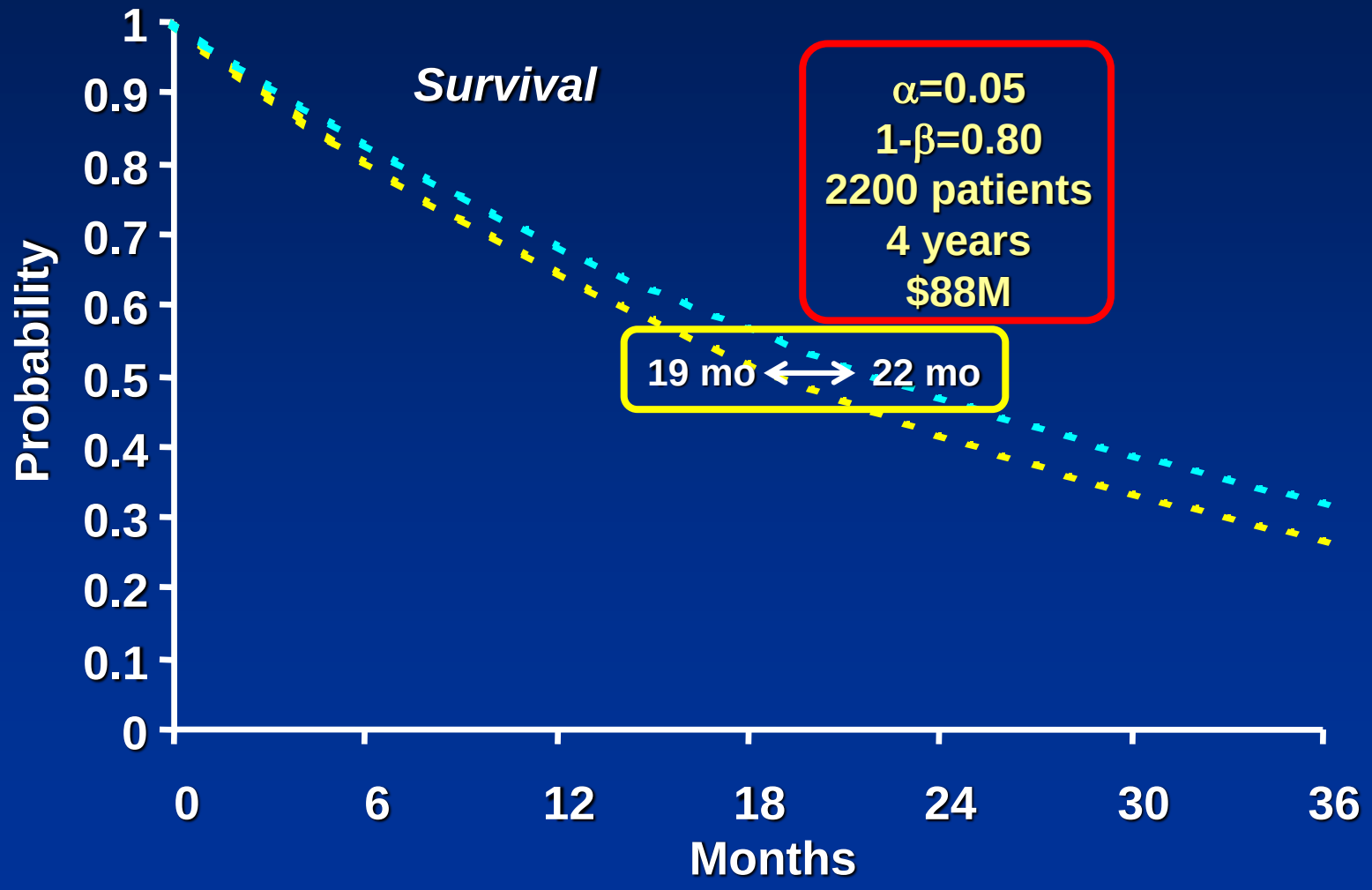
ICH E8 and E9

- Confirmatory trials should demonstrate clinical benefit
- The primary endpoint
  - Should provide the most clinically relevant and convincing evidence
  - Valid and reliable measure of some clinically relevant and important treatment benefit

Regular Approval Basis – "Clinical Benefit"

- **Longer life**
- Better life
- Established Surrogate for one of above

Survival Superiority Study Offers Too Little, Too Late, For Too Much

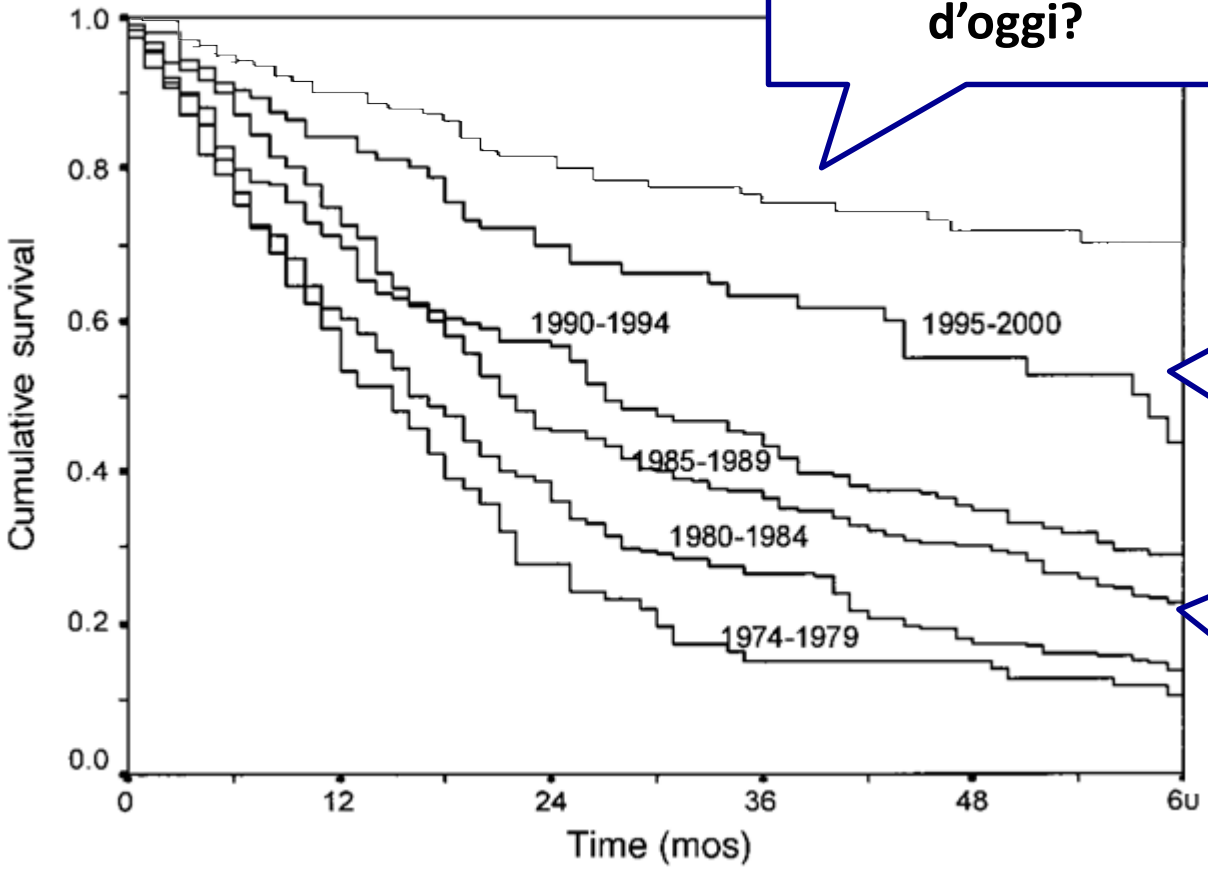


Assumes accrual = 100 patients/mo; follow-up = largest median + 2 mo (TTP) or 4 mo (survival)

L.L. Miller, 2003

Trends in Breast Cancer Survival/Giordano et al.
CANCER January 1, 2004 / Volume 100 / Number 1

Overall survival from time of recurrence

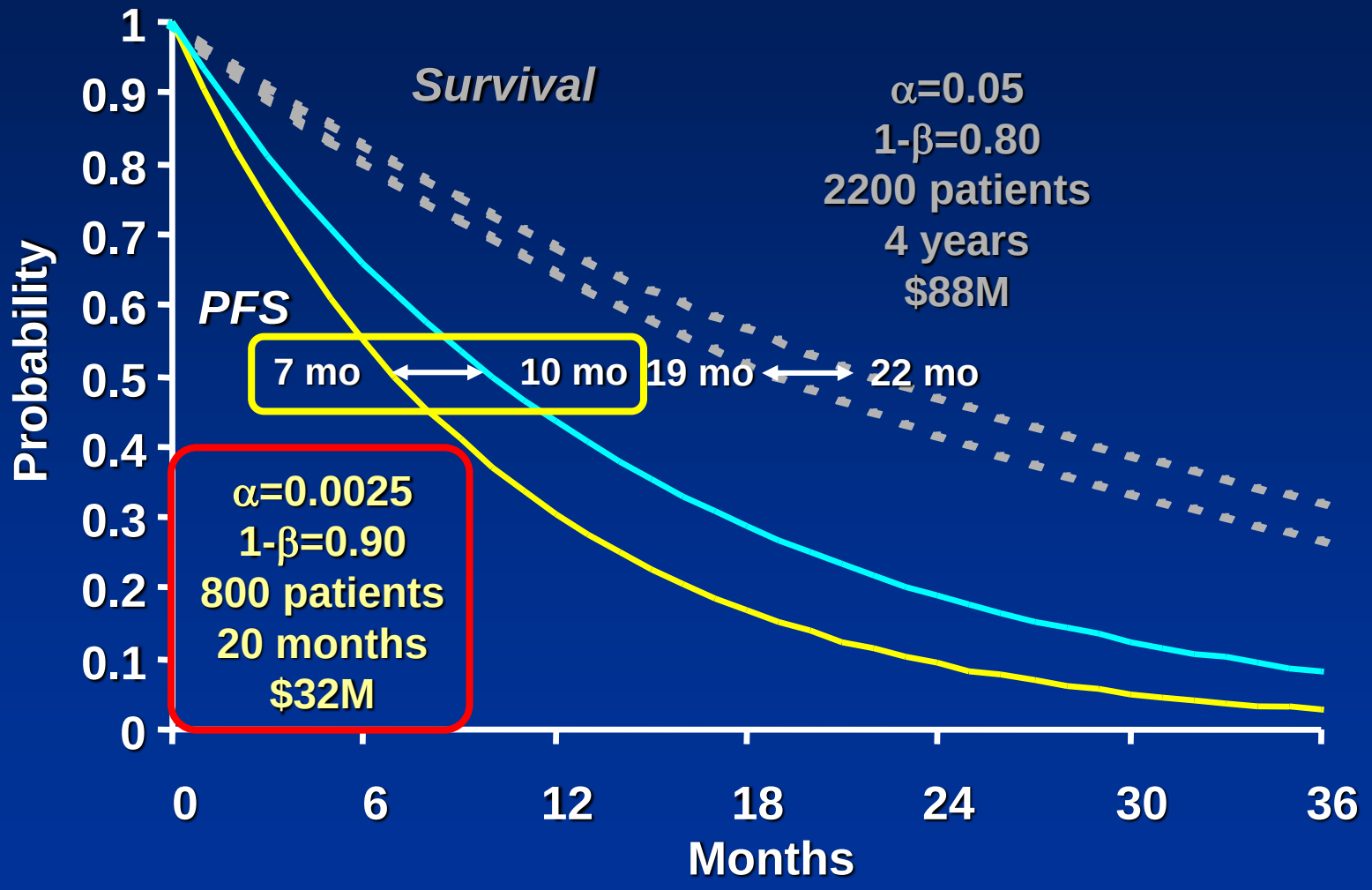


… e al giorno d'oggi?

Più difficile ottenere un beneficio relativo di Sopravvivenza

(abbastanza) facile ottenere un beneficio relativo di Sopravvivenza

Single Superiority Study Can Offer Highly Robust PFS Assessment (α=0.0025)



Assumes accrual = 100 patients/mo; follow-up = largest median + 2 mo (TTP) or 4 mo (survival)

L.L. Miller, 2003

Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: Results of a 24 week, double-blind, randomized Phase 3 trial

Eli M. Roth [a,*], Marja-Riitta Taskinen [b], Henry N. Ginsberg [c], John J.P. Kastelein [d], Helen M. Colhoun [e], Jennifer G. Robinson [f], Laurence Merlet [g], Robert Pordy [h], Marie T. Baccara-Dinet [i]

International Journal of Cardiology 176 (2014) 55–61

The primary endpoint was the percent change from baseline in calculated LDL-C at 24 weeks with alirocumab compared [illegible]h ezetimibe.

LDL-C…

- **Endpoint di attività?**
- **Endpoint di efficacia?**
- **Endpoint "intermedio" (surrogato?)**

The Treat-to-Target Trial

Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients

MATTHEW C. RIDDLE, MD[1] JOHN GERICH, MD[2]
JULIO ROSENSTOCK, MD[2]
ON BEHALF OF THE INSULIN GLARGINE 4002 STUDY INVESTIGATORS*

DIABETES CARE, VOLUME 26, NUMBER 11, NOVEMBER 2003

The primary outcome measure was the percentage of subjects achieving HbA_{1c} ≤7.0% without a single instance of [illegible]mp-tomatic nocturnal hypogl[illegible]on-

HbA_{1c}…

- **Endpoint di attività?**
- **Endpoint di efficacia?**
- **Endpoint "intermedio" (surrogato?)**

“Surrogate” endpoints

- **Issue:**
  - **Quicker, less expensive, less clinically relevant endpoint or**
  - **More expensive, clinically definitive endpoint?**

“Surrogate” endpoints

“Surrogate” endpoints

- **Issue:**
  - **Quicker, less expensive, less clinically relevant endpoint or**
  - **More expensive, clinically definitive endpoint?**
- **Hesitate to use the term "surrogate"**
- **Has a specific technical definition**

Mark Conaway, June 2006

Regular Approval Basis – "Clinical Benefit"

- **Longer life**
- Better life
- **Established Surrogate** for one of above

Validation of Surrogate Endpoints

Property of a Valid Surrogate

Effect of the Intervention
on the Clinical Endpoint

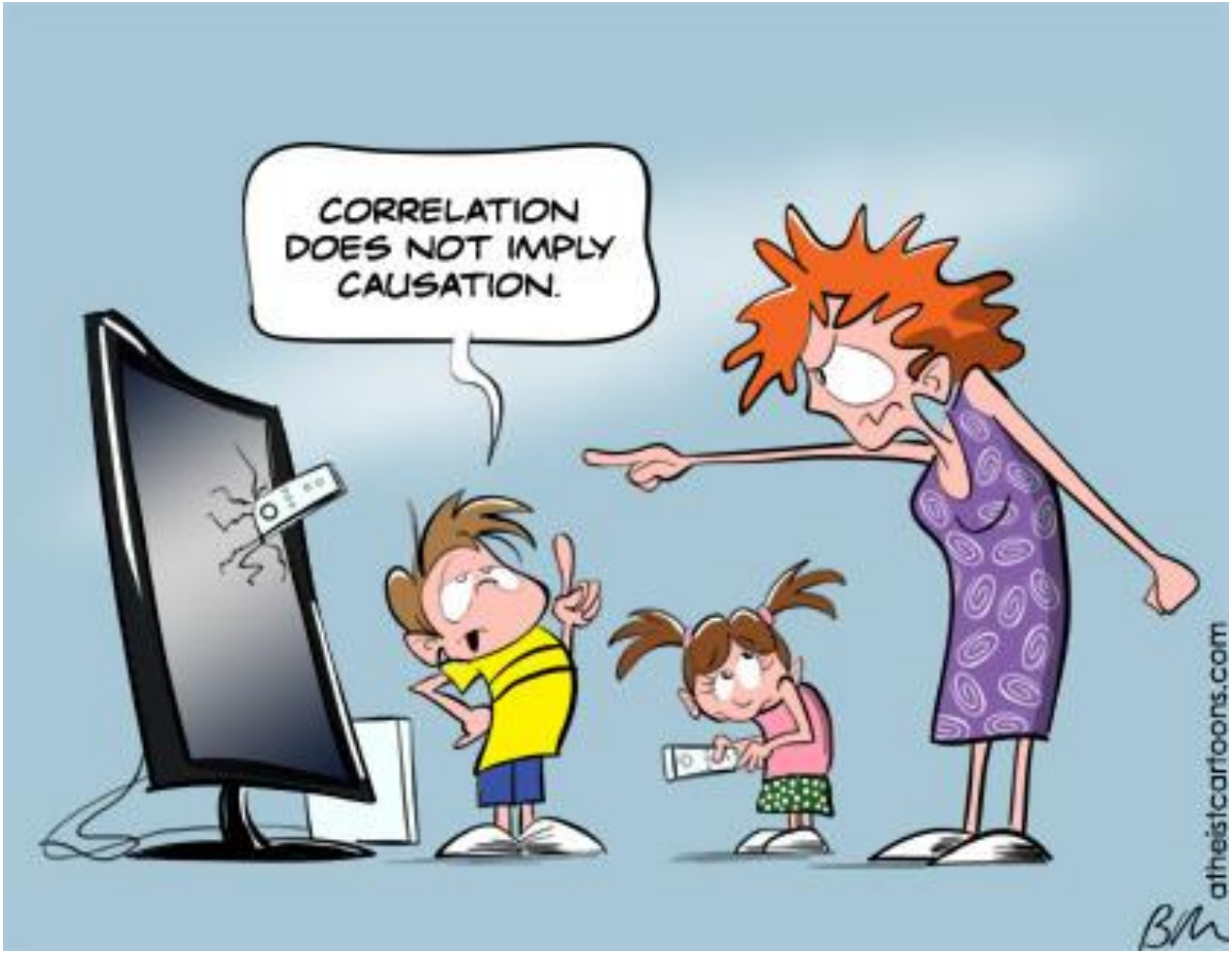
is reliably predicted by the

Effect of the Intervention
on the Surrogate Endpoint

D. Sargent, ASCO 2011

Prentice's Criteria

- To be a direct substitute for a clinical benefit endpoint on inferences of superiority and inferiority
  - The surrogate endpoint must be correlated with the clinical outcome
  - The surrogate endpoint must fully capture the net effect of treatment on the clinical outcome

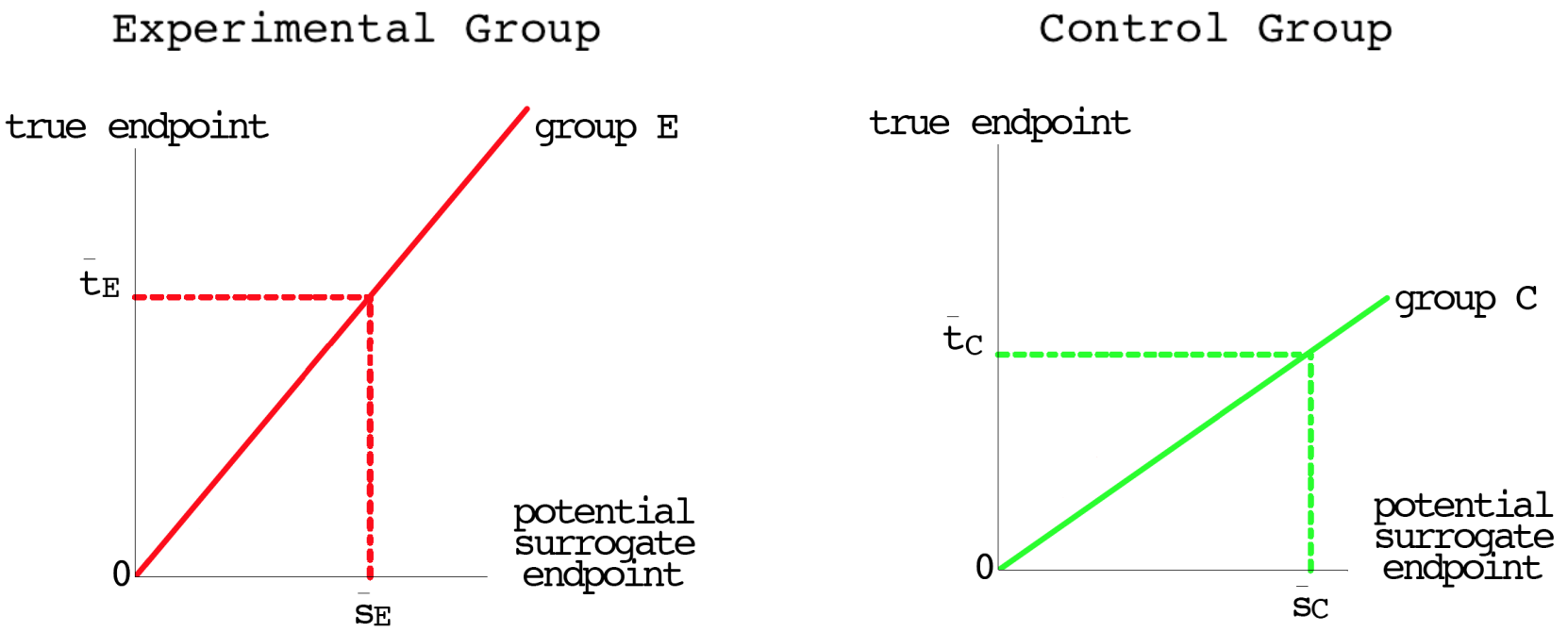

CORRELATION DOES NOT IMPLY CAUSATION.
atheistcartoons.com

A perfect correlate does not a surrogate make

Stuart G Baker*[1] and Barnett S Kramer[2]

BMC Medical Research Methodology 2003, **3**:16

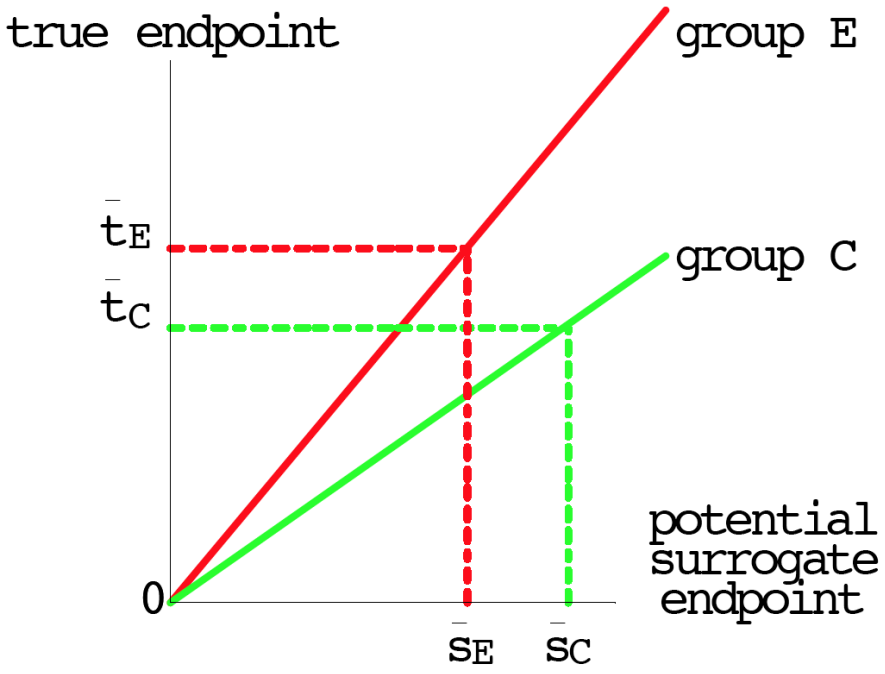
Background: There is common belief among some medical researchers that if a potential surrogate endpoint is highly correlated with a true endpoint, then a positive (or negative) difference in potential surrogate endpoints between randomization groups would imply a positive (or negative) difference in unobserved true endpoints between randomization groups.



A perfect correlate does not a surrogate make

Stuart G Baker*[1] and Barnett S Kramer[2]

BMC Medical Research Methodology 2003, **3**:16

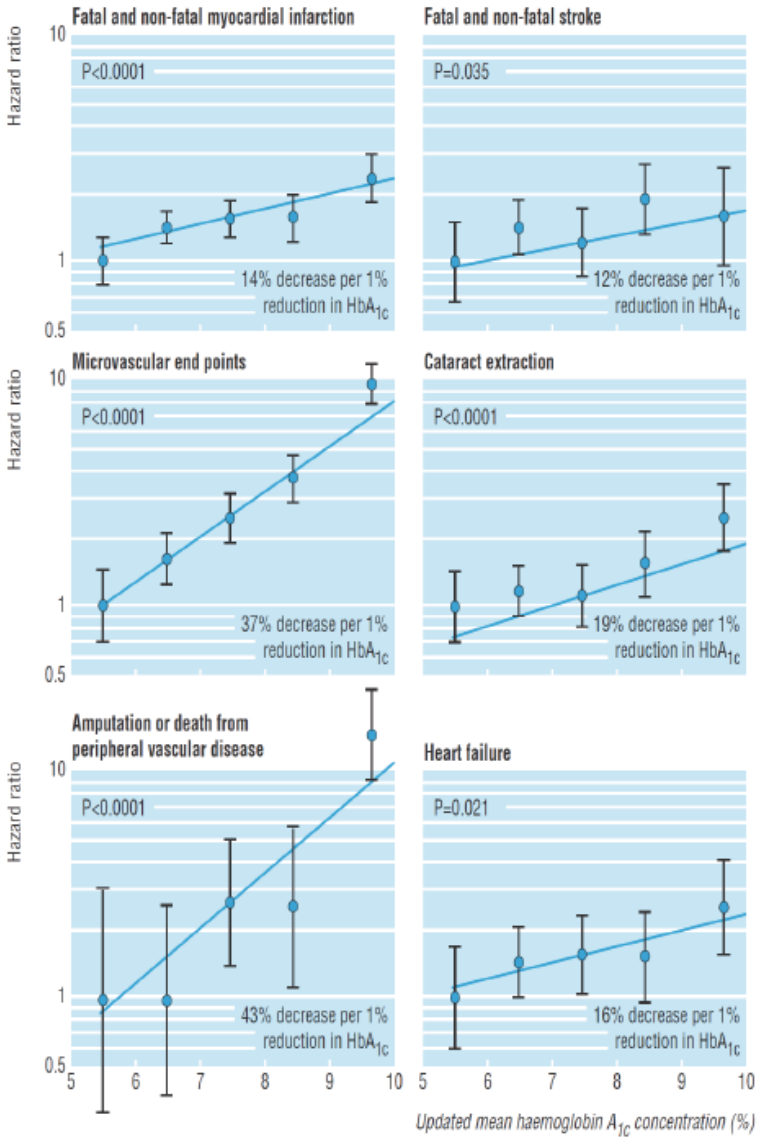


The mean surrogate outcome in the E group $\bar{s}_E$ is smaller than the mean surrogate outcome in the C group $\bar{s}_C$. However the mean true outcome in the E group $\bar{t}_E$ is larger than the mean true outcome in the C group $\bar{t}_C$, yielding the opposite conclusion for the effect of experimental intervention.

Conclusion: Perfect correlation between potential surrogate and unobserved true outcomes within randomized groups does not guarantee correct inference based on a potential surrogate endpoint.

HbA1c as Surrogate Endpoint in DM

- Measures average glucose level over 3 months
- Validated as a diagnostic marker and therapeutic target as recommended by
  - The American Diabetes Association (ADA)
  - World Health Organizations (WHO)
  - The American College of Endocrinologists (ACE)
  - Food and Drug Administration (FDA)
- Strongly associated with clinical outcomes
  - Microvascular complications
  - Macrovascular complications



Surrogate endpoints and emerging surrogate endpoints for risk reduction of cardiovascular disease

Crystal M Rasnake, Paula R Trumbo, and Therese M Heinonen

Nutrition Reviews® Vol. 66(2):76–81

Blood LDL cholesterol, as a surrogate marker for CVD risk, is supported by clinical trials of cholesterol-lowering drugs (e.g., bile acid sequestrants) that resulted in the lowering of blood LDL cholesterol concentration, as well as reduction in the rate of CHD. Furthermore, observational studies have positively correlated LDL cholesterol concentration with CHD rates.

Prentice's Criteria

- To be a direct substitute for a clinical benefit endpoint on inferences of superiority and inferiority
  - The surrogate endpoint must be correlated with the clinical outcome
  - The surrogate endpoint must fully capture the net effect of treatment on the clinical outcome

Prostate-Specific Antigen (PSA) as a Surrogate End Point for Survival in Prostate Cancer Clinical Trials

Laurence Collette

EUROPEAN UROLOGY 53 (2008) 6–9

Prognostic versus surrogate

A *prognostic factor* is a set of physical signs or laboratory measurements that occur in association with a pathologic process and are significantly associated with the disease evolution and survival of a patient. For example, biochemical relapse after radical prostatectomy is prognostic for clinical relapse.

A *surrogate* is a "(set of) biochemical measurements or clinical signs used as substitute for a clinical endpoint in the assessment of a therapeutic benefit."

Prostate-Specific Antigen (PSA) as a Surrogate End Point for Survival in Prostate Cancer Clinical Trials

Laurence Collette

EUROPEAN UROLOGY 53 (2008) 6–9

Prognostic versus surrogate

A *prognostic factor* is a set of physical signs or laboratory measurements that occur in association with a [illegible] and are significantly ass[illegible]lution and survival of [illegible]emical relapse after radical prostatectomy is prognostic for clinical relapse.

…in the individual patient

A *surrogate* is a "(set of) biochemical measurements [illegible] clinical signs used as [illegible]t in the assess-me[illegible]

…across groups of patients

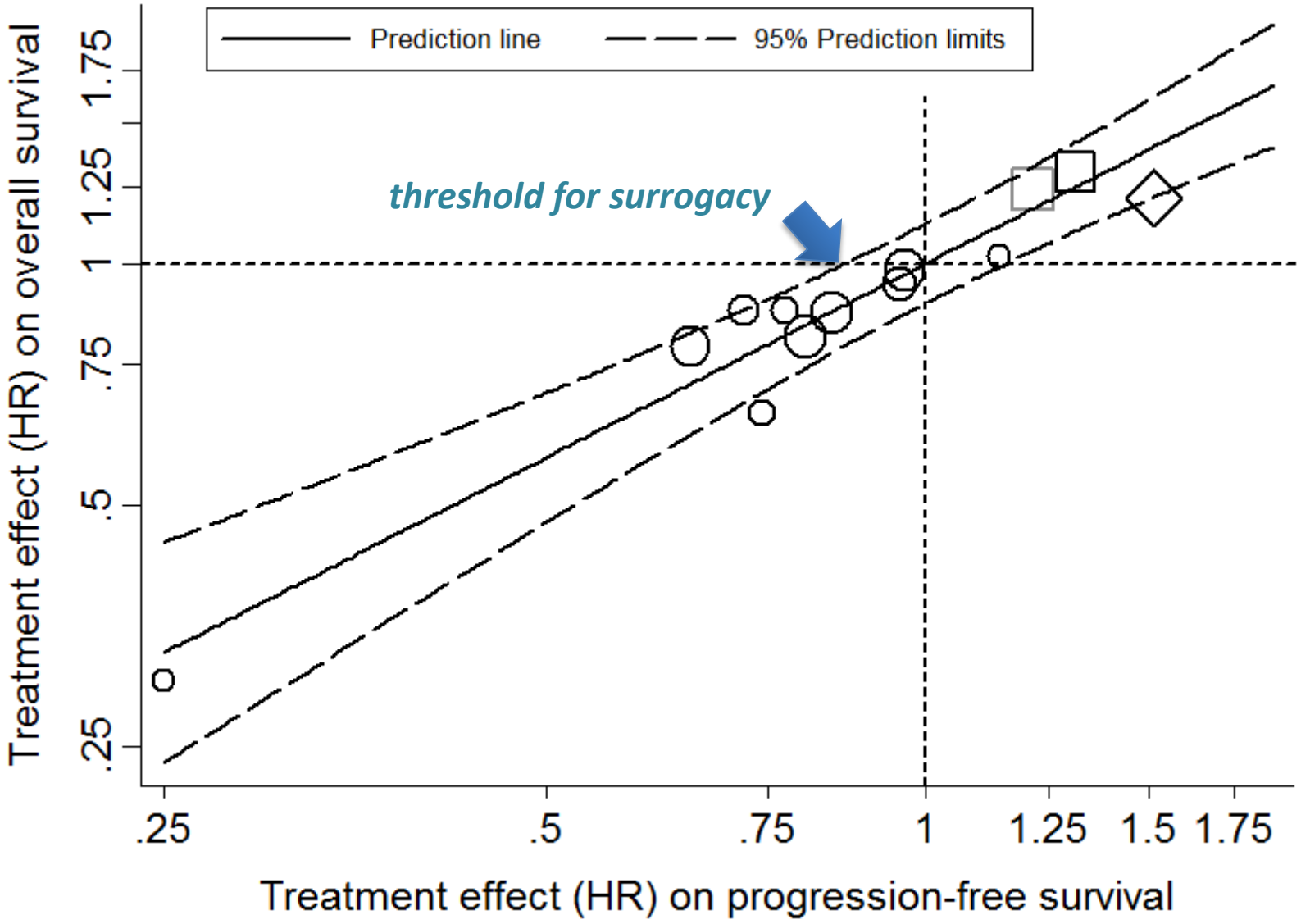
Quando si hanno dati di molti RCT…

… si deriva un modello di regressione:

- **che possa predire la magnitudine**
- **dell'effetto del trattamento sull'endpoint "vero"**
- **in base all'effetto del trattamento sull'end-point (candidato) surrogato**

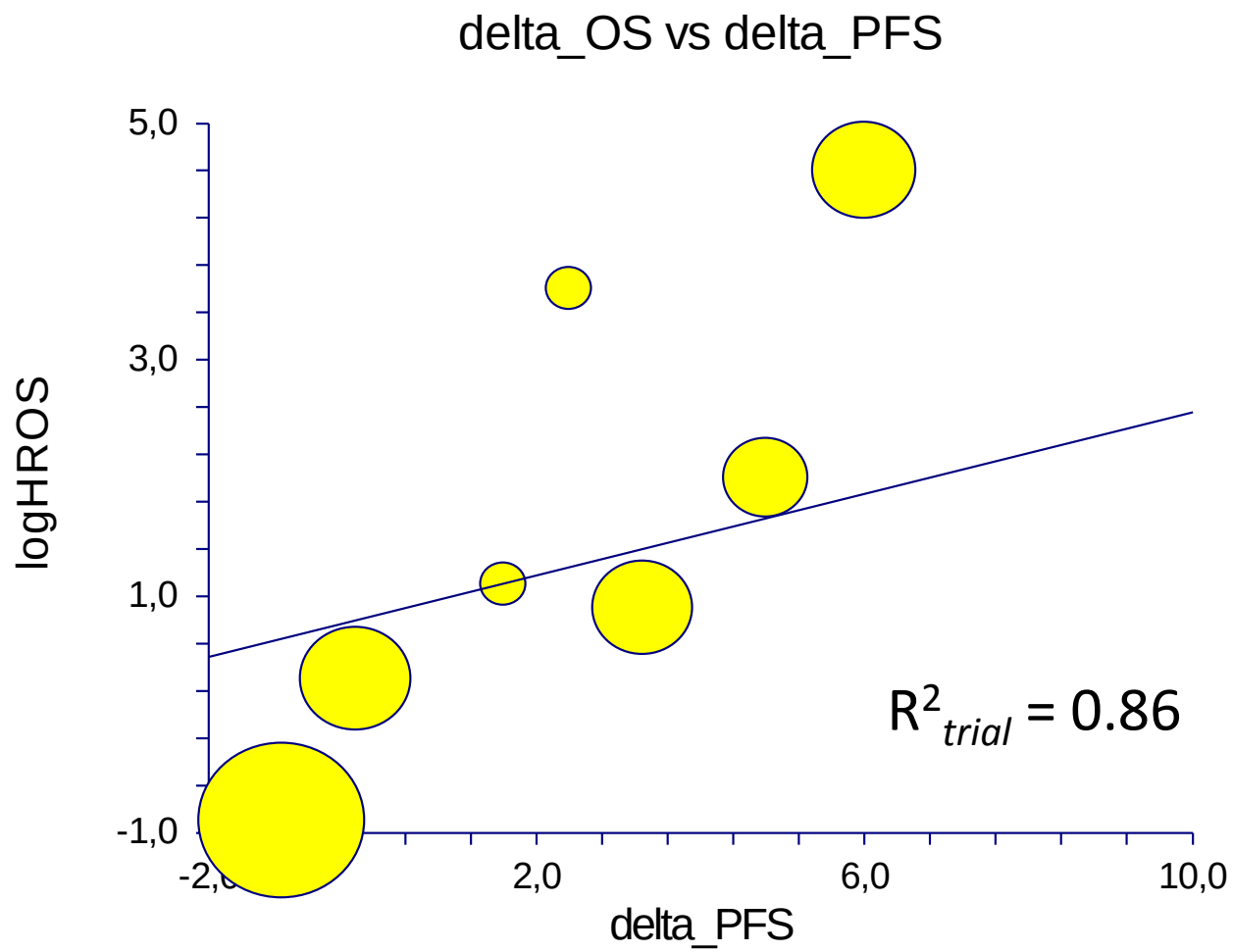
Il surrogato è tale se la predizione è sufficientemente precisa

TRIAL LEVEL CORRELATION BETWEEN EFFECTS



Burzykowski and Buyse, Pharmaceutical Statist 2006;5:173

Trial-level correlation between PFS and OS in 1st line mRCC

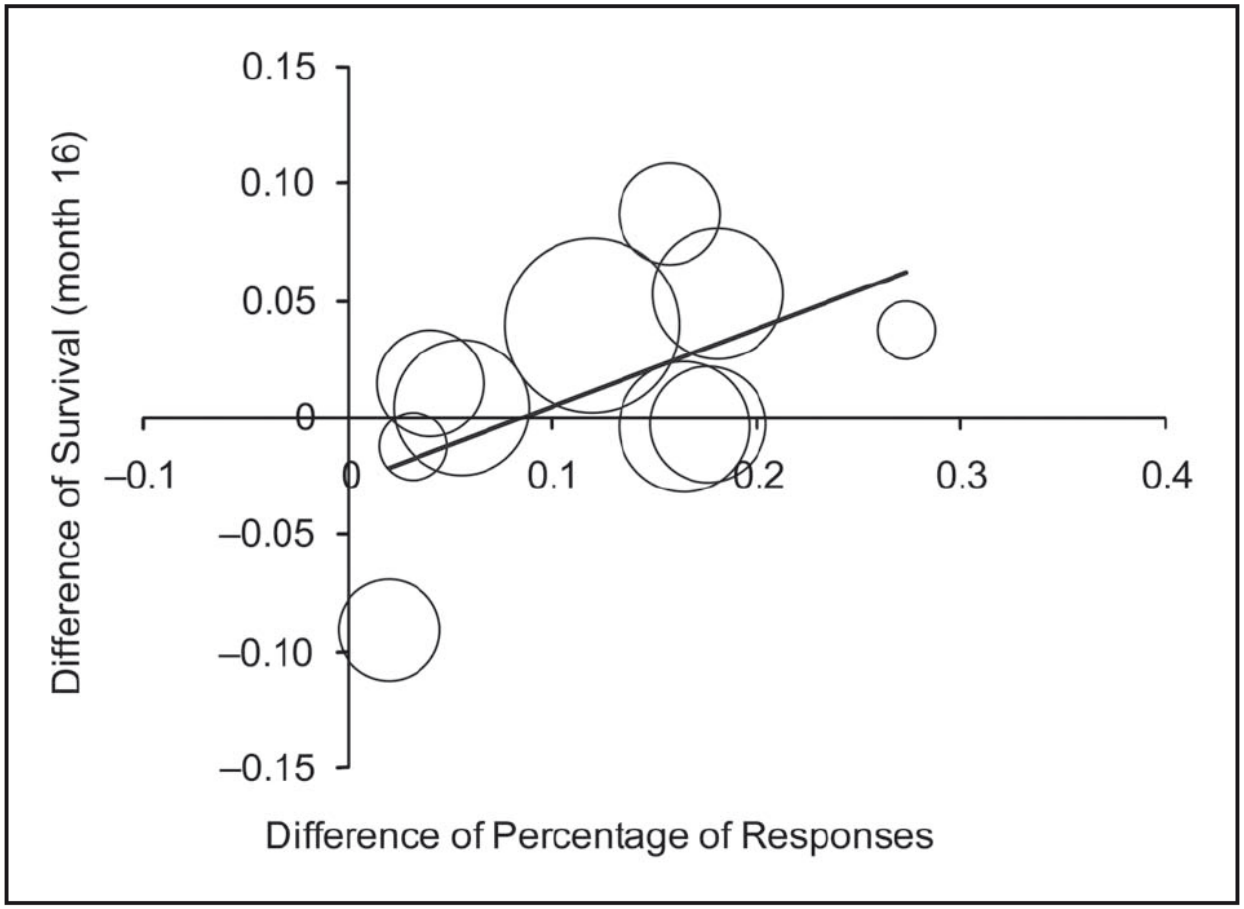


Petrelli F, 2014

Objective Response to Chemotherapy As a Potential Surrogate End Point of Survival in Metastatic Breast Cancer Patients

Paolo Bruzzi, Lucia Del Mastro, Maria P. Sormani, Lars Bastholt, Marco Danova, Christian Focan, George Fountzilas, James Paul, Riccardo Rosso, and Marco Venturini

J Clin Oncol 23:5117-5125. © 2005 by American Society of Clinical Oncology

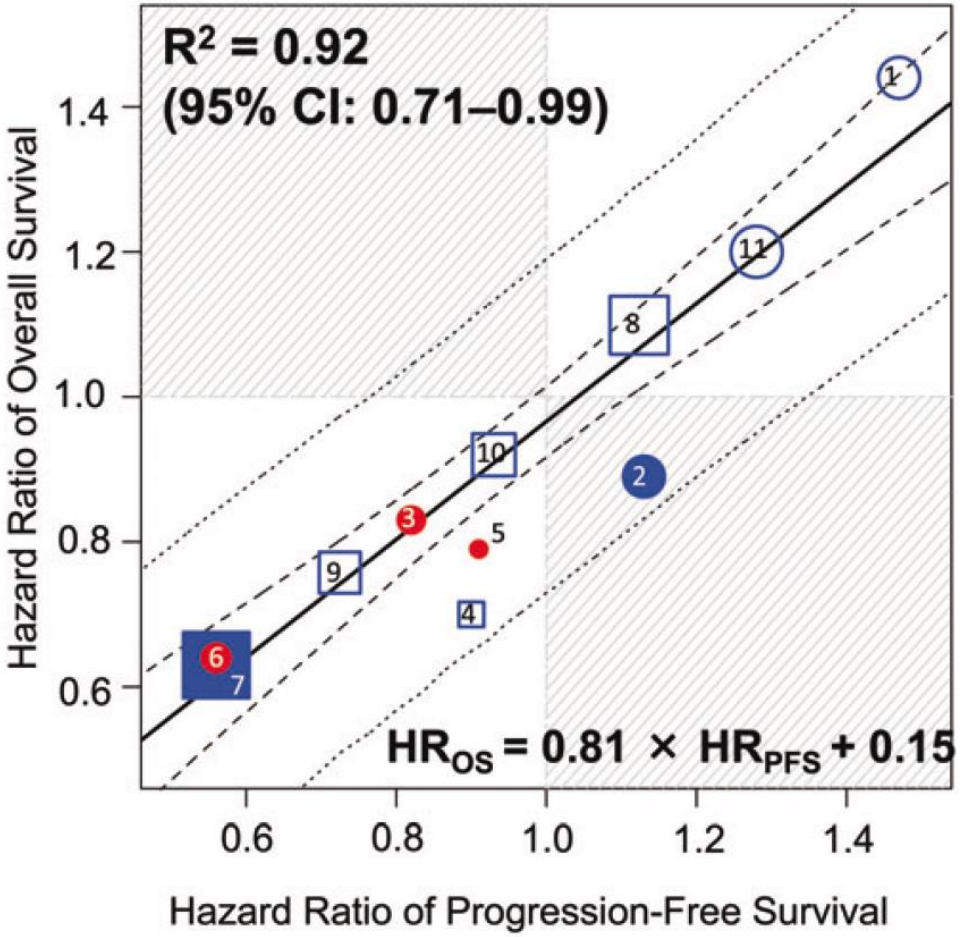


($R^2 = 0.20$; 95% CI, 0 to 0.65)

Progression-free survival as a surrogate endpoint for overall survival in glioblastoma: a literature-based meta-analysis from 91 trials

Kelong Han, Melanie Ren, Wolfgang Wick, Lauren Abrey, Asha Das, Jin Jin, and David A. Reardon

Neuro-Oncology 16(5), 696–706, 2014



Round symbols:	Glioblastoma
Square symbols:	Mixed high-grade glioma
Solid symbols:	Newly diagnosed
Hollow symbols:	Recurrent
———	Weighted linear fit
- - - - -	95% confidence interval
----------	95% prediction interval
Blue symbols:	Head-to-head comparison
Red symbols:	Single-arm trials using historical data as control

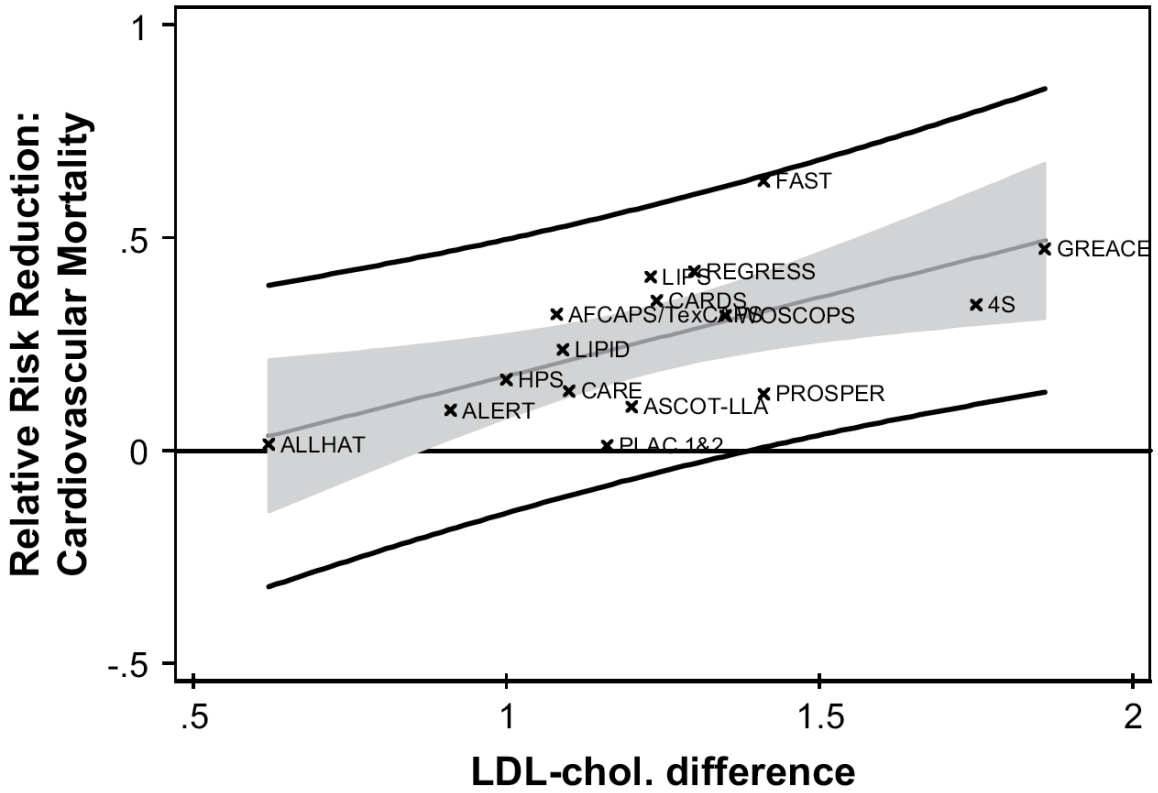
Linear regression determined that a 10% PFS risk reduction would yield an 8.1% ± 0.8% OS risk reduction.

LDL-cholesterol differences predicted survival benefit in statin trials by the surrogate threshold effect (STE)

Kent R. Johnson[a,*], Nick Freemantle[b], Danielle M. Anthony[a], Marissa N.D. Lassere[c]

[a]*Department of Clinical Pharmacology, University of Newcastle, Mater Hospital, Waratah NSW 2298, Australia*
[b]*Department of Primary Care and General Practice, University of Birmingham, Birmingham B15 2TT, UK*
[c]*Department of Rheumatology, University of New South Wales, St. George Hospital, Kogarah NSW 2217, Australia*

Journal of Clinical Epidemiology 62 (2009) 328−336



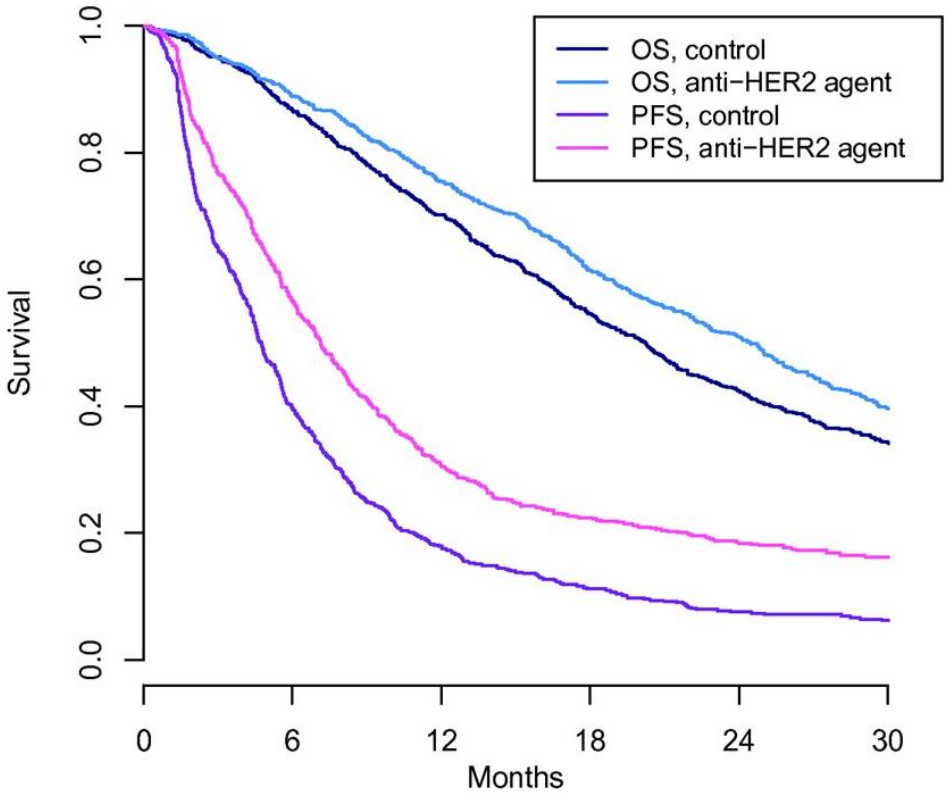
In 16 qualifying trials, regression analysis yielded a cardiovascular mortality model whose prediction bands demonstrated no cardiovascular survival benefit with LDL-cholesterol difference values below 1.4 mmol/L.

Progression-free survival (PFS) as surrogate endpoint for overall survival (OS) in clinical trials of HER2-targeted agents in HER2-positive metastatic breast cancer (MBC): An individual patient data (IPD) analysis.

S. Michiels[1,2], L. Pugliano[1,3], D. Grun[1], S. Marguet[2], J. Barinoff[4], D. Cameron[5], M. Cobleigh[6], A. Di Leo[7], S. Johnston[8], G. Gasparini[9], B.Kaufman[10], M. Marty[11], V. Nekjudova[12], S. Paluch-Shimon[13], F.Penault-Llorca[14], D. Slamon[15], C. Vogel[16], G. von Minckwitz[12], M. Buyse[17], M. Piccart[1,3]

ASCO 2013
CHICAGO
30 MAY - 04 JUN

Individual level ρ=0.66 (95% CI 0.65-0.66)

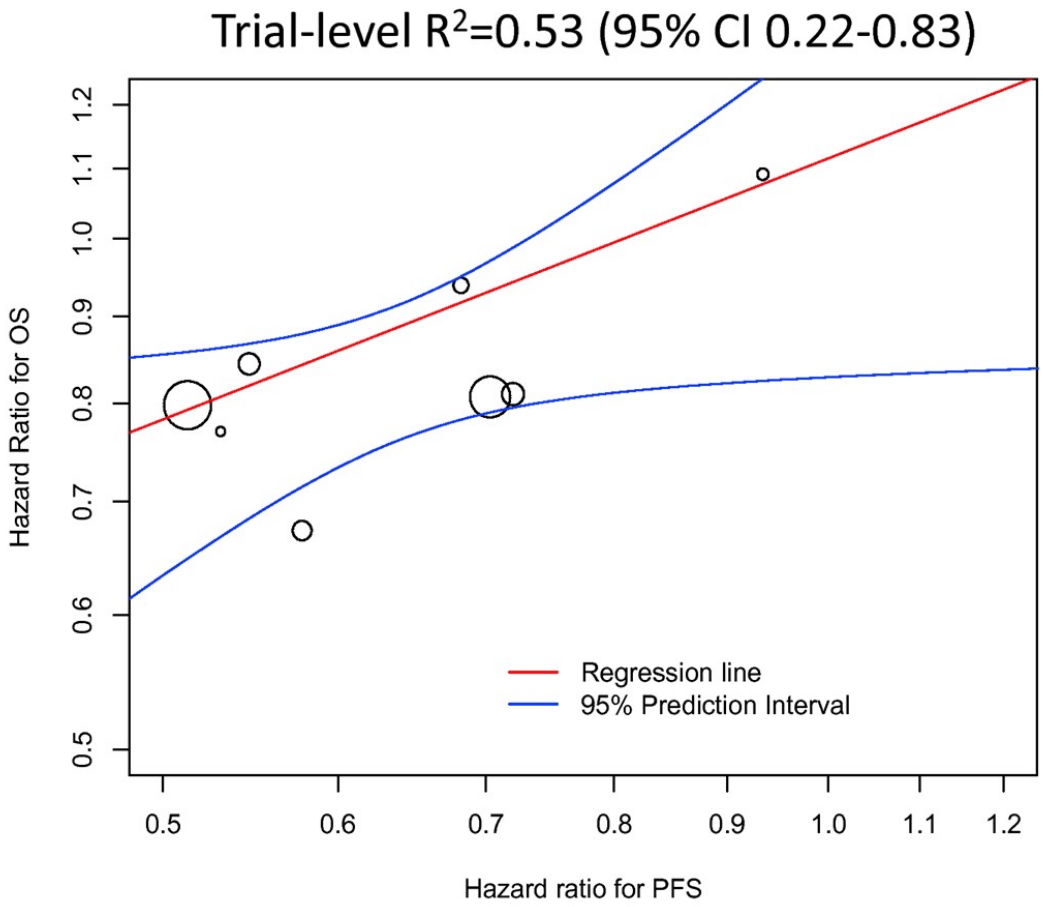


- For HER2-targeted therapies in HER2+ MBC, PFS is moderately correlated with OS at the individual level (ρ=0.66)

Progression-free survival (PFS) as surrogate endpoint for overall survival (OS) in clinical trials of HER2-targeted agents in HER2-positive metastatic breast cancer (MBC): An individual patient data (IPD) analysis.

S. Michiels[1,2], L. Pugliano[1,3], D. Grun[1], S. Marguet[2], J. Barinoff[4], D. Cameron[5], M. Cobleigh[6], A. Di Leo[7], S. Johnston[8], G. Gasparini[9], B.Kaufman[10], M. Marty[11], V. Nekjudova[12], S. Paluch-Shimon[13], F.Penault-Llorca[14], D. Slamon[15], C. Vogel[16], G. von Minckwitz[12], M. Buyse[17], M. Piccart[1,3]

ASCO 2013
CHICAGO
30 MAY - 04 JUN



- At the trial level, only 53% of the variation in treatment effects on OS can be explained by effects on PFS (trial-level R^2=0.53).

Reducing LDL with PCSK9 Inhibitors — The Clinical Benefit of Lipid Drugs

Brendan M. Everett, M.D., M.P.H., Robert J. Smith, M.D., and William R. Hiatt, M.D.

N ENGL J MED 373;17 NEJM.ORG OCTOBER 22, 2015

Aside from IMPROVE-IT, several trials with other non-statin medications that lower LDL cholesterol do not fully support the hypothesis that LDL cholesterol reduction will reduce cardiovascular risk regardless of a drug's mechanism of action.

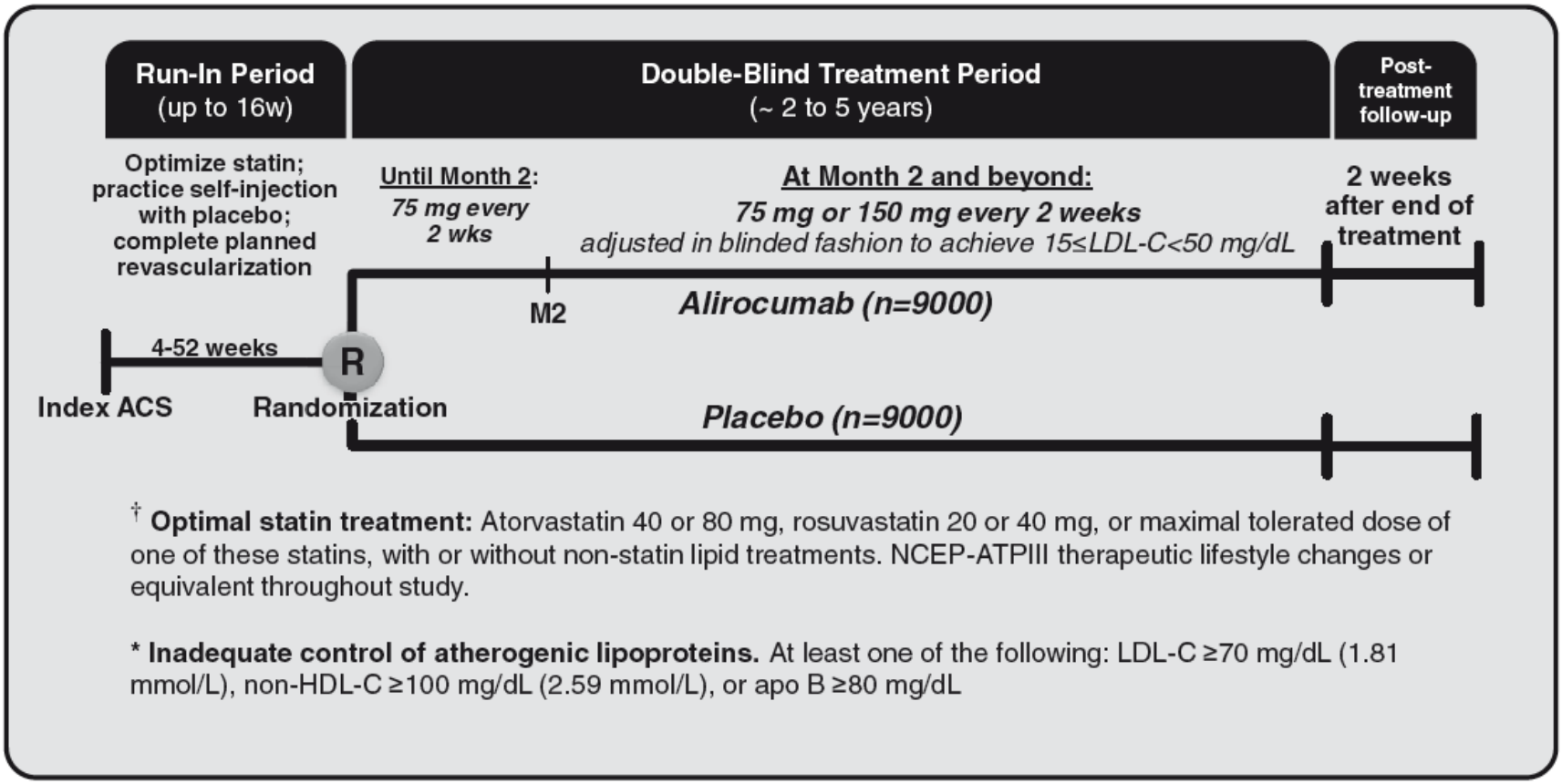
Selected Clinical Trials of Medications for Lowering LDL Cholesterol Levels Other Than Statins Alone and Their Effects on Cardiovascular Events.*

Trial	Study Drug	Comparison	Primary End Point	% Difference in LDL Cholesterol	Cardiovascular Outcome	
					Hazard Ratio (95% CI)	P Value
HERS	Estrogen (alone or in combination with medroxyprogesterone)	Placebo	Nonfatal myocardial infarction or death due to coronary heart disease	–11	0.99 (0.80–1.22)	0.91
FIELD	Fenofibrate	Placebo	Nonfatal myocardial infarction or death due to coronary heart disease	–12	0.89 (0.75–1.05)	0.16
ILLUMINATE	Torcetrapib–atorvastatin	Placebo plus atorvastatin	Nonfatal myocardial infarction, stroke, hospitalization for unstable angina, or death due to coronary heart disease	–27	1.25 (1.09–1.44)	0.001
HPS-2 THRIVE	Niacin–laropiprant	Placebo	Nonfatal myocardial infarction, death from coronary causes, stroke, or arterial revascularization	–16	0.96 (0.90–1.03)	0.29
IMPROVE-IT	Ezetimibe–simvastatin	Placebo plus simvastatin	Death due to cardiovascular causes, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke	–24	0.94 (0.89–0.99)	0.02

Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: Rationale and design of the ODYSSEY Outcomes trial

Gregory G. Schwartz, MD, PhD,[a,q] Laurence Bessac, MD,[b,c] Lisa G. Berdan, PA, MHS,[d] Deepak L. Bhatt, MD, MPH,[e] Vera Bittner, MD,[f] Rafael Diaz, MD,[g] Shaun G. Goodman, MD, MSc,[h] Corinne Hanotin, MD,[b,c] Robert A. Harrington, MD,[i] J. Wouter Jukema, MD, PhD,[j] Kenneth W. Mahaffey, MD,[i] Angèle Moryusef, MD,[b,c] Robert Pordy, MD,[k] Matthew T. Roe, MD, MPH,[d] Tyrus Rorick, RN,[d] William J. Sasiela, PhD,[k] Cheerag Shirodaria, MBBS,[l] Michael Szarek, PhD,[m] Jean-François Tamby, MD,[b,c] Pierluigi Tricoci, MD,[d] Harvey White, MBBS, DSc,[n] Andreas Zeiher, MD,[o] and Philippe Gabriel Steg, MD[p,q] *Denver, CO; Paris, France; Bridgewater, NJ; Durham, NC; Boston, MA; Birmingham, AL; Rosario, Argentina; Toronto, Canada; Stanford, CA; Leiden, the Netherlands; Tarrytown, NY; Oxford, United Kingdom; Brooklyn, NY; Auckland, New Zealand; and Frankfurt, Germany*

(Am Heart J 2014;168:682-689.e1.)



† **Optimal statin treatment:** Atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg, or maximal tolerated dose of one of these statins, with or without non-statin lipid treatments. NCEP-ATPIII therapeutic lifestyle changes or equivalent throughout study.

* **Inadequate control of atherogenic lipoproteins.** At least one of the following: LDL-C ≥70 mg/dL (1.81 mmol/L), non-HDL-C ≥100 mg/dL (2.59 mmol/L), or apo B ≥80 mg/dL

Surrogate outcome markers in research and clinical practice

Scott Twaddell

(Aust Prescr 2009;32:47–50)

Table 1

Surrogate markers often used in clinical practice

Generally accepted as valid		Doubt still exists about validity	
Surrogate marker	**Predicts**	**Surrogate marker**	**Predicts**
HbA1c	Diabetic microvascular complications	HbA1c	Diabetic macrovascular complications
FEV_1	Mortality in chronic obstructive pulmonary disease	Bone mineral density	Fracture risk
Blood pressure	Primary and secondary cardiovascular events	Prostate specific antigen	Prognosis of prostate cancer
Viral load	Survival in HIV infection	Suppression of arrhythmia	Long-term survival
Cholesterol concentration	Primary and secondary cardiovascular events	Carotid intima-media thickness	Coronary artery disease
Intraocular pressure	Visual loss in glaucoma	Albuminuria	Cardiovascular events

HbA1c glycated haemoglobin

FEV_1 forced expiratory volume in one second

Gli Endpoint surrogati

- Rivestono un ruolo molto importante
  - nella pratica
  - nella ricerca clinica
- la sola dimostrazione di associazione tra un biomarker e l'endpoint clinico
  - non fornisce una evidenza sufficiente di surrogacy
- data l'alta variabilità e la scarsa conoscenza sui meccanismi biologici che collegano il trattamento con l'outcome clinico,
  - il ruolo dei SE deve essere dimostrato e validato per ogni specifica malattia e per ogni singola classe di farmaco

Take home messages

V. Torri, AIOM 2014

Co-primary endpoints can be different medical assessments angled at different aspects of a disease, therefore, are used collectively to strengthen evidence for the treatment effect.

Li QH. Evaluating co-primary endpoints collectively in clinical trials. Biom J. 2009 Feb;51(1):137-45.

Guidance for Industry

E9 Statistical Principles for Clinical Trials

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
September 1998
ICH

5. *Multiple Primary Variables (2.2.5)*

It may sometimes be desirable to use more than one primary variable, each of which (or a subset of which) could be sufficient to cover the range of effects of the therapies.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy

Charles J. Ryan, M.D., Matthew R. Smith, M.D., Ph.D., Johann S. de Bono, M.B., Ch.B., Ph.D., Arturo Molina, M.D., Christopher J. Logothetis, M.D., Paul de Souza, M.B., Ph.D., Karim Fizazi, M.D., Ph.D., Paul Mainwaring, M.D., Josep M. Piulats, M.D., Ph.D., Siobhan Ng, M.D., Joan Carles, M.D., Peter F.A. Mulders, M.D., Ph.D., Ethan Basch, M.D., Eric J. Small, M.D., Fred Saad, M.D., Dirk Schrijvers, M.D., Ph.D., Hendrik Van Poppel, M.D., Ph.D., Som D. Mukherjee, M.D., Henrik Suttmann, M.D., Winald R. Gerritsen, M.D., Ph.D., Thomas W. Flaig, M.D., Daniel J. George, M.D., Evan Y. Yu, M.D., Eleni Efstathiou, M.D., Ph.D., Allan Pantuck, M.D., Eric Winquist, M.D., Celestia S. Higano, M.D., Mary-Ellen Taplin, M.D., Youn Park, Ph.D., Thian Kheoh, Ph.D., Thomas Griffin, M.D., Howard I. Scher, M.D., and Dana E. Rathkopf, M.D., for the COU-AA-302 Investigators*

METHODS

In this double-blind study, we randomly assigned 1088 patients to receive abiraterone acetate (1000 mg) plus prednisone (5 mg twice daily) or placebo plus prednisone. The coprimary end points were radiographic progression-free survival and overall survival.

Applied Clinical Trials Online

Composite Endpoints: Proceed with Caution

By Peter Kleist May 1, 2006

Multiple single endpoints are combined in order to confront an investigational drug with a higher number of events expected during the trial.

Statistical precision and efficiency will be increased, trials become smaller, less costly, and the results of promising new treatments will be available earlier.

The selected individual components of a composite endpoint, as reported in the biomedical literature, are not always clinically meaningful.

Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*

N Engl J Med 2013;368:699-708.

OUTCOME MEASURES

The primary efficacy outcome was the composite of symptomatic recurrent venous thromboembolism or death from any cause — an outcome consistent with that recommended in regulatory guidelines for trials of extended treatment for venous thromboembolic diseases.[16] Recurrent venous thromboembolism included fatal and nonfatal pulmonary embolism and deep-vein thrombosis. Death was classified as related to venous thromboembolism, related to cardiovascular disease, due to bleeding, or due to other causes.

Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial

The TIME Investigators

Lancet 2001; **358:** 951–957

The frequency of the composite endpoint (death, nonfatal myocardial infarction, and hospital admission for ACS) was much lower with revascularization; however, this was due to a marked difference in hospital admissions, which accounted for 75% of the events in the medical treatment group. In contrast, there were twice as many deaths in the invasive treatment group.

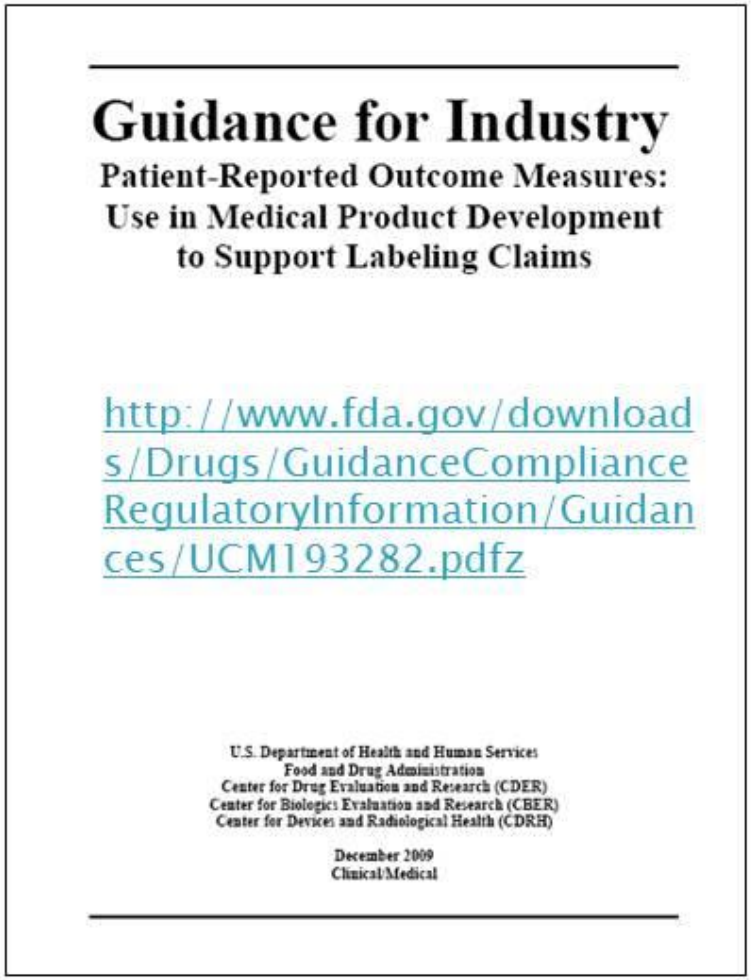
The question remains how to interpret the results and inform a patient who has to decide between conservative or surgical therapy.

Regular Approval Basis – "Clinical Benefit"

- Longer life
- **Better life**
- Established Surrogate for one of above

Definition of PROs

- "Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else"



Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdfz

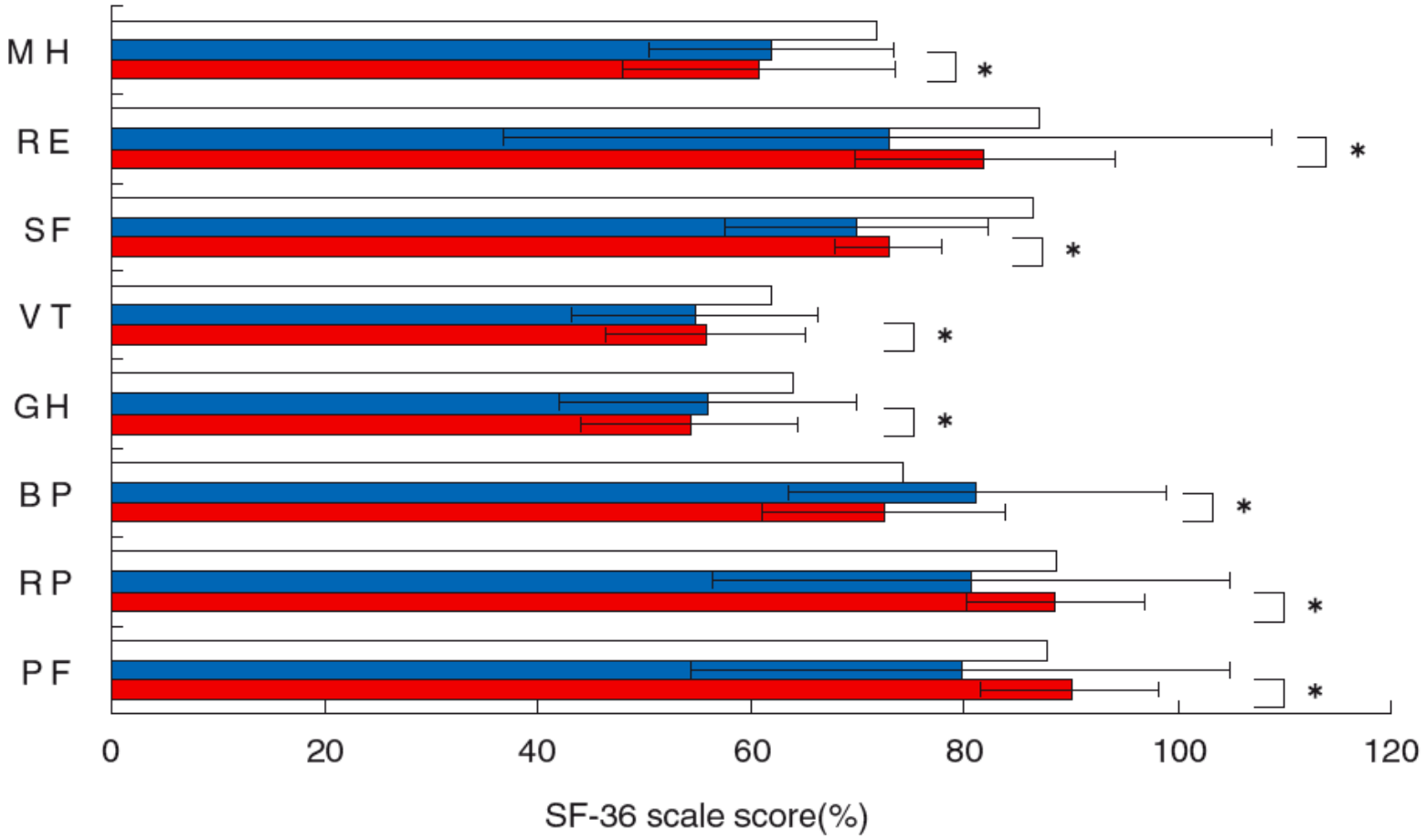
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

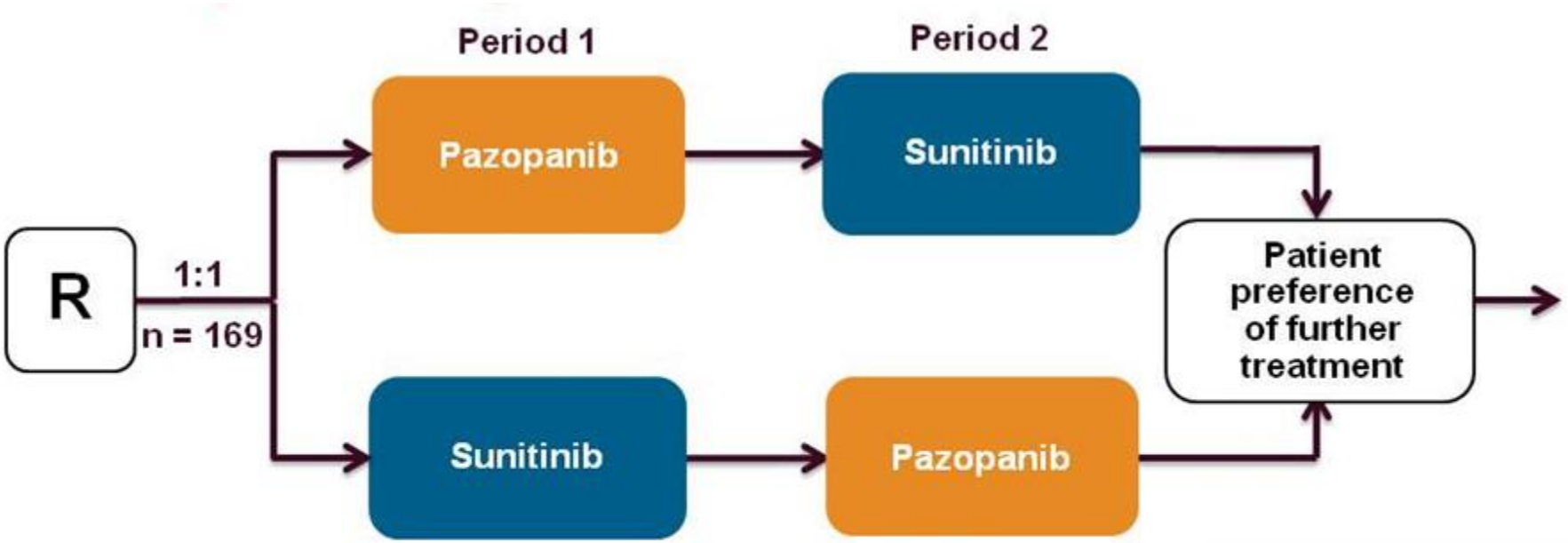
A pilot study of the assessment of the quality of life, functional results, and complications in patients with an ileal neobladder for invasive bladder cancer

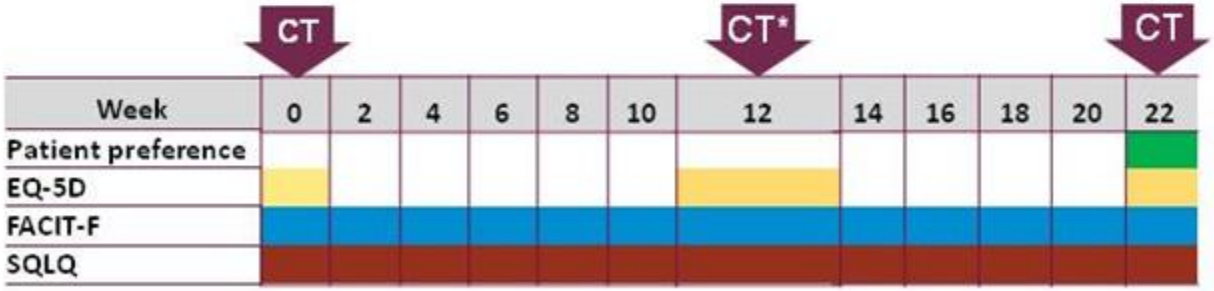
Masahiko Harano,[1] Masatoshi Eto,[1] Motonobu Nakamura,[2] Yoshihiro Hasegawa,[2] Motonori Kano,[3] Akito Yamaguchi[4] and Seiji Naito[1]

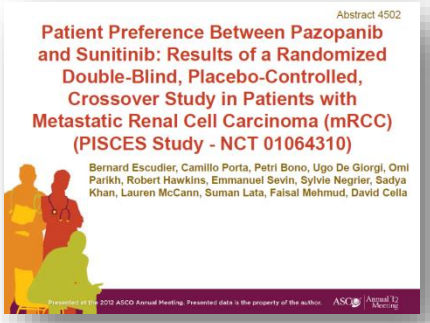
International Journal of Urology (2007) **14**, 112–117



Benefit to harm ratio







J Clin Oncol. 2014 May 10;32(14):1412-8

Symptom Endpoints (Patient-Reported Outcomes)

- Blinding is often difficult
- Data are often missing or incomplete
- Clinical significance of small changes unknown
- Few validated instruments

Symptom Endpoints (Patient-Reported Outcomes)

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The Minimal Clinical Interesting Difference (M.C.I.D.)

- **it's easily understood by clinicians as a key concept in the interpretability of PRO scores;**
- **will inform judgments about the success-fulness of an intervention;**
- **an individual patient achieving the score equal or greater than the MCID might be considered a beneficiary of the intervention, what would lead to the definition of a responder.**

Estimating a minimal clinically important difference for the EuroQol 5-dimension health status index in persons with multiple sclerosis

Christine G Kohn[1,2], Matthew F Sidovar[3], Kirandeep Kaur[1], Yungfen Zhu[1] and Craig I Coleman[1,2*]

Health and Quality of Life Outcomes 2014, **12**:66

In conclusion, the MCID estimate calculated in this study can aid researchers and clinicians when discriminating between patient groups for EQ-5D index scores of PwMS. Our MCID range of 0.050-0.084 for EQ-5D was within the range of MCID estimates of other disease states. In general, patients who have severe disability had higher MCIDs than patients who had mild-moderate disability.

Symptom Endpoints (Patient-Reported Outcomes)

- Blinding is often difficult
- Data are often missing or incomplete
- Clinical significance of small changes unknown
- Few validated instruments

Standards for PRO *Development*

- **Reliability**
  - **Test-retest**
  - **Internal consistency**
- **Validity**
  - **Content validity (qualitative)**
  - **Construct validity (discriminant)**
- **Ability to detect change**

Ethan Basch, 2010

Standards for PRO *Development*

- **Reliability**
  - **Te retest**
- Reliability means the consistency or repeatability of the measure.
  - Content validity (qualitative)
  - Construct validity (discriminant)
- Ability to detect change

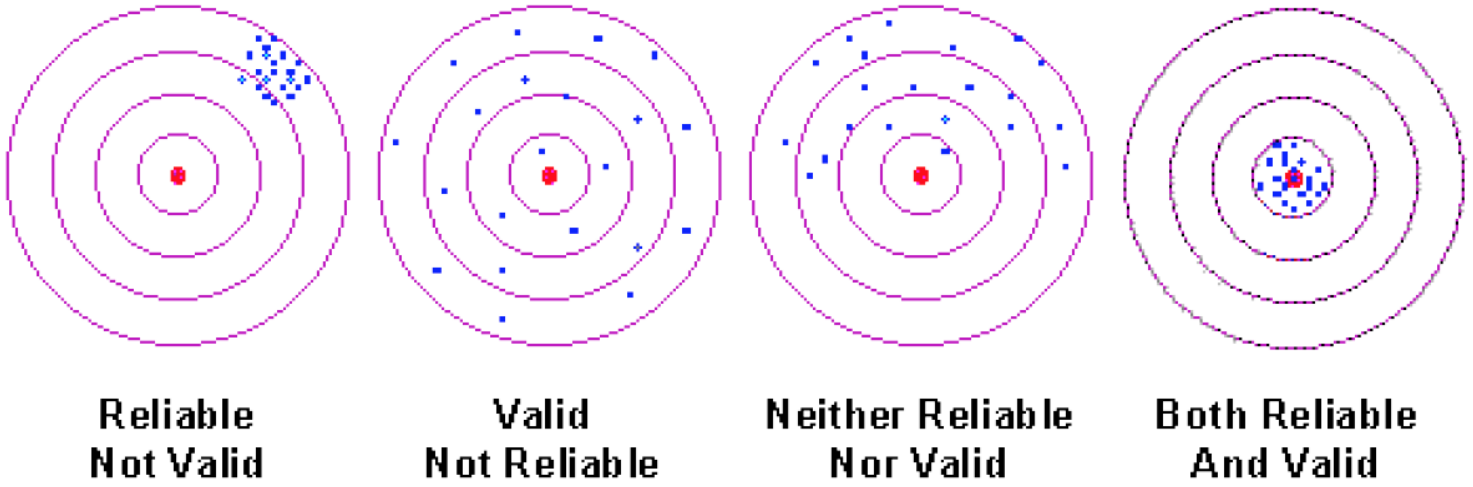
Ethan Basch, 2010

Standards for PRO *Development*

- Reliability
  - Test-retest
  - Internal consistency
- **Validity**
  - **Content validity (qualitative)**
  - **iscriminant)**
- **nge**

Validity means measuring what you claim to be measuring.

Ethan Basch, 2010



- In the first situation, you are consistently and systematically measuring the wrong value for all respondents. This measure is reliable, but no valid.
- In the second situation, you get a valid group estimate, but you are inconsistent. Here, you can clearly see that reliability is directly related to the variability of your measure.
- The third scenario shows a case where your hits are spread across the target and you are consistently missing the center. Your measure in this case is neither reliable nor valid.
- Finally, we see the "Robin Hood" scenario – you consistently hit the center of the target. Your measure is both reliable and valid.

Standards for PRO *Development*

- Reliability
  - Test-retest
  - Internal consistency
- Vali
  - C e)
  - Const t validity (discriminant)
- **Ability to detect change**

The PRO instrument can identify differences in scores over time

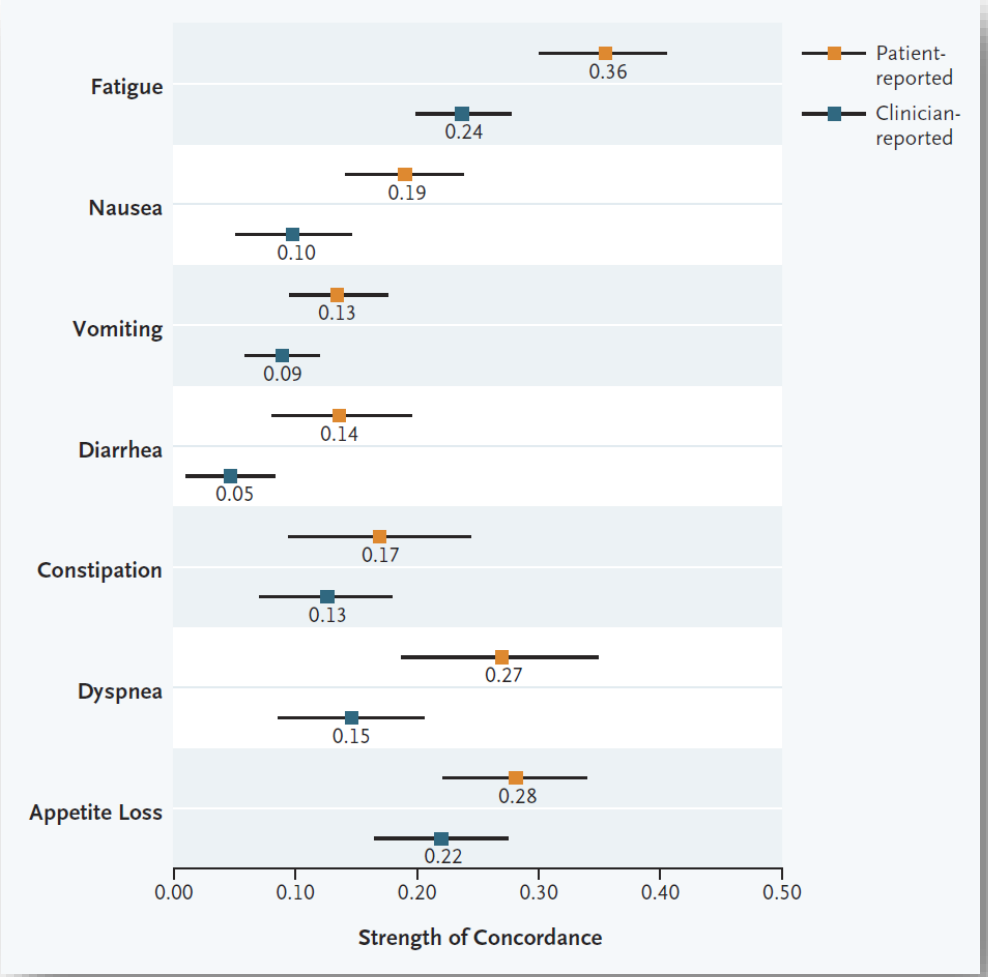
Ethan Basch, 2010

The Missing Voice of Patients in Drug-Safety Reporting

Ethan Basch, M.D.

N ENGL J MED 362;10 NEJM.ORG MARCH 11, 2010

Current methods for detecting adverse events in clinical trials are acknowledged to lack sensitivity,[4] and worrisome symptoms might well come to light earlier in the drug-development cycle if reporting by patients were standard practice.



National Cancer Institute
U.S. National Institutes of Health | www.cancer.gov

PRO-CTCAE
PATIENT SYMPTOM REPORTER

A system for patient self-reporting of adverse symptoms in cancer trials

- providing a more full picture of patient experience;
- compatible with existing adverse event reporting systems
- widely accepted and used;
- generating useful data for investigators, regulators, clinicians and patients

CTCAE vs. PRO-CTCAE Item Structures

CTCAE					
Adverse Event	Grade				
	1	2	3	4	5
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest; limiting self care ADL	-	-

PRO-CTCAE
Please think back over the past 7 days:
What was the severity of your WEAKNESS OR TIREDNESS at their WORST? None / Mild / Moderate / Severe / Very severe
How much the WEAKNESS OR TIREDNESS interfere with your usual daily activities? Not at all / A little bit / Somewhat / Quite a bit / Very much

Presented By Lori M. Minasian, MD at 2013 ASCO Annual Meeting (*modified)*

1. Riflettete da soli per 10 min. e compilate il form →
2. Confrontatevi con i Colleghi del Vostro tavolo per 15 min., declinate un W^3 condiviso e delegate un portavoce
3. Riportate sulla lavagna il Vostro W^3 condiviso su almeno due aspetti ritenuti rilevanti e impattanti sulla professione (in 5 min.)
4. Presentate ai Colleghi degli altri tavoli il Vostro W^3 condiviso

RIFLESSIONI E SINTESI
sui temi oggetto del Corso

WHAT?
Partendo da quanto ascoltato, seleziono quanto ritengo più importante (almeno due argomenti):

SO WHAT?
Il fatto che io abbia ritenuto alcuni argomenti più importanti è perché per me hanno un particolare significato. Quindi:

NOW WHAT?
Quali azioni potrei pensare di intraprendere in conseguenza di quanto sopra: