Evento ecm 1 (formazione di base)

METODOLOGIA: “A good foundation”

(Negrar, 22-23 gennaio 2016)

Evento ecm 2 (formazione avanzata)

CRITICITA’ INTERPRETATIVE: “Confidence, Directness, Relevance”

(Negrar, 5-6 febbraio 2016)

Con il Patrocinio di

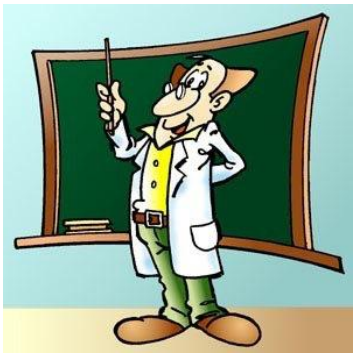
Aiom

STUDI CLINICI: METODOLOGIA

Coordinatore:
Dr.ssa Stefania Gori

Evento ECM MODULO 1
(formazione di base)
"A good foundation"

NEGRAR
22-23 Gennaio 2016
Centro Formazione
Ospedale Sacro Cuore
Don Calabria



+

WHAT?

Cosa è emerso di particolarmente saliente e rilevante?
(indicare almeno 2 risposte condivise)

SO WHAT?

Perché le cose emerse sono così rilevanti?
(indicare almeno 2 risposte condivise)

NOW WHAT?

Quali ricadute nell'immediato per la mia professione?
(indicare almeno 2 risposte condivise)

Con il Patrocinio di

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STUDI CLINICI: METODOLOGIA

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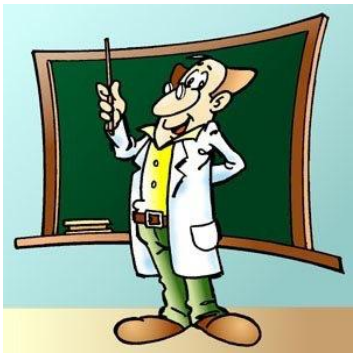

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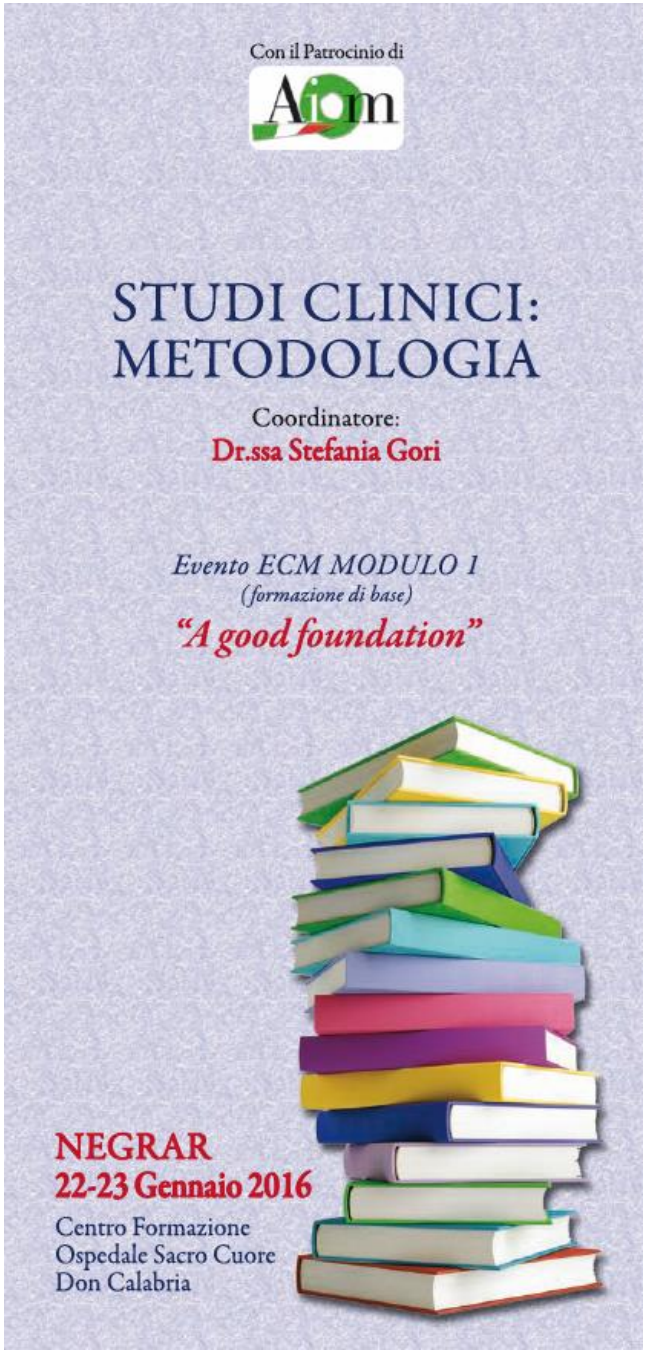

Venerdì 22 gennaio 2016

- Plausibilità e opportunità dello studio
  - ✓ criteri FINER
- Obiettivi (primario e secondari)
  - ✓ strutturazione sec. P.I.C.O.
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  - ✓ tipologie di disegno di studio
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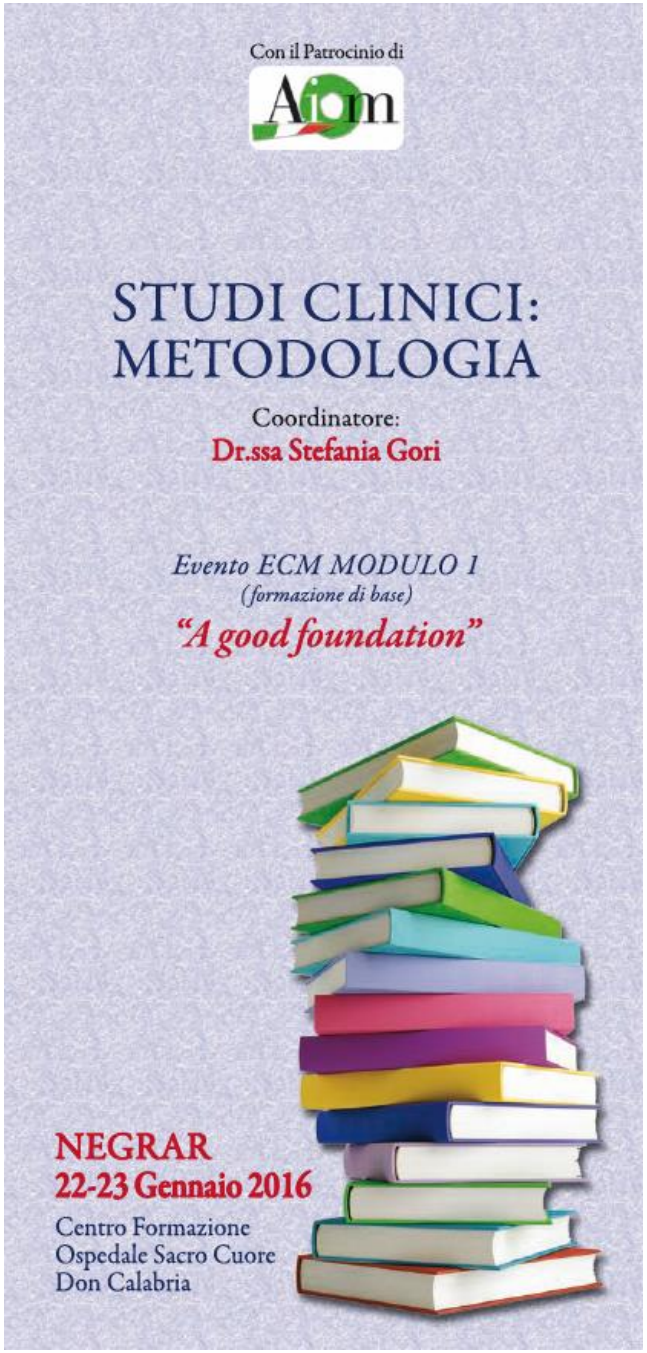
  - ✓ PROs
- Selezione dei pazienti
  - ✓ criteri restrittivi Vs inclusivi
  - ✓ conseguenze su trasferibilità e precisione delle evidenze



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FATTORI DA CONSIDERARE SULL'OPPORTUNITA' DI UNA SPERIMENTAZIONE CLINICA

① **Gravità dell'affezione.**

② **Efficacia delle terapie disponibili.**

③ **Tossicità (*scomodità*) delle terapie disponibili rispetto a quelle alternative.**

④ **Presumibile superiorità delle terapie sperimentali.**

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M., and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*

N Engl J Med 2012;366:109-19

① Approximately 20% of all breast cancers have gene amplification or overexpression (or both) of human epidermal growth factor receptor 2 (HER2),[1] a tyrosine kinase transmembrane receptor, resulting in a more aggressive phenotype and a poor prognosis.

② Treatment with the anti-HER2 humanized monoclonal antibody trastuzumab in addition to chemotherapy, as compared with chemotherapy alone, significantly improves progression-free and overall survival among patients with HER2-positive metastatic breast cancer.

③ However, in most patients with HER2-positive metastatic breast cancer, the disease progresses,[8] highlighting the need for new targeted therapies for advanced disease.

Pertuzumab prevents HER2 from dimerizing with other ligand-activated HER receptors, most notably HER3.

④ Because pertuzumab and trastuzumab bind to different HER2 epitopes and have complementary mechanisms of action, these two agents, when given together, provide a more comprehensive blockade of HER2 signaling and result in greater antitumor activity than either agent alone in HER2-positive tumor models.

The Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study assessed the efficacy and safety of pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel, as first-line treatment for patients with HER2-positive metastatic breast cancer.

Oral Apixaban for the Treatment of Acute 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., Urszula Masiukiewicz, M.D., Raphael Pak, Ph.D., John Thompson, Ph.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY Investigators*

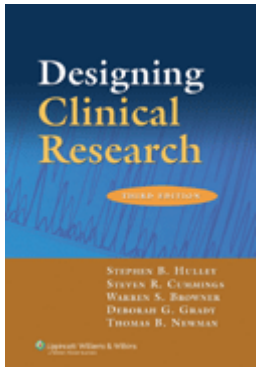
N Engl J Med 2013;369:799-808.

① Venous thromboembolism, with an annual incidence of 1 to 2 cases per 1000 persons in the general population, is the third most common cause of vascular death after myocardial infarction and stroke.[1] Conventional treatment consists of a parenteral anticoagulant, ② such as enoxaparin, for at least 5 days, and warfarin begun during this time and continued for at least 3 months.[2] Although effective, this regimen ③ presents a challenge because enoxaparin requires daily subcutaneous injections, and warfarin therapy requires coagulation monitoring and dose adjustment.

Apixaban may simplify the treatment of venous thromboembolism by eliminating the need for initial parenteral anticoagulant therapy and laboratory monitoring, a concept supported by recent studies.

④ In the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) trial, we compared apixaban with conventional anticoagulant therapy in patients with acute symptomatic venous thromboembolism.

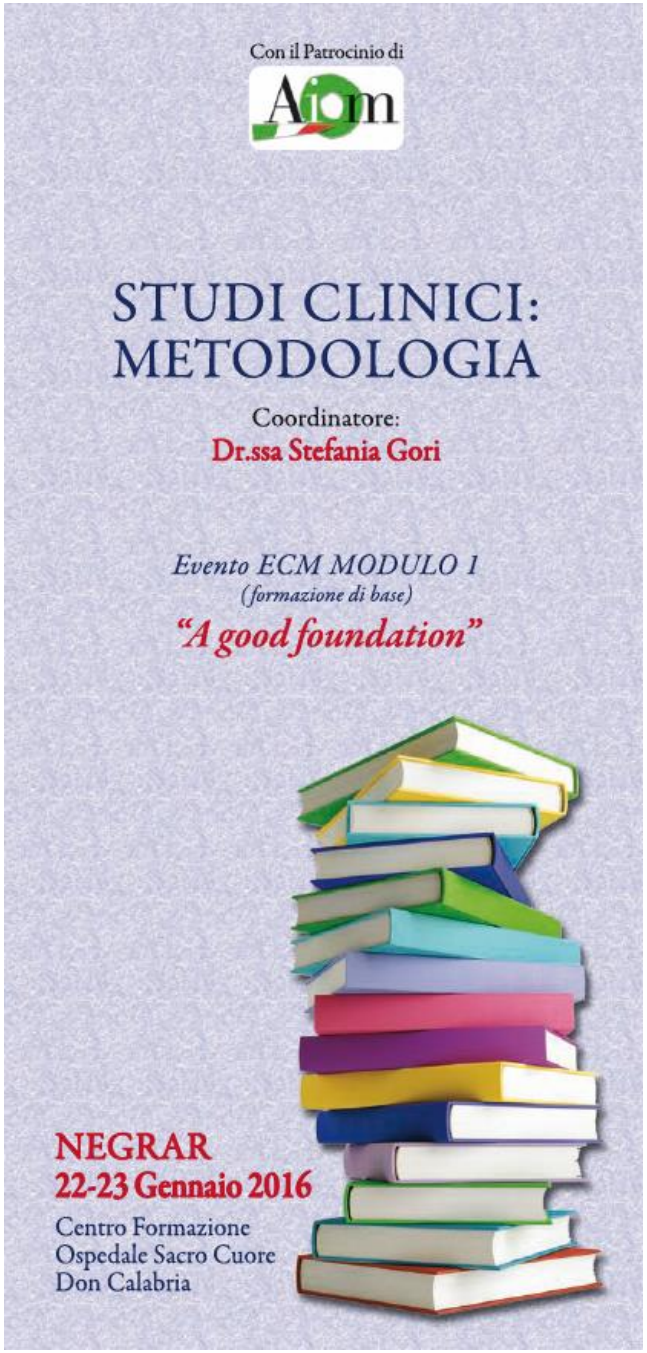
FATTORI DA CONSIDERARE SULL'OPPORTUNITA' DI UNA SPERIMENTAZIONE CLINICA



- **Gravità dell'affe**
- **Efficacia d**
- **Tossicità disponibil native.**
- **Presumibi speriment**

Il criterio FINER

- Feasible = "fattibile"
- Interesting = "interessante" (per il ricercatore)
- Novel = "nuova"
- Ethical = "etica"
- Relevant = "rilevante" (per la conoscenza)



Venerdì 22 gennaio 2016

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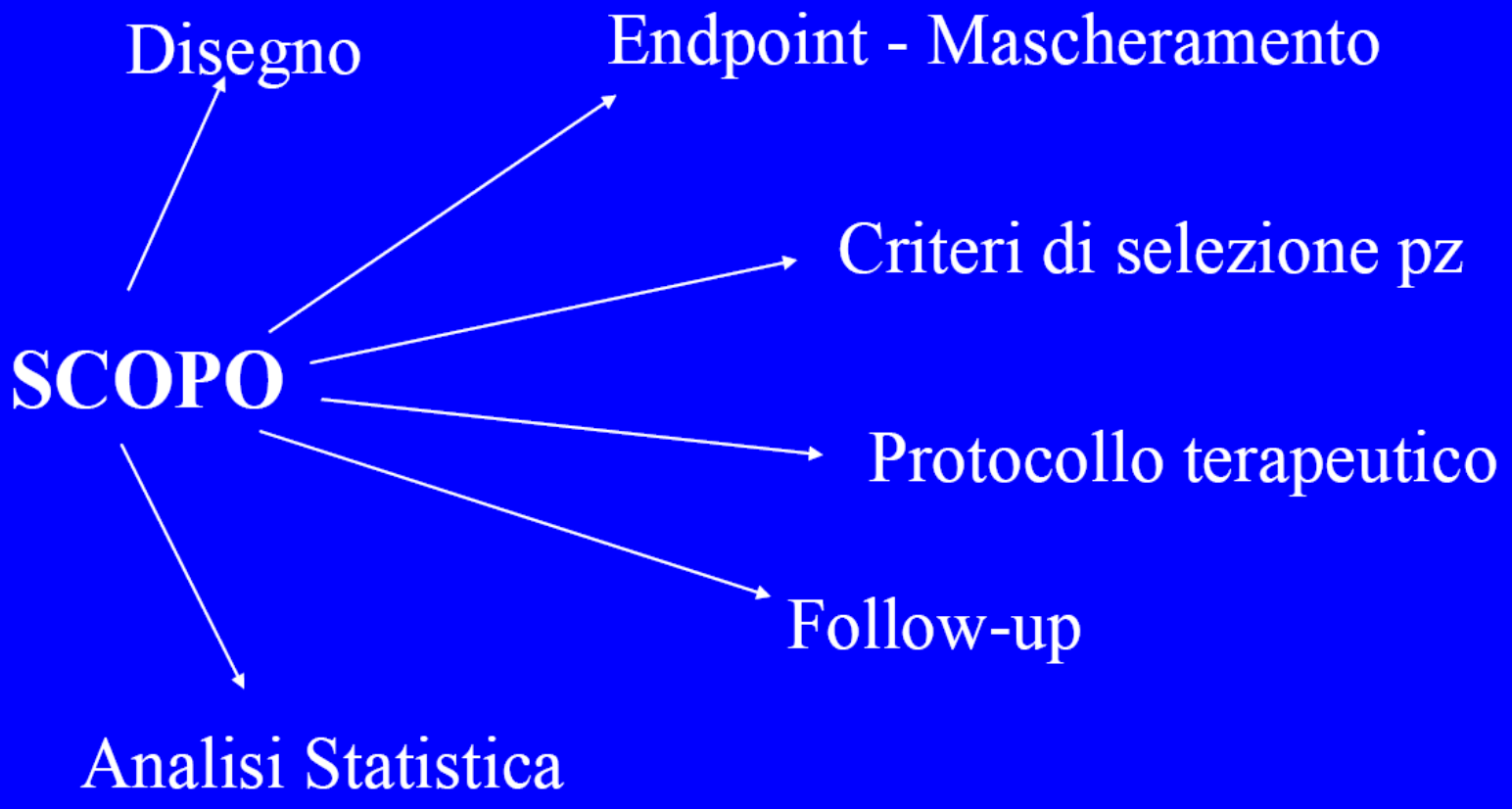
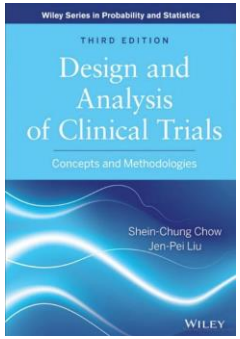
L'aspetto piu' importante di uno studio e' il suo scopo primario



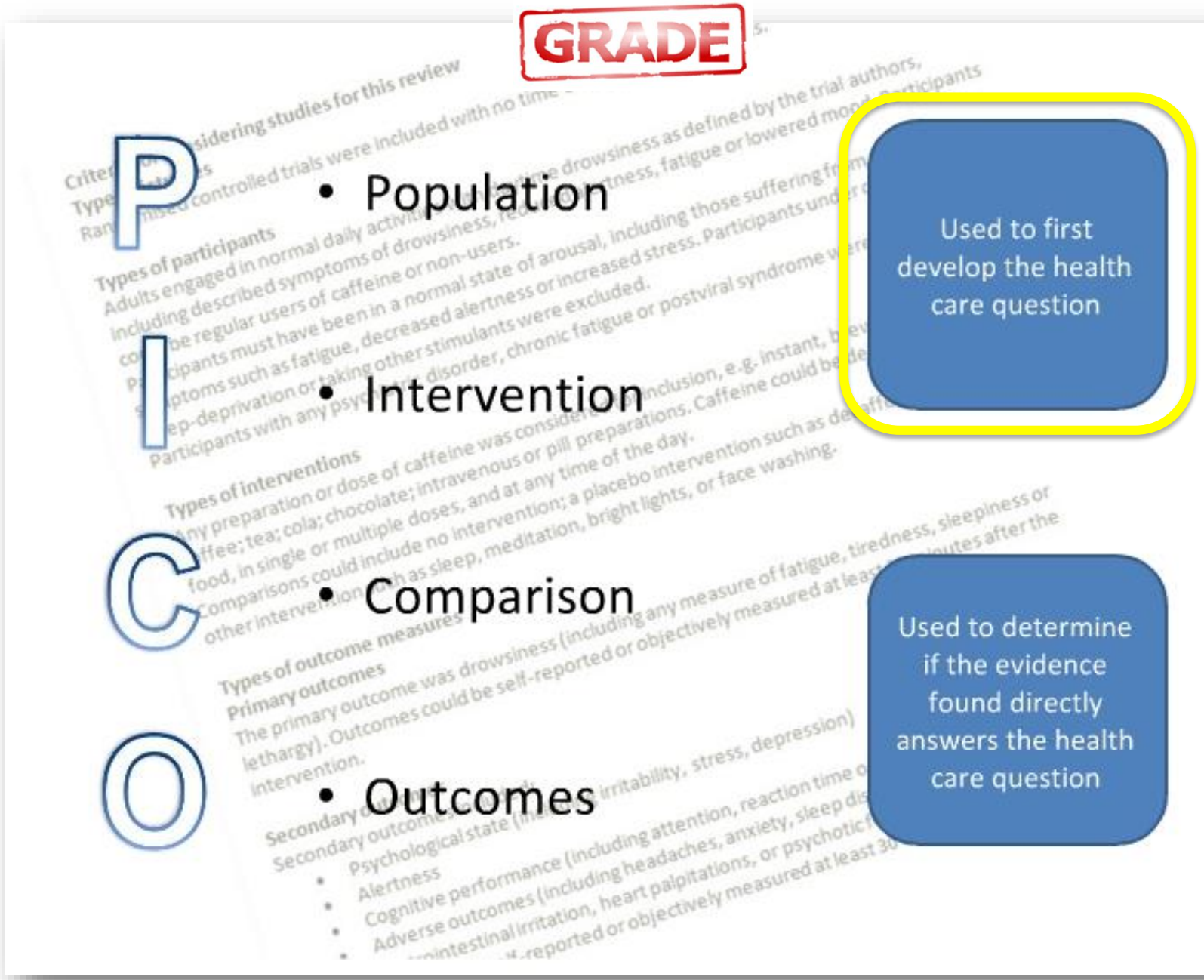
P. Bruzzi, qualche tempo fa…



The ultimate goal of clinical research is to obtain an unbiased inference with possibly best precision in order to scientifically address the clinical questions regarding the study drug under investigation with respect to a target patient population.

Scopo (obiettivo) Primario

- ✓ **quesito cui gli sperimentatori sono più interessati a rispondere e al quale lo studio vuole dare una risposta;**
- ✓ **determina il disegno dello studio e le dimensioni del campione**


GRADE
P
• Population
I
• Intervention
C
• Comparison
O
• Outcomes
Used to first develop the health care question
Used to determine if the evidence found directly answers the health care question

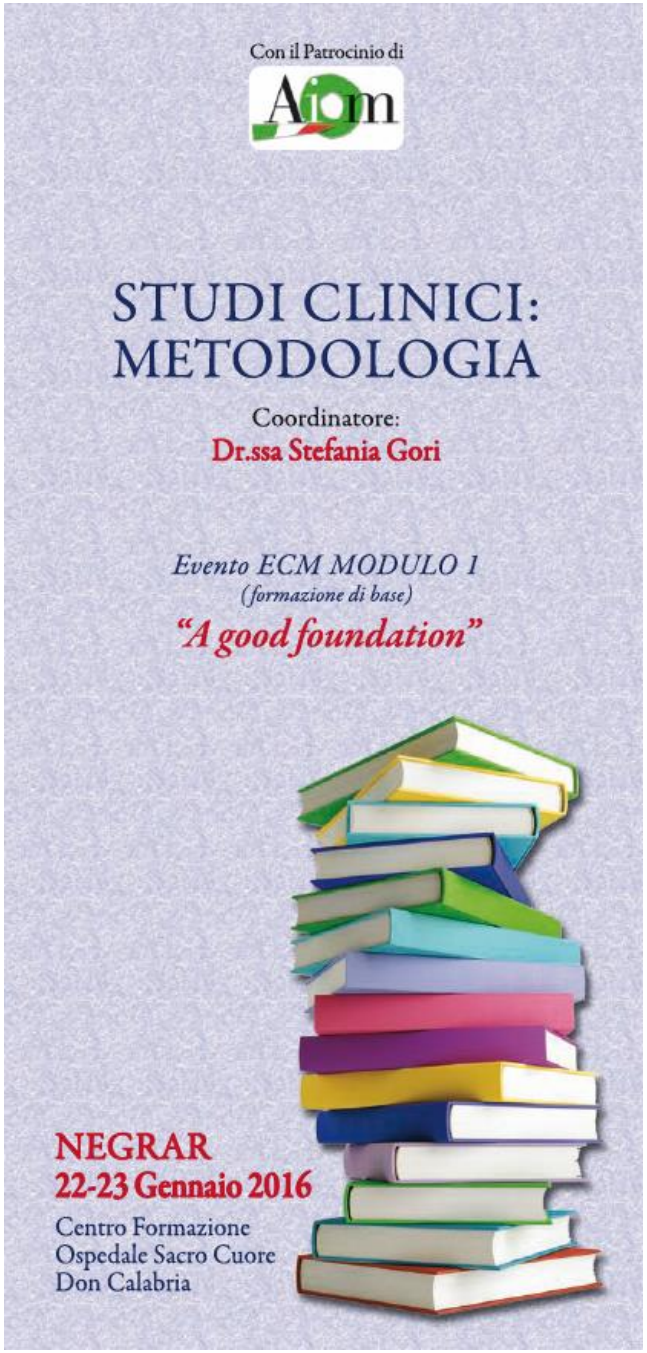
Primary and Secondary Questions/Objectives

- Common error – Sinking ship: Avoid overloading the study with too many objectives and too much data collection

- A single primary question around which to focus the development of the protocol and sample size estimates
- Secondary research questions: can be related to the primary question or to other hypotheses

Hypotheses and Objectives

- KISS – keep it simple, stupid
- Too many objectives compromise a trial
  - A single hypothesis and a few secondary hypotheses
  - Can't study everything
- If you can't power an endpoint, it shouldn't be a primary or secondary objective



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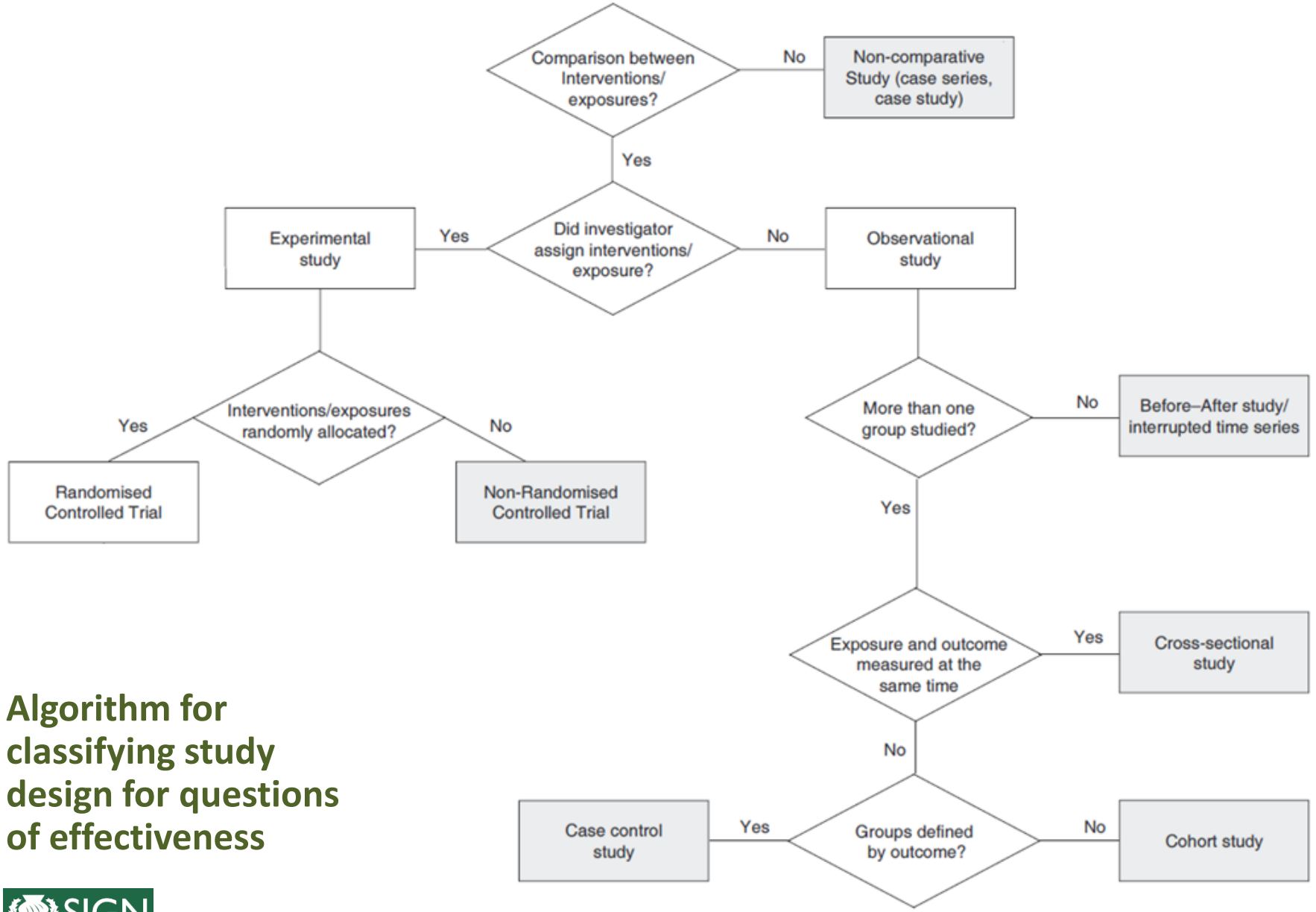
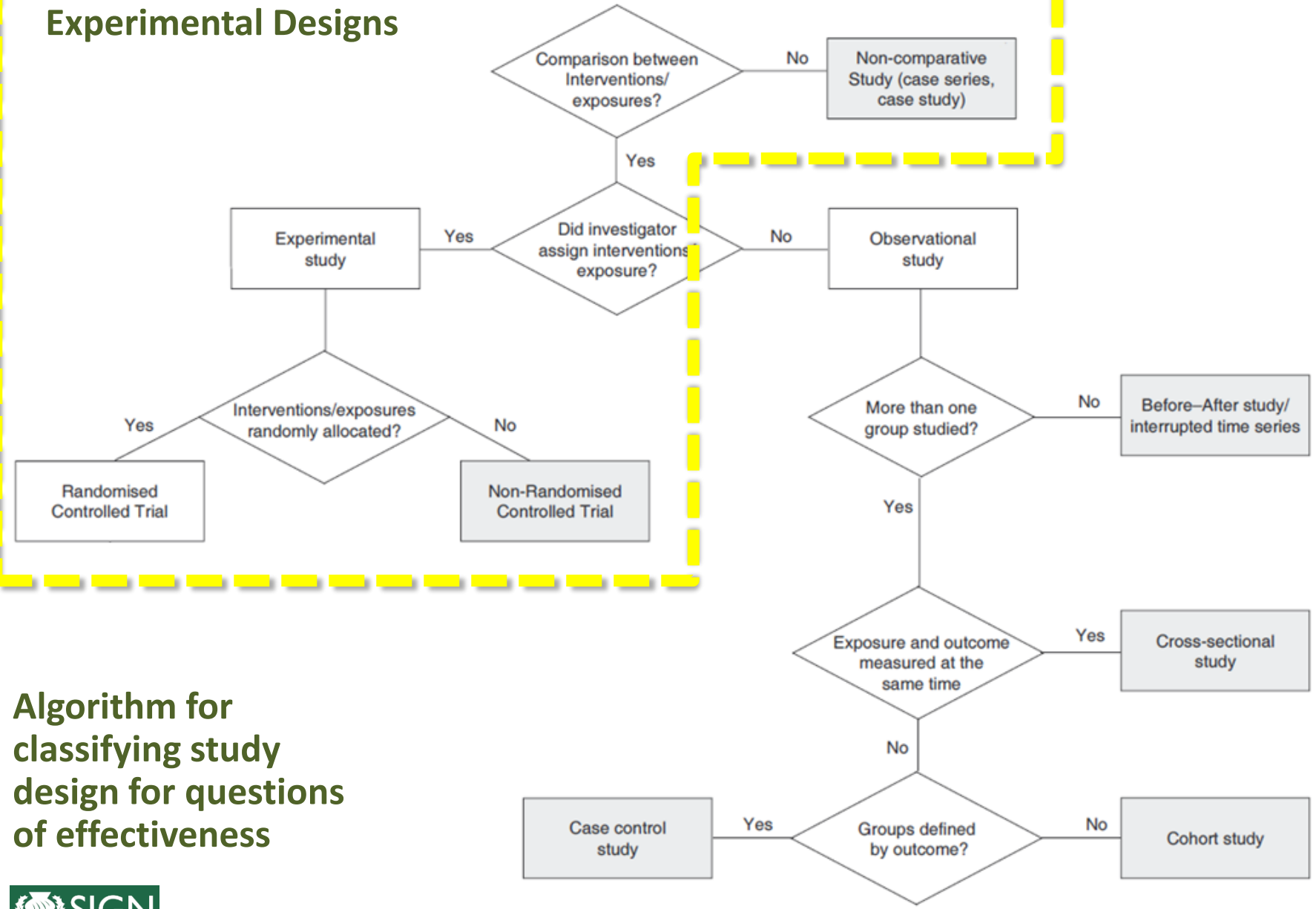
Algorithm for classifying study design for questions of effectiveness



SIGN
Scottish Intercollegiate Guidelines Network

Experimental Designs



Algorithm for classifying study design for questions of effectiveness

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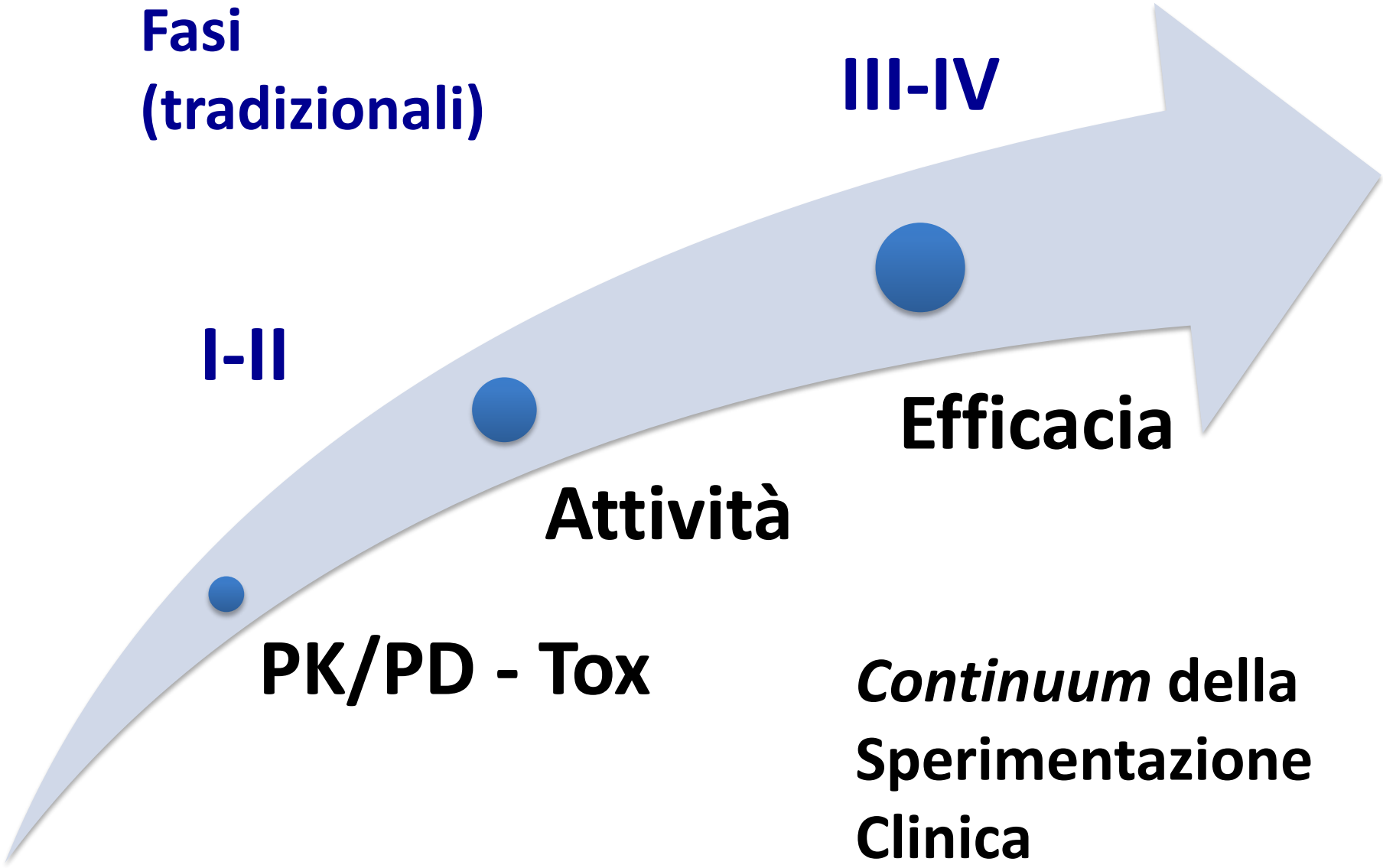
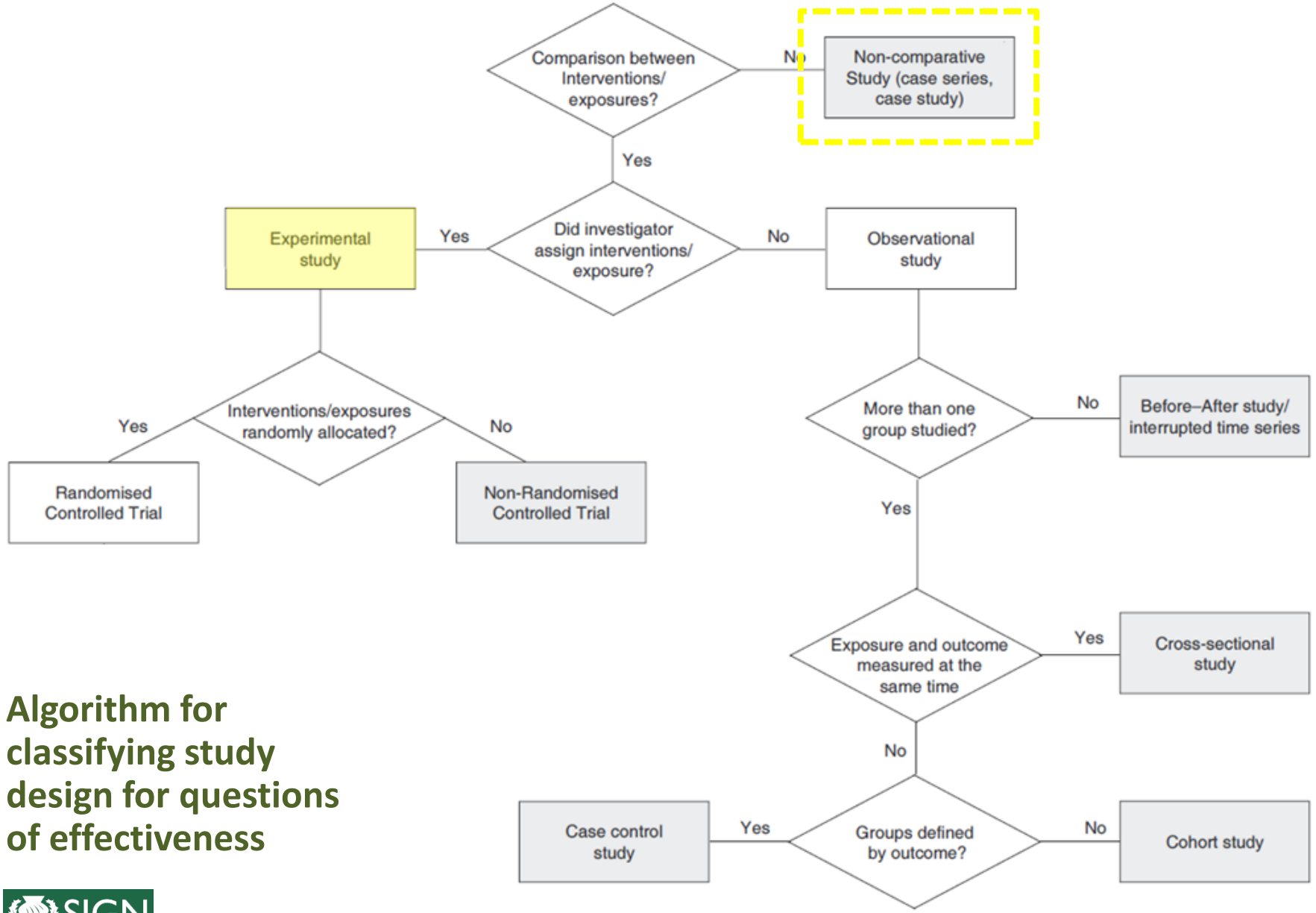

Fasi
(tradizionali)
III-IV
I-II
Efficacia
Attività
PK/PD - Tox
Continuum della
Sperimentazione
Clinica

Attività *vs* Efficacia

- **Attività**
  - **capacità di un trattamento di indurre le modificazioni attraverso le quali *si presume* di indurre dei benefici**
- **Efficacia**
  - **capacità di un trattamento di indurre i benefici per ottenere i quali esso viene somministrato**

Attività *vs* Efficacia

trattamento	*attività*	*efficacia*
diuretico	riduzione P.A.	riduzione malatt. C.V.
antidiab. orale	riduz. glicemia	riduz. mortalità
a.infiammat.	az. a.aggregante	riduzione malatt. C.V.
citotossico	riduz. tumorale	riduz. mortalità
citostatico	controllo malattia	riduz. mortalità
fatt. di crescita	stimolo crescita	riduz. complicanze



Algorithm for classifying study design for questions of effectiveness

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Urologia Internationalis

Urol Int 1998;61:220–226

Received: March 18, 1998
Accepted after revision: November 11, 1998

R. Hurle[a]
A. Manzetti[a]
A. Losa[a]
E. Micheli[a]
A. Ranieri[a]
D. Chinaglia[b]
A. Lembo[a]

Intravesical Instillation of Mitomycin-C in 242 Patients with Superficial Bladder Cancer at High Risk of Recurrence: Long-Term Results

Intravesical chemotherapy has been used for almost three decades with the aim of reducing recurrence and progression rates. Several drugs have given encouraging results in the prevention of recurrences [3–6] but uncertainty persists about the effect of prophylactic chemotherapy on disease progression [7, 8]. Mitomycin C (MMC) significantly reduces the recurrence rate of superficial bladder cancer [6, 9].

The present study assessed the long-term results of intravesical MMC instillation after TUR in 242 consecutive patients with superficial bladder cancer at high risk of recurrence.

Noncomparative (old-style) efficacy study

Disegno di studi di fase II

Random o non-random?

- **Studi di fase II non randomizzati (a singolo braccio)** *(Fleming-Simon)*
- **Randomized, Discontinuation Design**
- **Randomized, Selection Design**
- **Randomized, Screening Design**

Salvage Therapy with Capecitabine Plus Weekly Paclitaxel in Heavily Pretreated Advanced Breast Cancer

A Multicenter Phase II Study

Mario Bari,[1] Mario Rosario D'Andrea,[1] Giuseppe Azzarello,[1] Giovanni L. Pappagallo,[1] Donata Sartori,[1] Aldo Iop,[2] Ferdinando Gaion,[3] Francesco Rosetti,[1] Barbara Silvestri,[1] Salvatore Bonura,[2] Antonietta D'Alessio[3] and *Orazio Vinante[1]*

Am J Cancer 2005; 4 (5): 307-313

...we planned to test the null hypothesis that the true response rate was <25% (i.e. no clinical interest) against the alternative hypothesis that the true response rate was at least 40% (level of clinical interest), with $\alpha = 0.05$ and $1-\beta = 90\%$. Thus, according to Simon's 'optimal design',[17] 20 patients had to be enrolled, with an upper limit for first stage rejection of the null hypothesis of four responses; the planned maximum sample size was 49 patients (first plus second stage rejection), with an upper limit for second stage rejection of 14 responses.

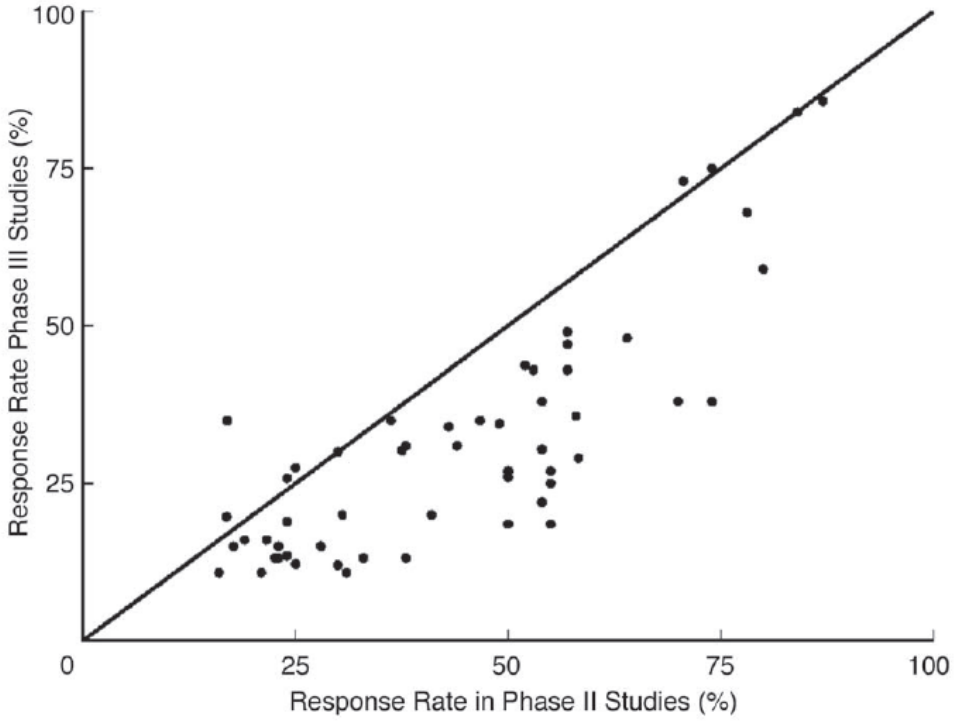
VOLUME 23 · NUMBER 28 · OCTOBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Comparison of Outcomes of Phase II Studies and Subsequent Randomized Control Studies Using Identical Chemotherapeutic Regimens

Mohammad I. Zia, Lillian L. Siu, Greg R. Pond, and Eric X. Chen



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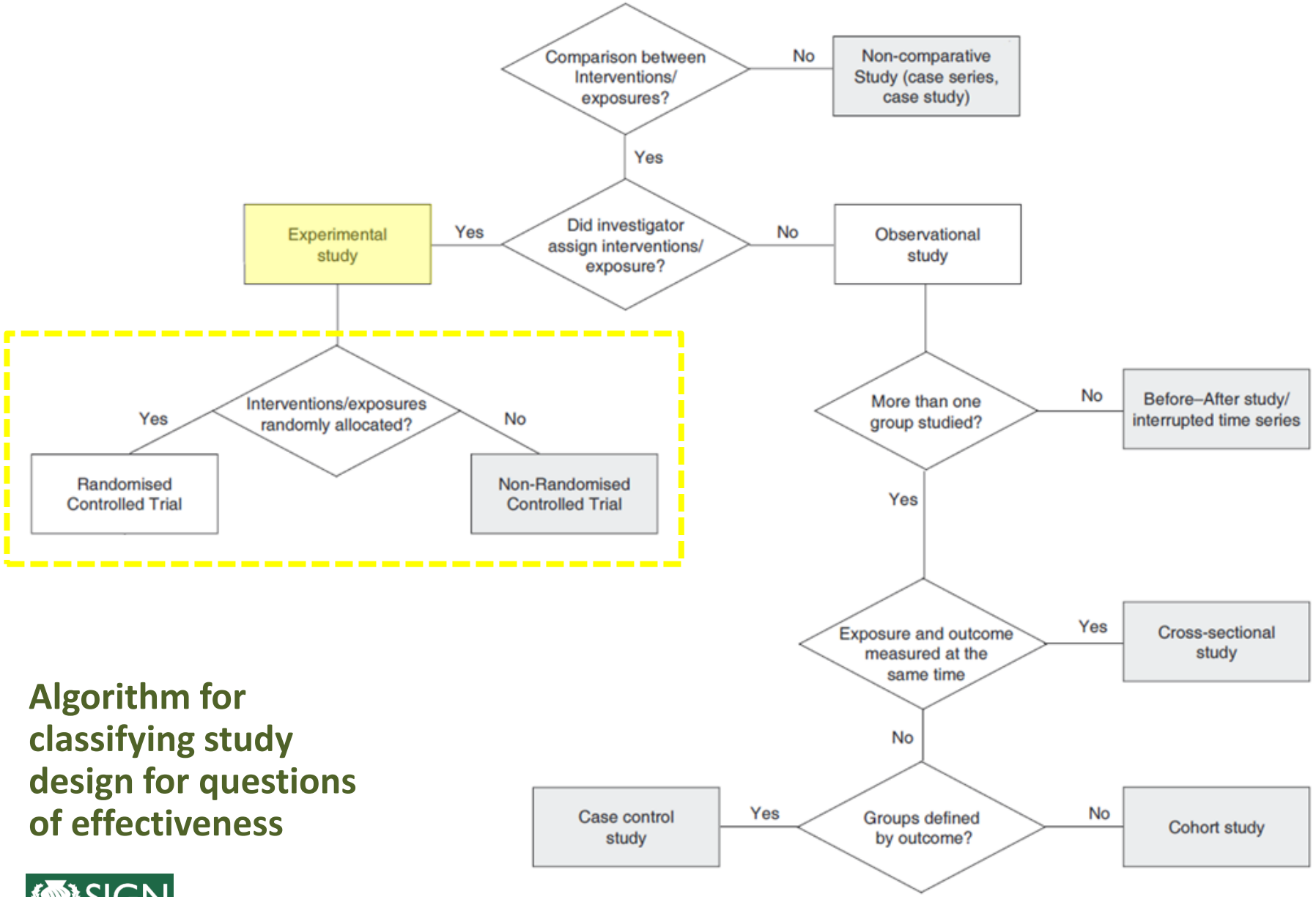

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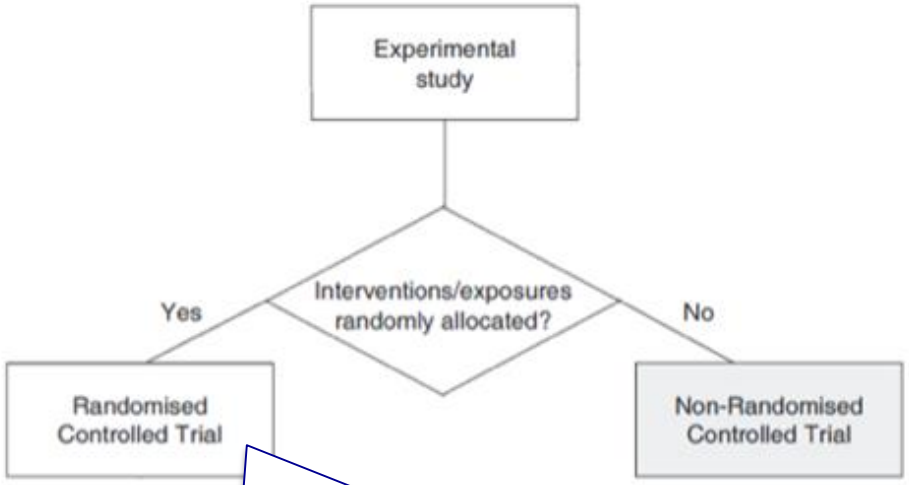
Randomization



Minimizes *allocation* ***bias***, balancing both known and unknown prognostic factors, in the assignment of treatments.

The 3 most important rules in drug development

- 1. Randomize
- 2. Randomize
- 3. Randomize

M Ratain, ASCO 2010

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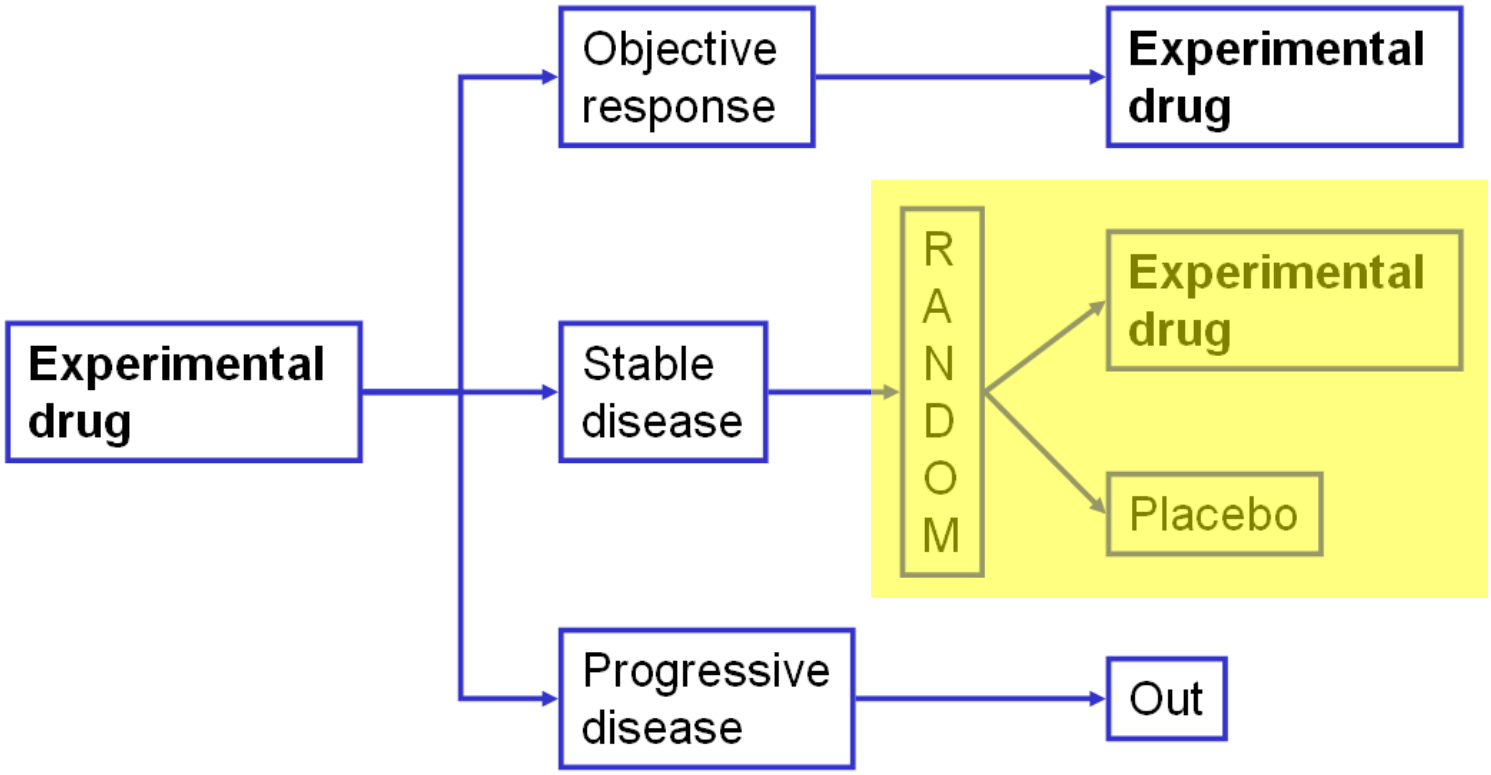
- **Randomized, Screening Design**

Randomized Discontinuation Design: Application to Cytostatic Antineoplastic Agents

By Gary L. Rosner, Walter Stadler, and Mark J. Ratain

J Clin Oncol 20:4478-4484. © 2002

Results: **By selecting a more homogeneous population, the randomized portion of the study requires fewer patients than would a study randomizing all patients at entry.**



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Randomized Phase II Selection Designs

- K experimental arms, no control arm
- Select arm with highest response rate or disease control rate further development

- Simon, Wittes, Ellenberg; Cancer Treatment Reports 69:1375, 1985

R. Simon, ASCO 2010

Disegno di studi di fase II

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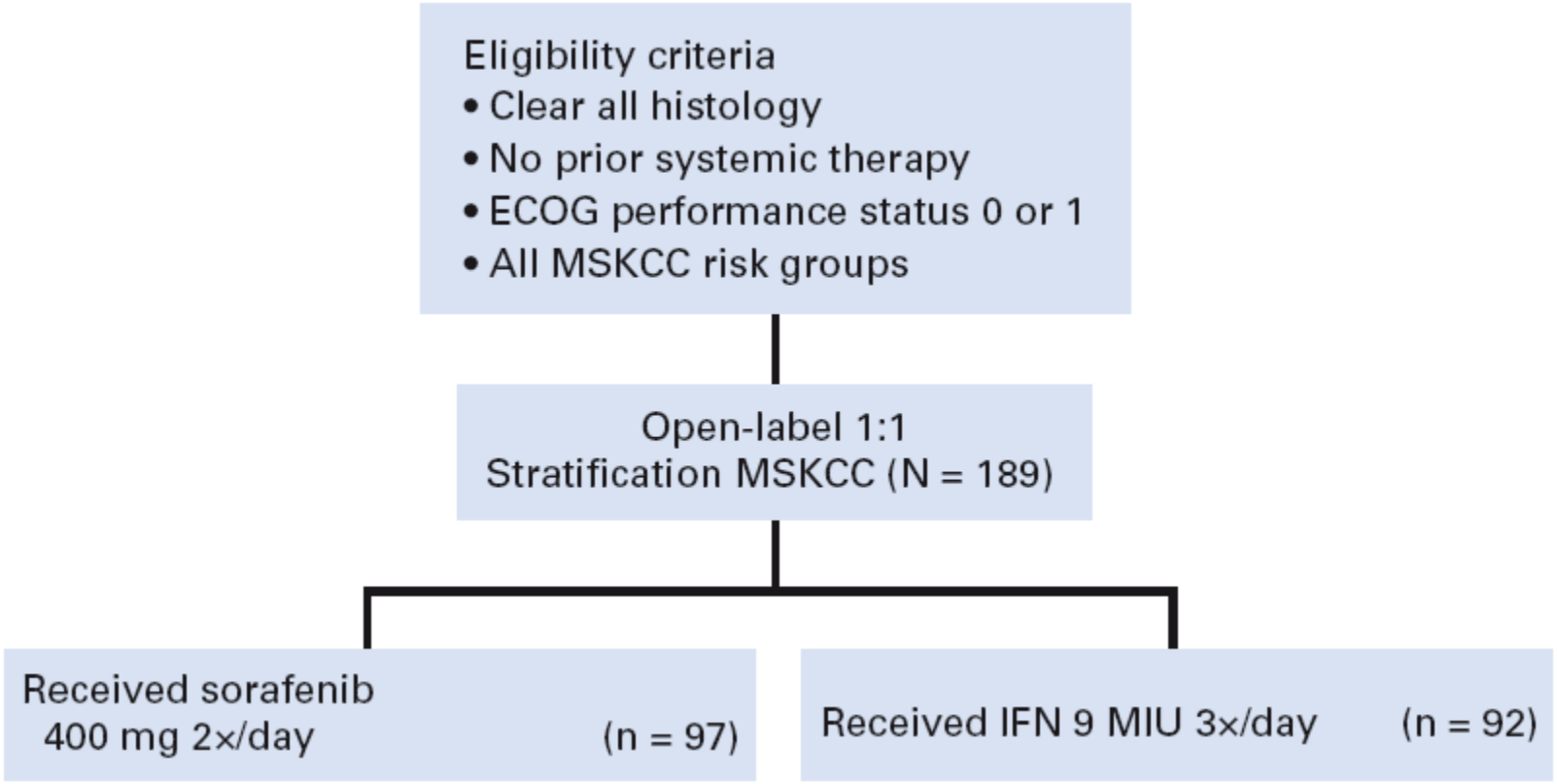
- **Randomized, Selection Design**
- **Randomized, Screening Design**

Randomized Phase II Trial of First-Line Treatment With Sorafenib Versus Interferon Alfa-2a in Patients With Metastatic Renal Cell Carcinoma

Bernard Escudier, Cezary Szczylik, Thomas E. Hutson, Tomasz Demkow, Michael Staehler, Frédéric Rolland, Sylvie Negrier, Nicole Laferriere, Urban J. Scheuring, David Cella, Sonalee Shah, and Ronald M. Bukowski

J Clin Oncol 27:1280-1289.



Design Issues of Randomized Phase II Trials and a Proposal for Phase II Screening Trials

Lawrence V. Rubinstein, Edward L. Korn, Boris Freidlin, Sally Hunsberger, S. Percy Ivy, and Malcolm A. Smith

RANDOMIZED PHASE II SCREENING DESIGNS

The most important caveat in using the phase II screening design is that it may compromise the ability to conduct definitive phase III trials. The screening design should not be applied unless investigators can be reasonably certain that a positive result in their small study will not be appreciated as definitive and will not preclude conduct of a definitive phase III test of the experimental regimen.

Superiorità Vs Non-inferiorità

Si ritiene che il trattamento in esame "A" abbia le potenzialità per migliorare il trattamento standard "B" almeno di una quantità Δ

studio di superiorità

A > B di una quantità Δ di interesse clinico

studio di non inferiorità

A < B non oltre una quantità M di rilevanza clinica

Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract

Joaquim Bellmunt, Christine Théodore, Tomasz Demkov, Boris Komyakov, Lisa Sengelov, Gedske Daugaard, Armelle Caty, Joan Carles, Agnieszka Jagiello-Gruszfeld, Oleg Karyakin, François-Michel Delgado, Patrick Hurteloup, Eric Winquist, Nassim Morsli, Yacine Salhi, Stéphane Culine, and Hans von der Maase

J Clin Oncol 27:4454-4461. © 2009 by American Society of Clinical Oncology

The estimated number of events was based on the following clinical hypothesis: median survival time of 6 months for the study arm and 4 months for the control arm. A total of 290 events would be needed for the detection of survival superiority with a type I error rate of 5% and a power of 90%, using a two-sided log-rank test and a 2:1 random assignment. Sample size estimation also took into account projected accrual time and losses to follow-up; thus, 364 patients were planned for inclusion.

eriorità

Vista la **migliore tollerabilità** del trattamento in esame “A”, si è disposti ad accettarne una eventuale minore efficacia rispetto al trattamento standard “B” purché questa non vada oltre un **margine M**

studio di superiorità

A > B di una quantità Δ di interesse clinico

studio di non inferiorità

A < B non oltre una quantità M di rilevanza clinica

EUROPEAN UROLOGY 63 (2013) 462–472

Final Results of an EORTC-GU Cancers Group Randomized Study of Maintenance Bacillus Calmette-Guérin in Intermediate- and High-risk Ta, T1 Papillary Carcinoma of the Urinary Bladder: One-third Dose Versus Full Dose and 1 Year Versus 3 Years of Maintenance

Jorg Oddens[a,*], *Maurizio Brausi*[b], *Richard Sylvester*[c], *Aldo Bono*[d], *Cees van de Beek*[e], *George van Andel*[f], *Paolo Gontero*[g], *Wolfgang Hoeltl*[h], *Levent Turkeri*[i], *Sandrine Marreaud*[c], *Sandra Collette*[c], *Willem Oosterlinck*[j]

Background: The optimal dose and duration of intravesical bacillus Calmette-Guérin (BCG) in the treatment of non–muscle-invasive bladder cancer (NMIBC) are controversial.

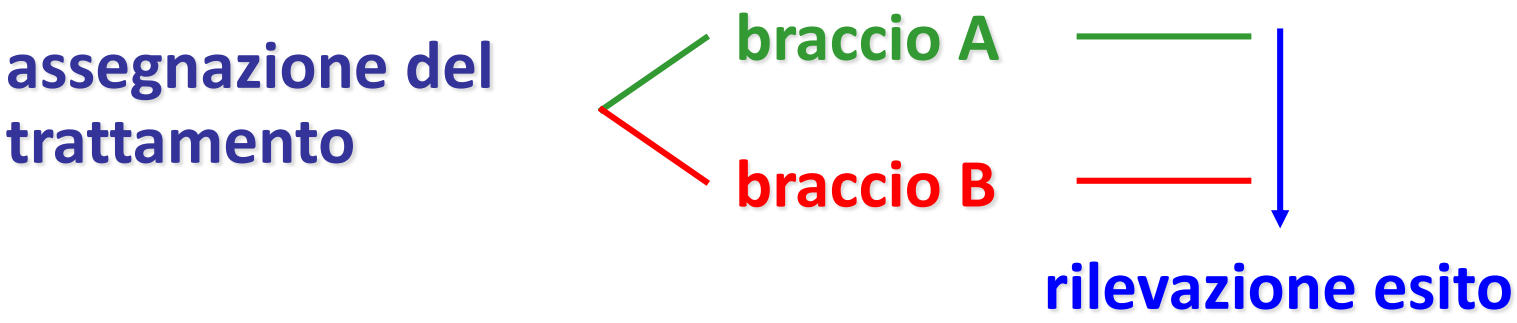
Objective: To determine if a one-third dose (1/3D) is not inferior to the full dose (FD), if 1 yr of maintenance is not inferior to 3 yr of maintenance, and if 1/3D and 1 yr of maintenance are associated with less toxicity.

Design, setting, and participants: After transurethral resection, intermediate- and high-risk NMIBC patients were randomized to one of four BCG groups: 1/3D-1 yr, 1/3D-3 yr, FD-1 yr, and FD-3 yr.

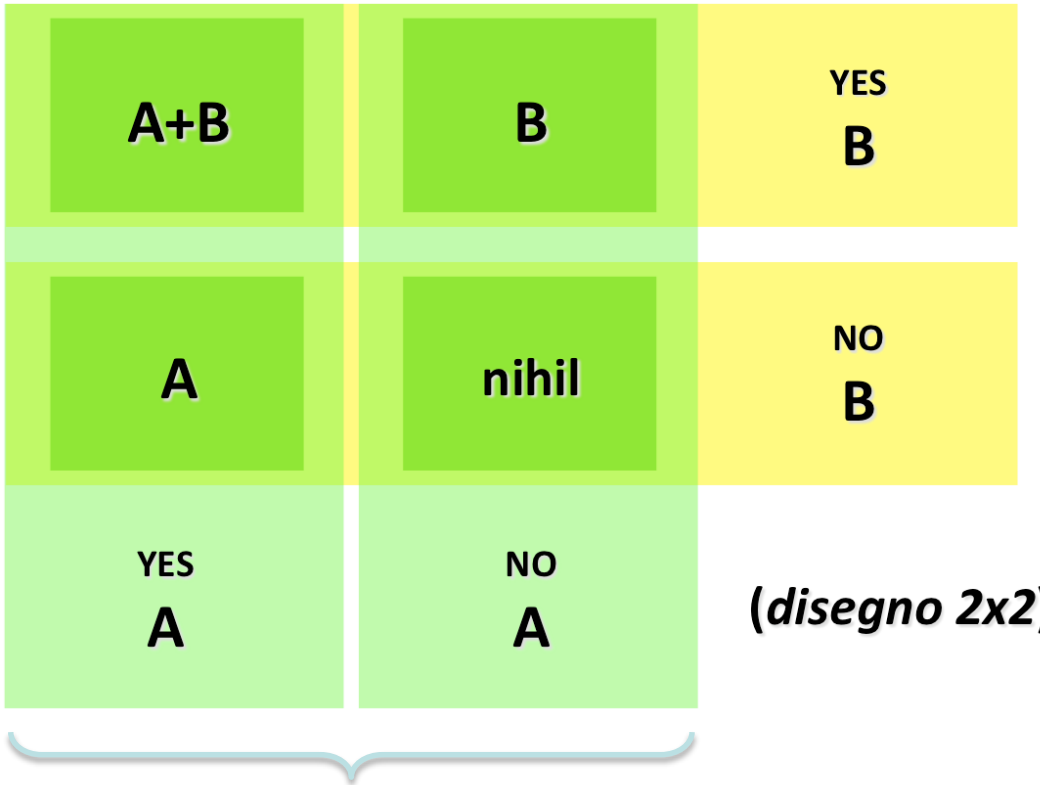
Outcome measurements and statistical analysis: The trial was designed as a noninferiority study with the null hypothesis of a 10% decrease in the disease-free rate at 5 yr.

DISEGNO A BRACCI PARALLELI

Assegnazione del paziente a un gruppo di trattamento, al quale si appartiene per l'intera durata dello studio:



DISEGNO FATTORIALE



Prerequisito: non interazione tra gli effetti degli interventi ("righe Vs colonne")

EFFECTS OF TOCOPHEROL AND DEPRENYL ON THE PROGRESSION OF DISABILITY IN EARLY PARKINSON'S DISEASE

THE PARKINSON STUDY GROUP*

(N Engl J Med 1993;328:176-83.)

Tocopherol + Deprenyl	Tocopherol	YES Tocopherol
Deprenyl	Placebo	NO Tocopherol
YES Deprenyl	NO Deprenyl	

EFFECTS OF TOCOPHEROL AND DEPRENYL ON THE PROGRESSION OF DISABILITY IN EARLY PARKINSON'S DISEASE

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(N Engl J Med 1993;328:176-83.)

Tocopherol + Deprenyl	Tocopherol	YES Tocopherol
YES Deprenyl	NO Deprenyl	

Conclusions. Deprenyl (10 mg per day) but not tocopherol (2000 IU per day) delays the onset of disability associated with early, otherwise untreated Parkinson's disease.

Gruppo Italiano Mammella (GIM) Studies

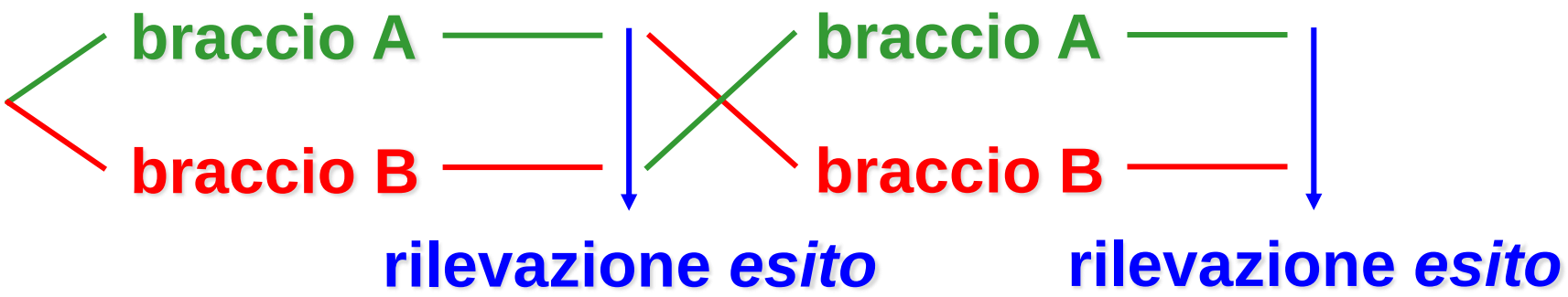
Source: Trial Sponsors > Index > G > Gruppo Italiano Mammella (GIM)

Pazienti

- Carcinoma mammario operato
- Postmenopausa
- ER or PgR +

DISEGNO CROSSOVER

Ciascun paziente riceve entrambi i trattamenti oggetto di sperimentazione clinica (*within patient* vs *between patient*):

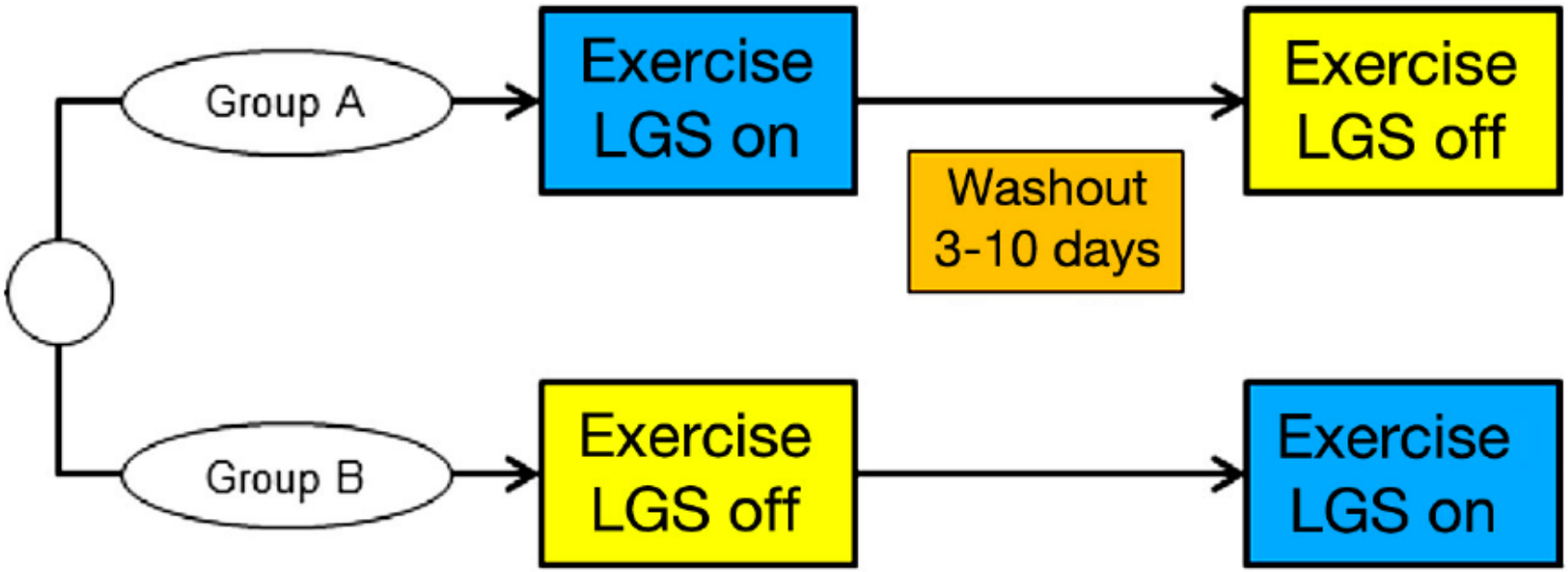


Viene "sottratta" dal confronto dei trattamenti l'influenza delle caratteristiche del paziente, le quali possono influire sulla misura di *outcome* → dimensione campionaria minore rispetto a uno studio a bracci paralleli.

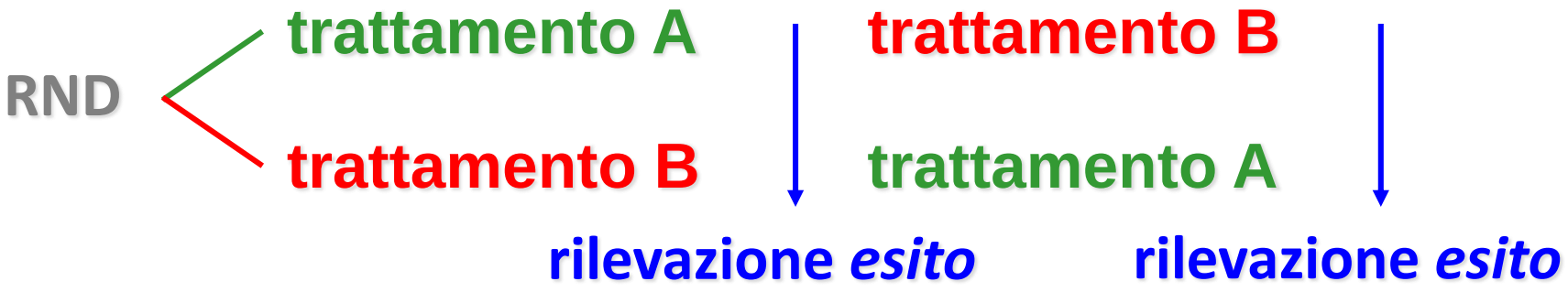
The ASPIRE Study: Design and Methods of an In-Clinic Crossover Trial on the Efficacy of Automatic Insulin Pump Suspension in Exercise-Induced Hypoglycemia

Ronald L. Brazg, M.D.,[1] Timothy S. Bailey, M.D.,[2] Satish Garg, M.D.,[3] Bruce A. Buckingham, M.D.,[4] Robert H. Slover, M.D.,[3] David C. Klonoff, M.D., FACP,[6] Xuan Nguyen, B.S.,[6] John Shin, Ph.D.,[6] John B. Welsh, M.D., Ph.D.,[6] and Scott W. Lee, M.D.[6]

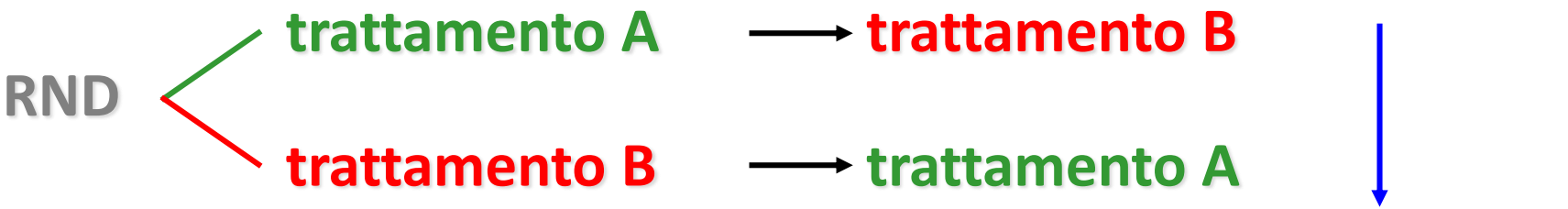
J Diabetes Sci Technol Vol 5, Issue 6, November 2011



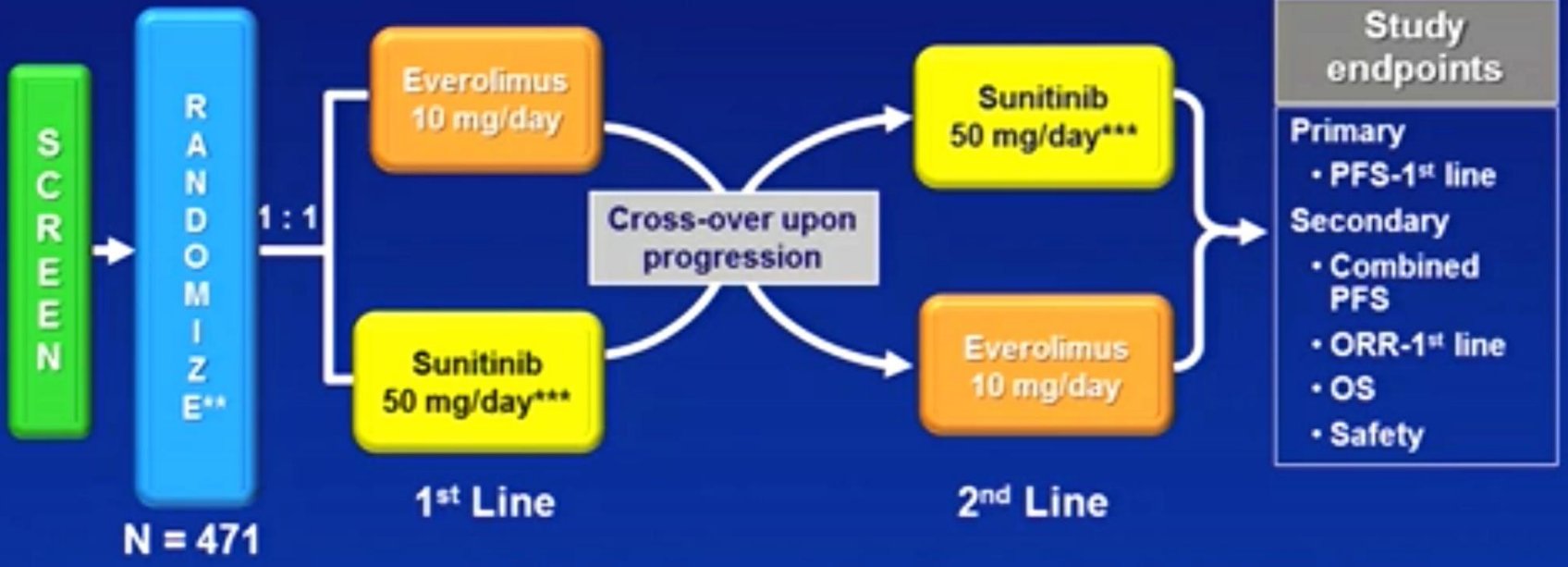
ATTENZIONE A NON CONFONDERE UN DISEGNO CROSSOVER…



…CON UN DISEGNO A BRACCI PARALLELI DI TIPO SEQUENZIALE



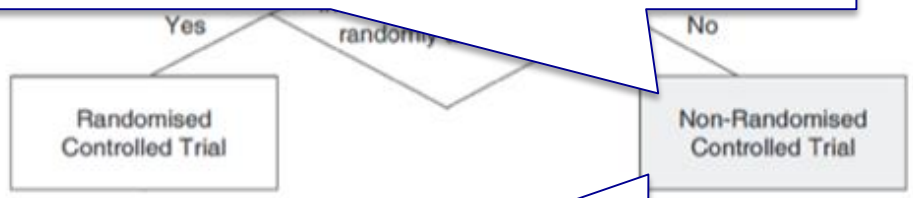
Study Design*



*NCT00903175. **Stratified by MSKCC prognostic factors. ***4 weeks on and 2 weeks off.

Nonrandomized Studies

A possible **bias** occurs because there is no random assignment of units in a target population to treatments.

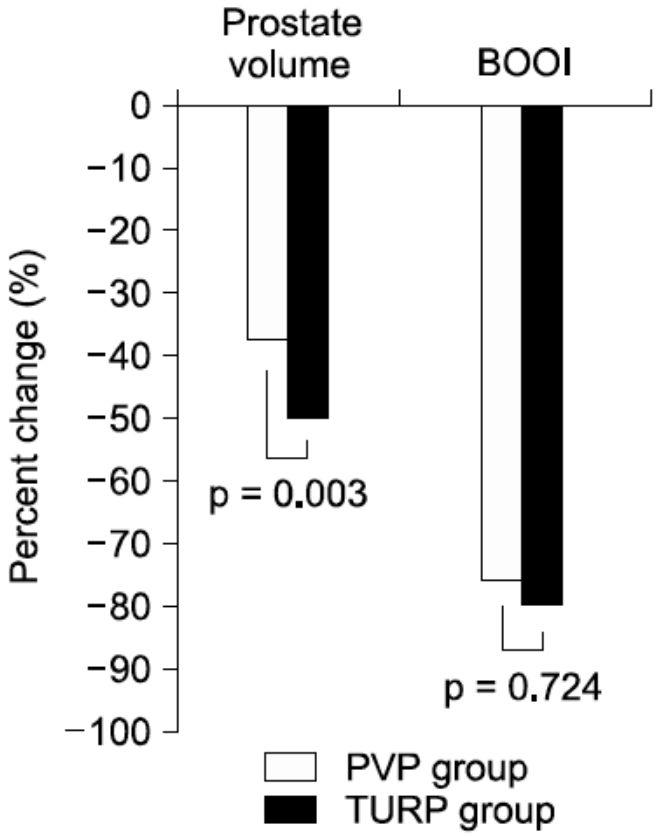


Any observed difference between the outcomes of study arms may be attributable to baseline differences rather than to a true treatment effect.

Can 80 W KTP Laser Vaporization Effectively Relieve the Obstruction in Benign Prostatic Hyperplasia?: A Nonrandomized Trial

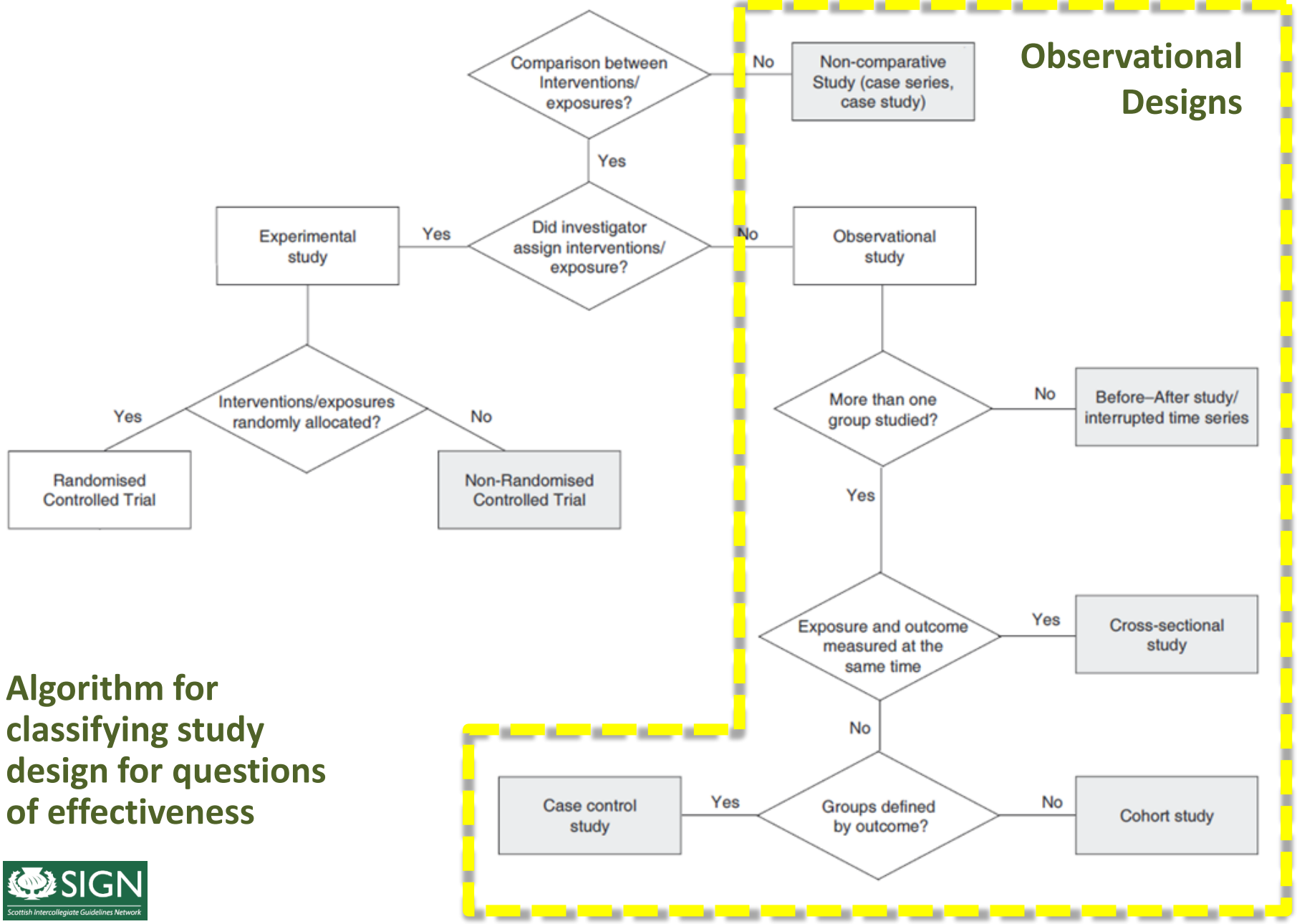
Deok Hyun Han[1], Seol Ho Choo[1], Jin Woo Chung[1], Jeong Hee Hong[2], Sung Won Lee[1]

World J Mens Health 2012 December 30(3): 160-165



This study has several limitations because it was performed under a nonrandomized design. The preoperative prostate volume and obstruction severity was higher in the TURP group than the PVP group.

Observational Designs



Algorithm for classifying study design for questions of effectiveness

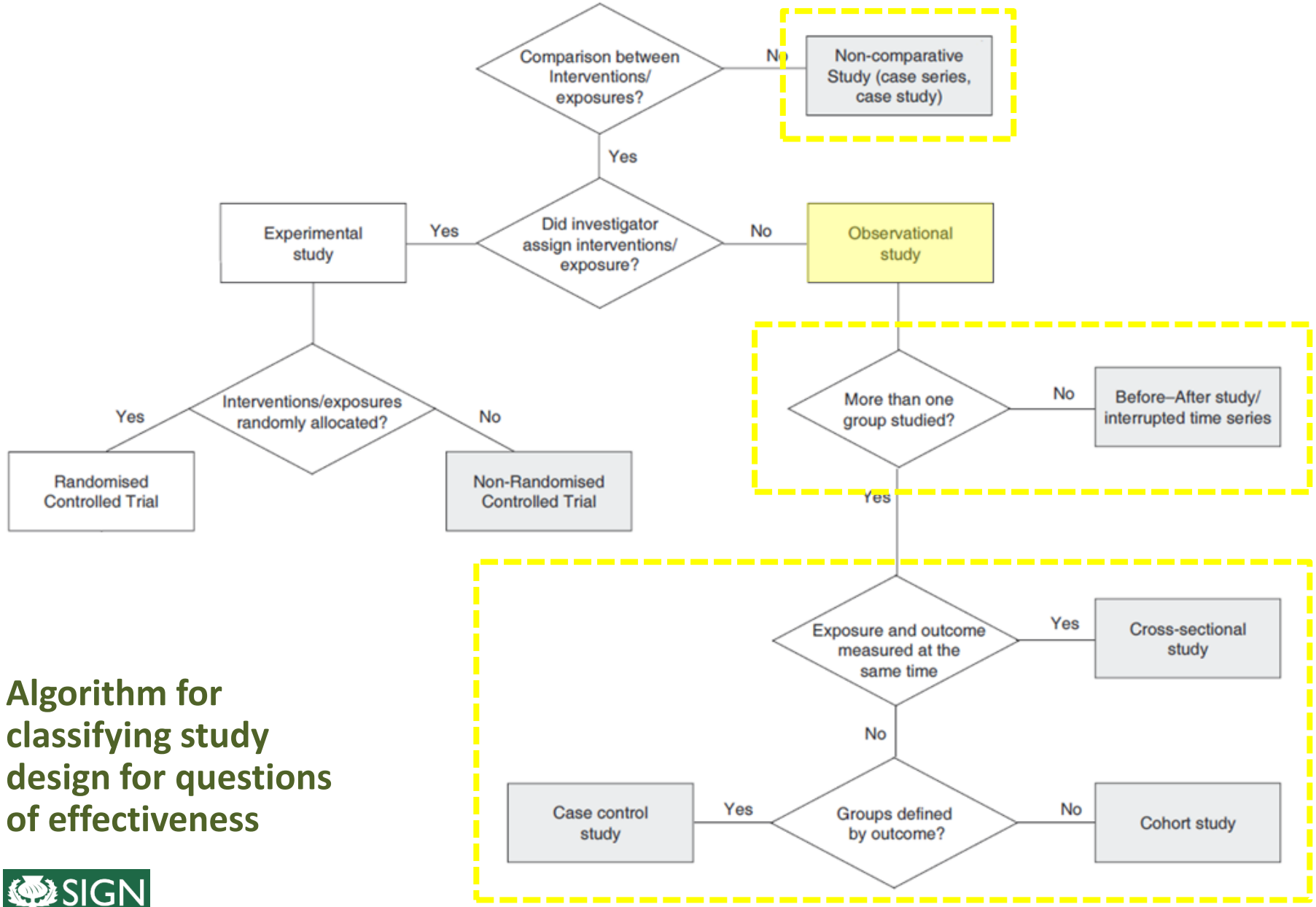
SIGN
Scottish Intercollegiate Guidelines Network

OBSERVATIONAL STUDY: A DEFINITION

An observational study draws inferences from a sample to a population where the independent variable is **not under the control** of the researcher.

The term observational study covers a wide range of study designs, a common feature of which is that they are noninterventional, in the sense that the **study protocol does not determine the** precise **features of any therapy** given to the participants in the study.

Algorithm for classifying study design for questions of effectiveness



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Observational Studies

"EPIDEMIOLOGIC" Vs "THERAPEUTIC"

Before-After

Surveys disease status before and after an intervention

Cross-Sectional

Provide information on prevalence of a particular condition at a single time point (time window)

Case-Control

Identify predictors of a particular outcome

Cohort

Identify the incidence of a particular outcome over time

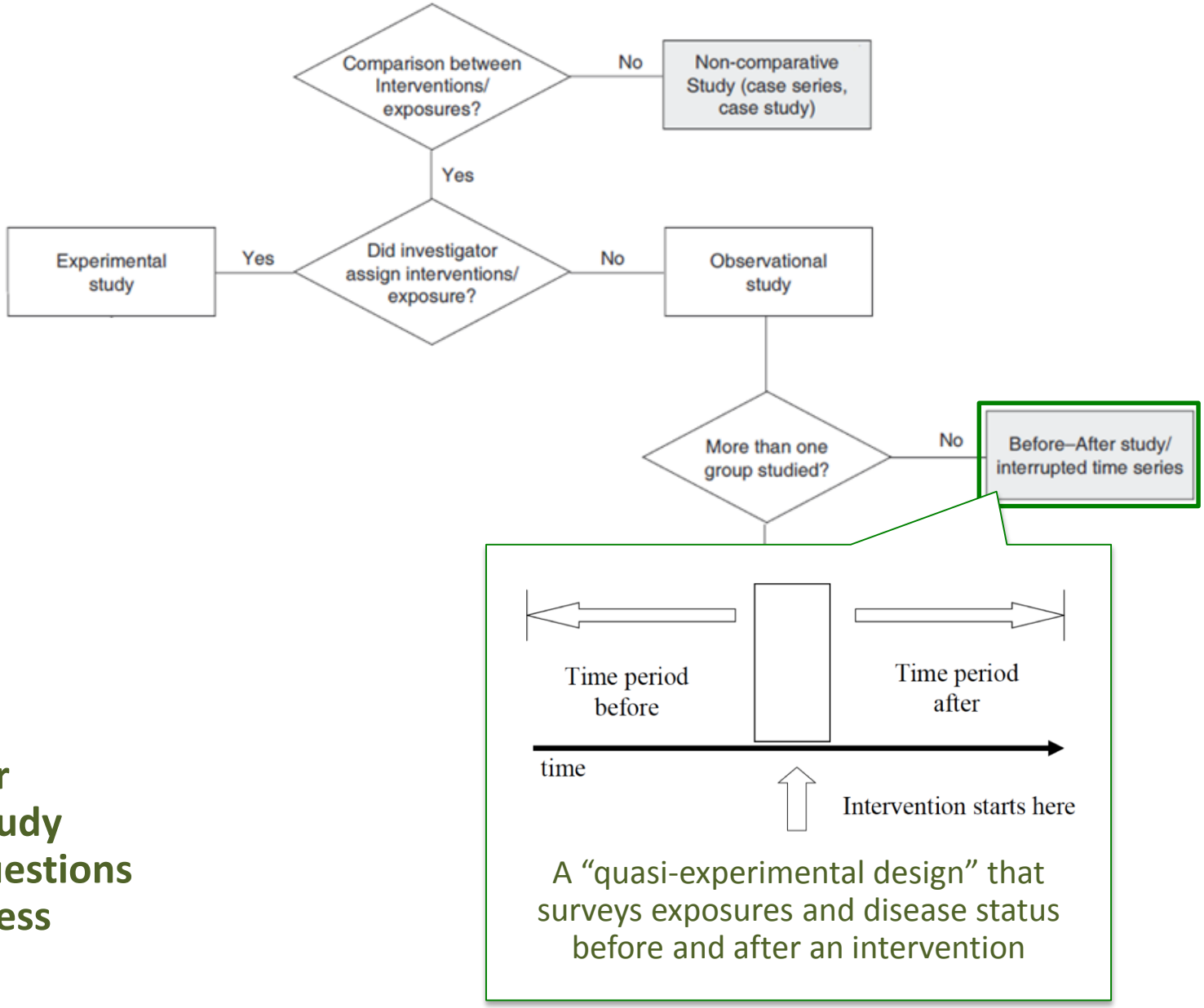
Non-comparative case series

Report outcomes of patients who received a specific intervention

Comparative case series

Compare outcomes between patients who received different interventions

Algorithm for classifying study design for questions of effectiveness



A "quasi-experimental design" that surveys exposures and disease status before and after an intervention

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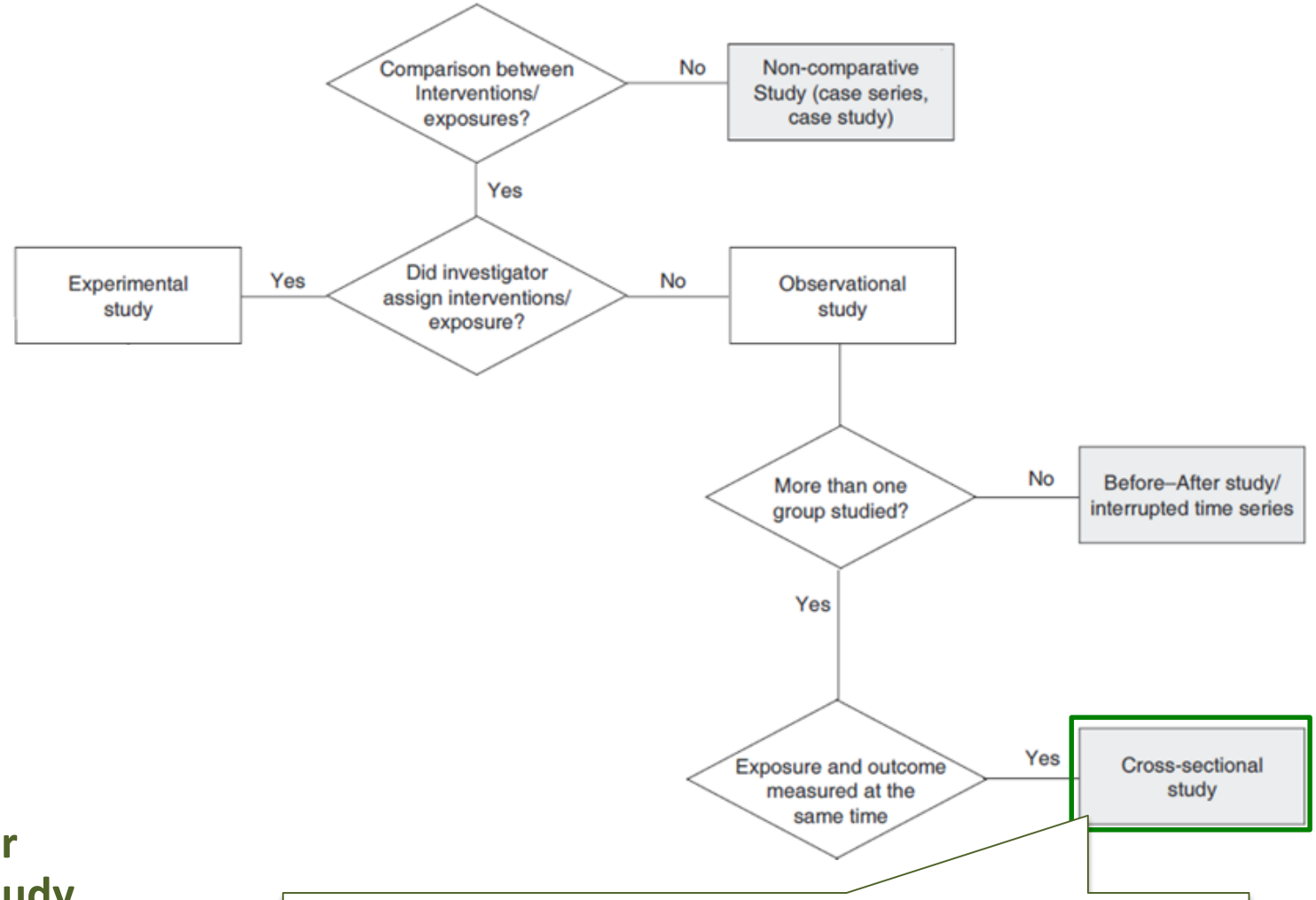

Subjects selected irrespective of the presence or absence of the characteristics of interest. Similar to a case series, except that the purpose of the analysis is to record associations between variables, rather than merely to report frequencies of their occurrence

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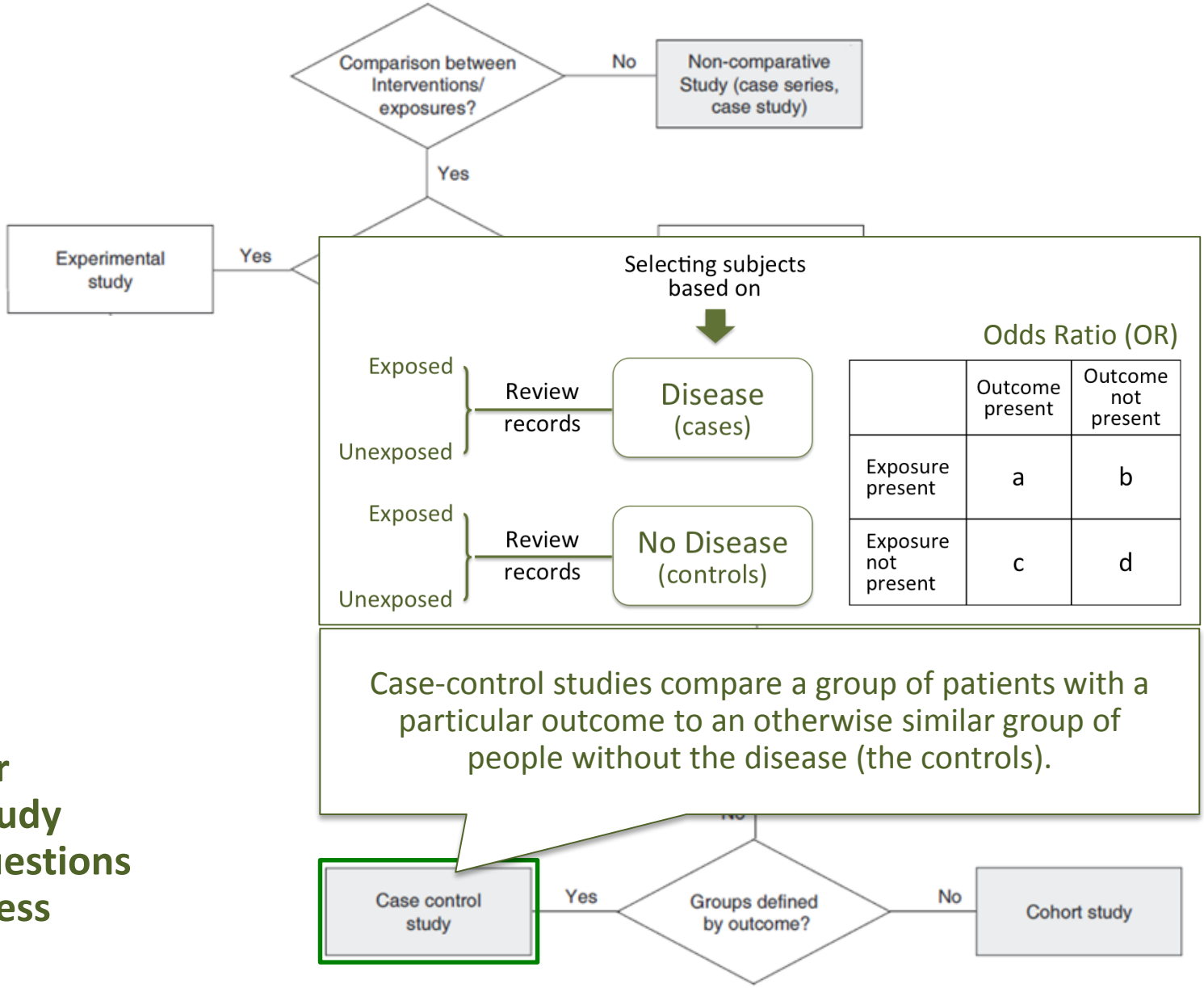

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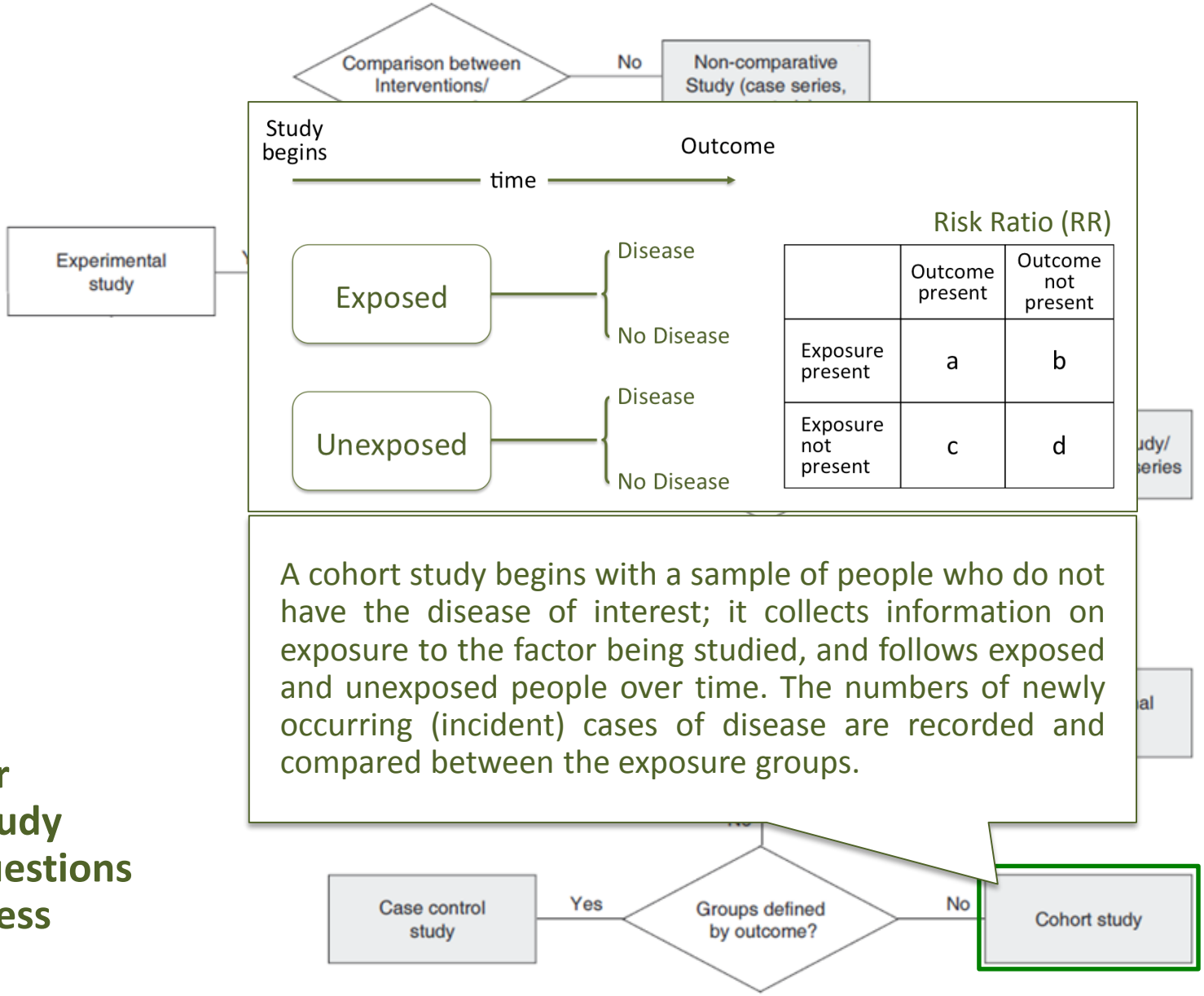

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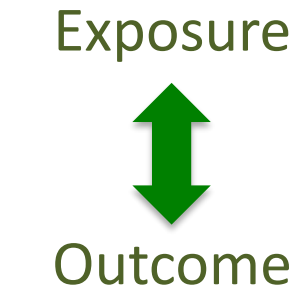
Time matters…



Cross-Sectional Studies
(exposure and outcome measured at the same time)

Case-Control Studies
(groups defined by the outcome)

Cohort Studies
(groups not defined by the outcome)

Observational Studies

"EPIDEMIOLOGIC" Vs "THERAPEUTIC"

Before-After

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Effectiveness Versus Efficacy: More Than a Debate Over Language

Julie M. Fritz, PT, PhD, ATC[1] *Joshua Cleland, PT, DPT, OCS*[2]

To some, the best evidence may be viewed as research that minimizes bias to the greatest extent possible, while others may prioritize research that is d[illegible]med most pertinent to clinical practice.

Qualità = eliminare (ridurre) le fonti di bias?

From Randomized Controlled Trials to Observational Studies

Stuart L. Silverman, MD

The American Journal of Medicine (2009) 122, 114-120

Table 1 Randomized Controlled Trial Methodology

Strengths	
Well-defined study population	Excludes many patients requiring clinical treatment
Design maximizes internal validity	Outcomes are difficult to extrapolate to a more general patient population
Tightly controlled treatment conditions	Short duration and modest sample sizes limit ability to identify rare or long-term adverse events
Compliance maximized through strict protocols	

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Qualità = trasferibilità alla pratica clinica?

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Integrating real-life studies in the global therapeutic research framework

*Nicolas Roche, Helen K Reddel, Alvar Agusti, Eric D Bateman, Jerry A Krishnan, Richard J Martin, Alberto Papi, Dirkje Postma, Mike Thomas, Guy Brusselle, Elliot Israel, Cynthia Rand, Alison Chisholm, David Price, on behalf of the Respiratory Effectiveness Group

www.thelancet.com/respiratory **Vol 1 December 2013**

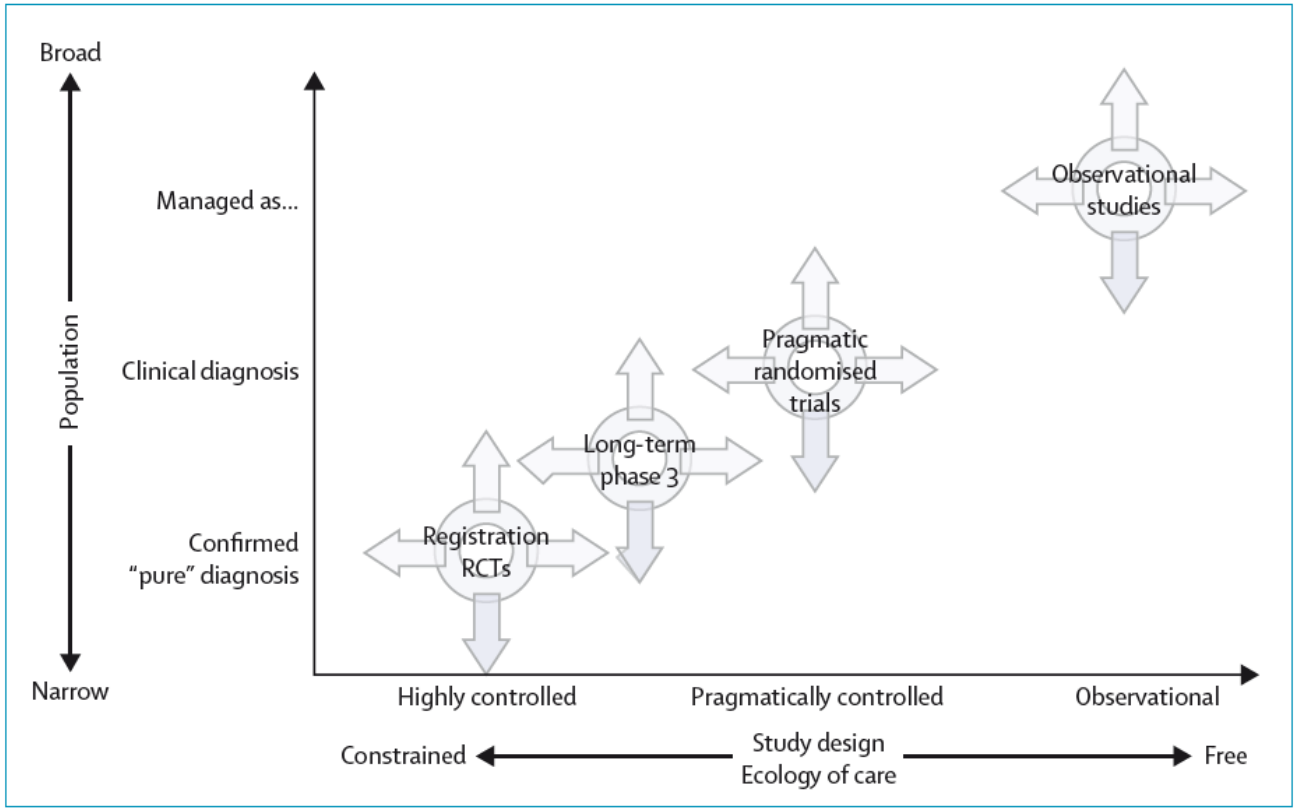


Figure 1: **A conceptual framework for therapeutic research**

Retrospective, non comparative efficacy analysis

Mature results on metastatic breast cancer patients with prolonged (≥1 year) exposure to first-line bevacizumab combined with paclitaxel from a large observation study

P2 – 16 - 03

M Schmidt[1], A Schneeweiss[2], F Foerster[3], M Geberth[4], C Schumacher[5], W Hollburg[6], U Söling[7], B Aktas[8], S Kümmel[9]

[1]*University Hospital Mainz, Mainz, Germany;* [2]*University of Heidelberg, National Center for Tumor Diseases, Heidelberg;* [3]*University of Applied Sciences Zwickau, Zwickau;* [4]*SPGO-Mannheim, Mannheim;* [5]*St Elisabeth-Krankenhaus, Köln;* [6]*Hämatologisch-Onkologische Praxis Altona im Struenseehaus, Hamburg;* [7]*Clinical Practice, Kassel;* [8]*University Clinic, Essen;* [9]*Kliniken Essen-Mitte, Essen, Germany*

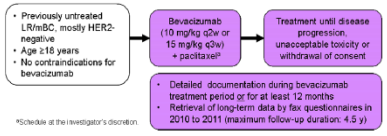
Background

- Combining first-line bevacizumab with standard chemotherapy significantly improved PFS and response rate compared with chemotherapy alone in three randomised phase III trials in HER2-negative locally recurrent or metastatic breast cancer (LR/mBC).[1–4]
- The efficacy and tolerability observed in these randomised phase III trials was supported by results of large cohort studies in routine oncology practice, with 'real-life' patient selection and treatment procedures:
  - The multinational ATHENA study, evaluating first-line bevacizumab-containing therapy in 2264 patients from overall 37 countries.[5,6]
  - A German non-interventional study evaluating first-line bevacizumab–paclitaxel, according to the European label, in 865 patients.[7]
- In both of the 'real-life' studies and in two smaller prospective/ambispective studies conducted in Japan[8] and France[9] a considerable proportion of patients received bevacizumab for prolonged periods.
- We report the final analysis of efficacy and safety, including mature long-term follow-up, in the subset of patients who received bevacizumab for ≥1 year in the German non-interventional study.

Methods – Study design

- The design of this non-interventional study is shown in Figure 1.
  - Endpoints were efficacy (overall response rate, PFS, OS) and safety (adverse events [AEs], AEs of special interest, serious AEs).
- Paclitaxel schedule, diagnostics and frequency of follow-up visits were at the discretion of the physician.
  - Detailed therapy data were collected during bevacizumab therapy, at least for up to 1 year, with further follow-up for efficacy at several time points after the end of intensely documented observation or discontinuation of bevacizumab, up to a maximum of 4.5 years (y).
- For this analysis, data from patients treated with bevacizumab for ≥1 year were extracted and analyzed retrospectively.
- Data base closure was in July 2012.

Figure 1. Study design



*Schedule at the investigator's discretion.

Results

Patients

Between May 2007 and September 2009, a total of 1123 patients were documented in this observational study
- Of these, 865 patients received a bevacizumab–paclitaxel combination as 1st line therapy.
- Of these, 167 (20%) had received bevacizumab for ≥1 year.

- Baseline characteristics of bevacizumab-paclitaxel patients with antibody treatment < or ≥1 year are shown in Table 1.
- Patients with long-term bevacizumab treatment typically show characteristics which are generally associated with less aggressive disease: fewer patients with G3 tumors, disease-free interval ≤ 12 months, ≥3 metastatic sites, liver lesions, hormone receptor or triple-negative status, previous (neo)adjuvant chemotherapy, and ECOG performance ≥1.

Treatment exposure

- In 78% of those treated for ≥1 year, bevacizumab was continued as a single agent after discontinuation of chemotherapy. Other changes of the cytotoxic regimen during 1st line were rare.
- 9% of patients treated for ≥1 year, and 12% in the complementary group received bevacizumab beyond progression (ie in combination with second- or later lines of chemotherapy).
- In the first cycle, 80% of patients in this subgroup received bevacizumab at a dose of 10 mg/kg, administered every two weeks. Dose reductions of the antibody were rare in the total study population (2% of patients) and not distinctly more common in the long-term subgroup (3%). Respective numbers for chemotherapy dose reductions were 21% and 28%.
- The corresponding numbers for treatment delays were 11% and 12% for bevacizumab, based on cycles, and 61% and 50%, based on patients (at least once). For chemotherapy these rates were generally higher, with 17% and 18% of cycles, 81% and 67% of patients, respectively.

Table 1. Baseline characteristics

Characteristic	Bevacizumab for <1 year (n=698)	Bevacizumab for ≥1 year (n=167)
Median age, years (range)	58 (26–87)	57 (28–79)
Metastatic at initial diagnosis, %	20	18
Grading G3 at diagnosis, %	42	32
Disease-free interval <12 months, %	26	14
Metastatic sites, %		
≥3	34	29
Liver	44	35
Lung	33	43
Bone	54	53
Hormone receptor-positive disease, %	70	75
Triple-negative disease (TNBC), %	20	12
Prior endocrine therapy for mBC, %	26	33
Prior (neo)adjuvant chemotherapy, %	67	61
Prior trastuzumab therapy, %	4	4
ECOG status		
0	41	49
1	50	43
2	8	8
3	1	1

Efficacy

- The overall response rate (ORR) in patients treated for ≥1 year was 80%, including complete responses in 19% of patients. The same ORR was observed in the TNBC subgroup.
  - In the population with bevacizumab for < 1 year, the overall response rate was 57%, including complete responses in 9%.
- Long-term median progression-free survival (PFS, Fig. 2) was:
  - 9.6 months in the overall population (715/865 events observed, 83%).
  - 18.4 months in patients treated for ≥1 year (125/167 events observed, 75%)
  - 8.0 months in patients treated for <1 year (590/698 events observed, 85%)
- Median overall survival (OS, Fig. 3) was:
  - 21.6 months in the overall population (524/865 events observed, 61%).
  - 35.7 months in patients treated for ≥1 year (72/167 events observed, 43%)
  - 18.0 months in patients treated for <1 year (452/698 events observed, 65%)

Figure 2. Progression-free survival by duration of bevacizumab treatment (<1 vs. ≥ 1 year)

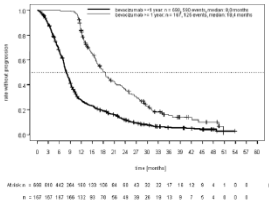
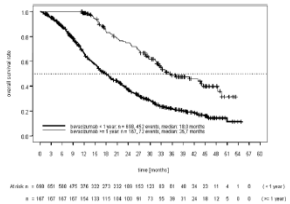


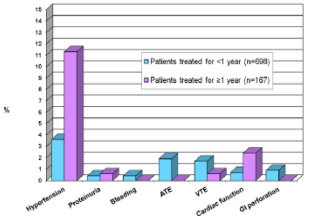
Figure 3. Overall survival by duration of bevacizumab treatment (<1 vs. ≥ 1 year)



Safety

- Grade 3/4 adverse events of special interest for bevacizumab (those reported in previous clinical trials) are shown in Figure 4.
- The most common grade 3/4 adverse events in patients treated with bevacizumab for ≥1 year were:
  - Hypertension (11% of patients)
  - Pain (9%)
  - Leukopenia (8%).
- There were no cases of gastrointestinal perforation or arterial thromboembolic events in those treated for ≥1 year. No confirmed reversible posterior leukoencephalopathy syndrome was reported in the total observation study population.
- In relation to the subgroup with bevacizumab for < 1 year, long-term treatment patients showed distinctly higher frequencies (all grades) with respect to hypertension (35% vs. 25%), proteinurea (17% vs. 9%), and sensory neuropathy (43% vs. 26%). However, the latter is obviously due to the higher amount of paclitaxel chemotherapy administered in the ≥1 year subgroup.

Figure 4. Grade ≥3 adverse events of special interest for bevacizumab



Comparison to ATHENA results

	This study	ATHENA[5,6]
Patient no. (recruitment)	865 (2007 – 2009)	2264 (2008 – 2009)
Country	Germany	multinational (37 countries)
Concurrent chemotherapy	paclitaxel only	paclitaxel (35%), docetaxel (33%) others/combinations (32%)
Median age / rate ≥ 70 y	58 years / 16%	53 years / 8%
Total population efficacy (ORR/ median PFS/ median OS/ 1 y OS rate)	57% / 9.6 mo / 21.8 mo / 73%	52% / 9.7 mo / 25.2 mo / 73%
Rate with treatment ≥ 1 y	20%	21%
Characteristics associated with no prolonged bevacizumab treatment (≥ 1 y)	G3, disease-free interval ≤ 12mo, ≥3 metastatic sites, liver lesions, HR- or triple-neg. status, previous adjuvant chemotherapy, ECOG ≥1	identical findings, except for missing impact of adjuvant chemotherapy (grading not reported)
Maturity of OS data	events observed in 43%	events observed in 27%[6]
≥ 1 y bevacizumab treatment population efficacy (ORR/ median PFS/ OS)	80% / 18.4 mo / 35.7 mo	68% / 19.9 mo / 29.6 mo

Discussion and Conclusions

- A notable proportion of patients seems to derive benefit from prolonged exposure to first-line bevacizumab-containing therapy.
- In the present analysis, baseline characteristics appeared more favorable in the subset of patients treated for ≥1 year than in the overall population. However, this might be an underlying association without a specific causal relation to antibody treatment duration.Typically, only these conventional parameters are collected in non-interventional studies, preventing the analysis and identification of new characteristics. Therefore, further prospective clinical research is needed to detect predictive biomarkers for bevacizumab.
- Efficacy data obviously have a bias towards improved outcome in those able to continue bevacizumab for ≥1 year, as these patients had sustained disease control for ≥1 year. This is a common limitation in single-cohort studies, when comparing time-related outcomes in patients treated for different durations.
- Nevertheless, the favorable survival outcomes of prolonged bevacizumab-containing therapy are of interest and suggest that some patients achieve sustained disease control with continued first-line bevacizumab–paclitaxel with limited side effects.
- Although our study is clearly different from the ATHENA project with respect to geographical, demographic and therapeutic homogeneity, the results reveal some striking similarities in "long-term" patient numbers and characterization, efficacy and safety endpoints. (The moderate dissimilarity in median OS is easily explained by the 5 year difference in median age.)
- Moreover, we confirmed and extended the positive findings from ATHENA, both in a population distinctly shifted to elderly patients, and based on a more mature overall survival data coverage.

References and acknowledgments

1. Miller K, et al. N Engl J Med 2007;357:2666-76.
2. Miles D, et al. J Clin Oncol 2010;28:3239–47.
3. Robert N, et al. J Clin Oncol 2011;29:1252–60.
4. Miles DW, et al. Ann Oncol 2013; published online: July 25, 2013.
5. Smith IE, et al. Ann Oncol 2011;22:595-602.
6. Smith I, et al. Breast Cancer Res Treat 2011;130:133–43.
7. Klare P, et al. J Clin Oncol 2011;29(suppl): abstract 1079.
8. Aogi K, et al. Breast Cancer Res Treat 2011;129:829–38.
9. Saghatchian M et al. ESMO Congress 2012, abstr. 937

The ML21185 study was sponsored by Roche Germany. Support for third-party writing assistance for this poster was provided by Roche Germany.
Presented at the 36th San Antonio Breast Cancer Symposium, December 10 to 14, 2013.

VICTOR: Vinflunine (Vin) in advanced metastatic Transitional Cell Carcinoma of the Urothelium (TCCU): A retrospective analysis of the use of Vinfluinine in multi-centre real life setting as second line chemotherapy through the free of charge programme (FOCP) for patients in the UK and Ireland.

S.A.Hussain[1,2], J. Ansari[3], R. Huddart[4], Alison Hassall[2], E. Harrold[5], D.G. Power[5], J. Lyons[6], J. Wylie[6], M. Vilarino-Varela[7], D.Wilkinson[8], R. McMenemin[8], L.M. Pickering[9], G. Faust[10], S. Chauhan[1], R. J. Jackson[1]

Real-World Vinflunine Outcomes in Bladder Cancer in a Single-Institution Study: Moving Beyond Clinical Trials

Guillaume Moriceau,[1] Alexis Vallard,[2] Romain Rivoirard,[1] Benoîte Méry,[1] Sophie Espenel,[2] Julien Langrand-Escure,[2] Majed Ben Mrad,[2] Guoping Wang,[2] Peng Diao,[2] Cécile Pacaut,[1] Aline Guillot,[1] Olivier Collard,[1] Pierre Fournel,[1] Nicolas Magné[2]

Clinical Genitourinary Cancer, Vol. 13, No. 6, 588-92 © 2015 Elsevier Inc.

Effectiveness, toxicity, and economic evaluation of vinflunine for the treatment of patients with transitional cell carcinoma in the Spanish outpatient setting

Beatriz Guglieri-López[a], Alejandro Pérez-Pitarch[b], Begoña Porta-Oltra[a], Francisco Ferriols-Lisart[b], Mónica Climente-Martí[a] and Manuel Alós-Almiñana[b]

Anti-Cancer Drugs 2015, **26**:860–865

Treatment of relapsed urothelial bladder cancer with vinflunine: real-world evidence by the Hellenic Genitourinary Cancer Group

Nikolaos Pistamaltzian[a], Kimon Tzannis[b], Vassiliki Pissanidou[e], Stavros Peroukidis[g], Georgia Milaki[h], Vasilis Karavasilis[e], Iraklis Mitsogiannis[c], Ioannis Varkarakis[c], Athanasios Papatsoris[c], Athanasios Dellis[d], Ioannis Adamakis[d], Konstantinos Stravodimos[d], Dimitra Molyva[f], Ilias Athanasiadis[a], Nikos Androulakis[h], Charalambos Andreadis[f], Charalambos Kalofonos[g], Dionisios Mitropoulos[d], Charalambos Deliveliotis[c], Constantinos Constantinides[d], Meletios A. Dimopoulos[b] and Aristotelis Bamias[b]

Anti-Cancer Drugs 2015, **00**:000–000

Safety and effectiveness of vinflunine in patients with metastatic transitional cell carcinoma of the urothelial tract after failure of one platinum-based systemic therapy in clinical practice

Daniel Castellano[1], Javier Puente[2], Guillermo de Velasco[3], Isabel Chirivella[4], Pilar López-Criado[5], Nicolás Mohedano[6], Ovidio Fernández[7], Icíar García-Carbonero[8], María Belén González[9] and Enrique Grande[10*]

BMC Cancer 2014, **14**:779

POSTER P268 (ECCO 2013)

HISTORICAL DATA IN REAL LIFE FROM PATIENTS TREATED BY VINFLUNINE FOR ADVANCED OR METASTATIC UROTHELIAL CARCINOMA (UC): RESULTS OF THE CURVE STUDY.

J.Médioni[1], A.Guillot[2], D.Spaeth[3], M.Di Palma[4], C.Théodore[5]

1 - Georges Pompidou Hospital, Paris, France; 2 - Lucien Neuwirth Cancerology Institute, Saint Priez en Jarez, France; 3 - Gentilly Oncology Centre, Nancy, France; 4 - Gustave Roussy Institute, Villejuif, France; 5 - Foch Hospital, Suresnes France

POSTER P130 (ECC 2015)

EFFECTIVENESS AND POSSIBLE MOLECULAR FACTORS PREDICTIVE OF CLINICAL OUTCOMES IN PATIENTS WITH TRANSITIONAL CELL CARCINOMA OF THE UROTHELIAL TRACT (TCCU) TREATED WITH VINFLUNINE: A MULTICENTER RETROSPECTIVE STUDY (MOVIE) OF THE GRUPPO ONCOLOGICO ITALIANO DI RICERCA CLINICA (GOIRC)

R. Passalacqua[1], R. Montironi[2], S. Lazzarelli[1], M. Donini[1], B. Perrucci[1], F. Nolè[3], G.L. Ceresoli[4], S. Pignata[5], F. Torricelli[6], P. Giannatempo[7], L. Doni[6], M. Ungari[1], S. Panni[1], A. Necchi[7], E. Betri[1], U. De Giorgi[8], R. Sabbatini[9], E. Rondini[10], M. Sequino[11], C. Caminiti[11].

1-Istituti Ospitalieri, Cremona, Italy. 2-University of Ancona, Italy. 3-IEO, Milano, Italy. 4-Humanitas Gavazzeni, Bergamo, Italy. 5-Istituto Tumori, Napoli, Italy. 6-Ospedale Careggi, Firenze, Italy. 7-INT, Milano, Italy. 8-IRST, Meldola, Italy. 9-Ospedale Universitario, Modena, Italy. 10-Arcispedale Santa Maria Nuova, Reggio Emilia, Italy. 11-University Hospital, Research, Parma, Italy.

The Value of Observational Cohort Studies for Cancer Drugs

Randomized controlled trials — the gold standard for clinical drug evaluation — can't always predict adverse events in real-world settings. For the new cancer therapies, observational cohort studies (OCSs) can help evaluate their effects in broader populations and provide valuable information for future clinical trials.

BY DAVID R. SPIGEL, MD **BIOTECHNOLOGY HEALTHCARE** · SUMMER 2010

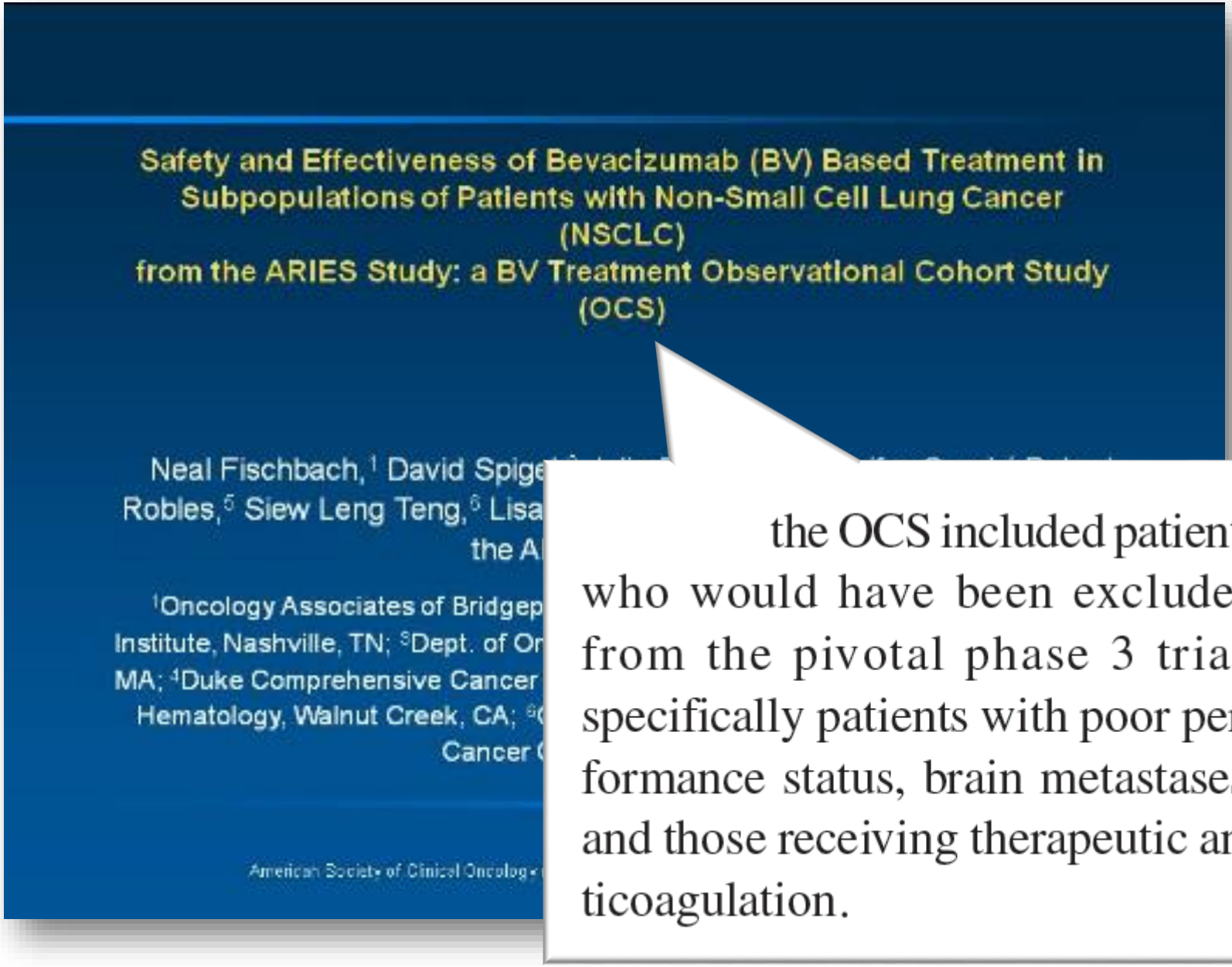
WHAT IS AN OCS?

An OCS is an analysis of a group of individuals who have specific features in common and who are followed over a defined period of time.

Prospective OCSs are designed to examine predefined primary outcomes.

Post-approval OCSs generally follow a single cohort, although patient subgroups may be analyzed separately.

To represent a broad and diverse patient base and to detect rare adverse events, large community-based, multicenter OCSs are useful in the post-approval setting for new therapeutics.



the OCS included patients who would have been excluded from the pivotal phase 3 trial, specifically patients with poor performance status, brain metastases, and those receiving therapeutic anticoagulation.

CONCLUSIONS

- ARIES NSCLC includes patient subpopulations excluded from or underrepresented in prior RCTs (e.g. elderly patients, patients with brain metastases, patients with poor PS, and patients on concurrent therapeutic AC or antiplatelet medications at baseline), providing important clinical information to clinicians about the effects of BV in a more general population.
- To date, the observed toxicities among patients in ARIES NSCLC have been consistent with toxicities identified in the BV treatment cohorts of prior RCTs (including E4599).
  - The incidence of Grade ≥3 bleeding (PH and CNS) in ARIES NSCLC was not higher than incidence in the RCTs, despite the inclusion in ARIES of patients with known brain metastases, patients with a history of hemoptysis, and patients on therapeutic AC.
- A variety of first-line regimens are utilized in ARIES NSCLC, providing additional safety information on combination of BV with non-carboplatin/paclitaxel (E4599) regimens.
- Effectiveness analyses, in specific subpopulations (including the elderly and patients with poor PS) and by chemotherapy regimen, will be conducted when data are mature.
- ARIES is an ongoing OCS and will continue to enroll NSCLC patients to a target number of 2000.

Genentech, Inc., provided support for the preparation of this poster.

First-line bevacizumab plus taxane-based chemotherapy for locally recurrent or metastatic breast cancer: safety and efficacy in an open-label study in 2251 patients

I. E. Smith[1*], J.-Y. Pierga[2], L. Biganzoli[3], H. Cortés-Funes[4], C. Thomssen[5], X. Pivot[6], A. Fabi[7], B. Xu[8], D. Stroyakovskiy[9], F. A. Franke[10], B. Kaufman[11], P. Mainwaring[12], T. Pienkowski[13], B. De Valk[14], A. Kwong[15], J. L. González-Trujillo[16], I. Koza[17], K. Petrakova[18], D. Pereira[19] & K. I. Pritchard[20], on behalf of the ATHENA Study Group

Annals of Oncology 22: 595–602, 2011

First-line Bevacizumab–Paclitaxel in 220 Patients with Metastatic Breast Cancer: Results from the AVAREG Study

MAGDOLNA DANK[1], LASZLO BUDI[2], BELA PIKO[3], LASZLO MANGEL[4], JOZSEF ERFAN[5], JOZSEF CSEH[6], AGNES RUZSA[7] and LASZLO LANDHERR[8]

ANTICANCER RESEARCH *34*: 1275-1280 (2014)

Vinflunine in routine clinical practice for the treatment of advanced or metastatic urothelial cell carcinoma - data from a prospective, multicenter experience

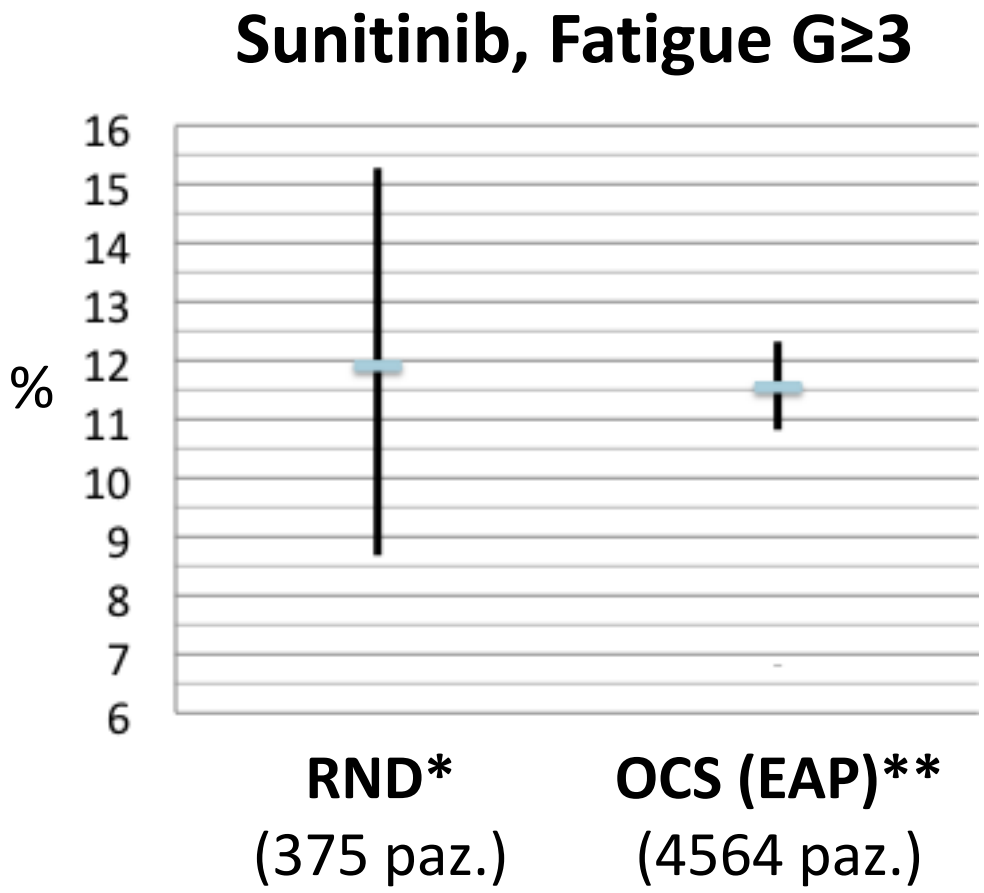
Margitta Retz[1*], Patrick de Geeter[2], Peter J. Goebell[3], Ullrich Matz[4], Wito de Schultz[5] and Axel Hegele[6]

BMC Cancer (2015) 15:455

Methods

In compliance with the German Drug Law (AMG) the non-interventional study was reported to the competent authority and approved by the ethics committee of the scientific leader (ethics committee of the Technische Universitaet München, Germany). The prospective NIS included patients with histologically confirmed locally advanced or metastatic UCC who experienced failure of a prior platinum-based chemotherapy.

Studio RND registrativo vs OCS (EAP)



Quale dei due studi è più UTILE per la Clinica?

* Motzer, NEJM 2007; ** Gore, Lancet Oncol 2009

Rizzo M, 2013

Observational Studies

"EPIDEMIOLOGIC" Vs "THERAPEUTIC"

Before-After

Surveys disease status before and after an intervention

Cross-Sectional

Provide information on prevalence of a particular condition at a single time point (time window)

Case-Control

Identify predictors of a
outcome

Cohort

Identify the incidence
particular outcome ove

Non-comparative case series

Report outcomes of patients who received a specific intervention

Comparative case series

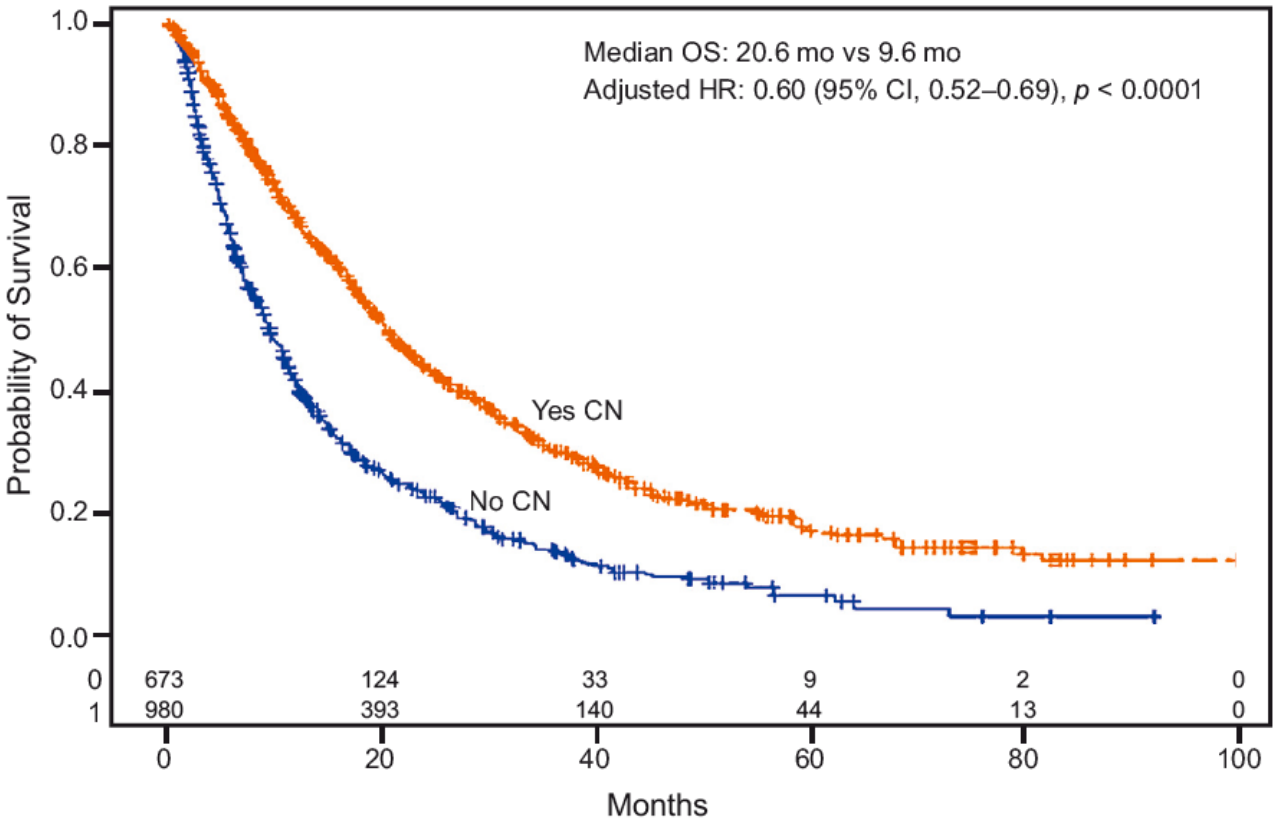
Compare outcomes between patients who received different interventions

Any observed difference between the outcomes of study arms may be attributable to baseline differences rather than to a true treatment effect.

Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium

Daniel Y.C. Heng[a,*,†], *J. Connor Wells*[a,†], *Brian I. Rini*[b], *Benoit Beuselinck*[c], *Jae-Lyun Lee*[d], *Jennifer J. Knox*[e], *Georg A. Bjarnason*[f], *Sumanta Kumar Pal*[g], *Christian K. Kollmannsberger*[h], *Takeshi Yuasa*[i], *Sandy Srinivas*[j], *Frede Donskov*[k], *Aristotelis Bamias*[l], *Lori A. Wood*[m], *D. Scott Ernst*[n], *Neeraj Agarwal*[o], *Ulka N. Vaishampayan*[p], *Sun Young Rha*[q], *Jenny J. Kim*[r], *Toni K. Choueiri*[s]

EUROPEAN UROLOGY 66 (2014) 704–710

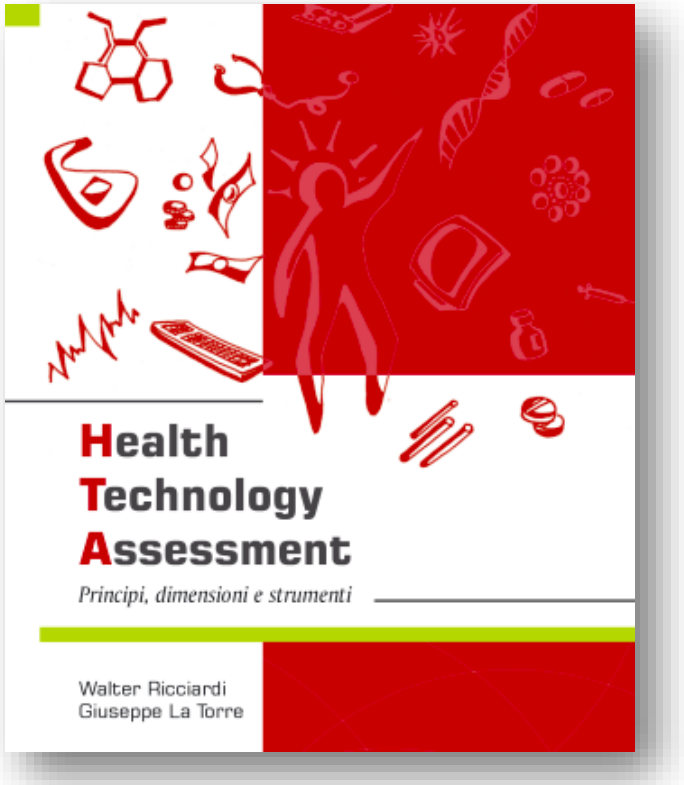


Reconciling the Use of Cytoreductive Nephrectomy in the Targeted Therapy Era

Stephen H. Culp *

EUROPEAN UROLOGY 66 (2014) 711–712

Although retrospective, the results of this study are strengthened by the number of patients examined, inclusion of patients from institutions around the world, and lack of patient exclusion based on RCC histology or type of targeted agent.



Bias

La fonte di errore non casuale, in termine epidemiologico, è detta bias. Il bias è un errore metodologico e sistematico, che inficia la misura valida del fenomeno in studio, qualsiasi sia l'ampiezza del campione.

Comparative Effectiveness of Gemcitabine Plus Cisplatin Versus Methotrexate, Vinblastine, Doxorubicin, Plus Cisplatin as Neoadjuvant Therapy for Muscle-Invasive Bladder Cancer

Matthew D. Galsky, MD[1†]; Sumanta K. Pal, MD[2†]; Simon Chowdhury, MRCP[3]; Lauren C. Harshman, MD[4]; Simon J. Crabb, MRCP[5]; Yu-Ning Wong, MD[6]; Evan Y. Yu, MD[7]; Thomas Powles, MRCP[8]; Erin L. Moshier, PhD[9]; Sylvain Ladoire, MD[10]; Syed A. Hussain, MD[11]; Neeraj Agarwal, MD[12]; Ulka N. Vaishampayan, MD[13]; Federica Recine, MD[14]; Dominik Berthold, MD[15]; Andrea Necchi, MD[16]; Christine Theodore, MD[17]; Matthew I. Milowsky, MD[18]; Joaquim Bellmunt, MD[4]; and Jonathan E. Rosenberg, MD[19]; for the Retrospective International Study of Cancers of the Urothelial Tract (RISC) Investigators

Cancer 2015;121:2586-93.

Study Population

We identified 656 patients in the database who had received neoadjuvant chemotherapy between 2005 and 2012. Of these, 370 patients did not meet the inclusion criteria, and an additional 74 patients had missing data. The final data set was comprised of 212 patients (146 in the GC cohort and 66 in the MVAC cohort).

Comparative Effectiveness Research in Oncology Methodology: Observational Data

Dawn L. Hershman and Jason D. Wright

J Clin Oncol 30:4215-4222. © 2012 by American Society of Clinical Oncology

Propensity Score Analysis

Propensity score analyses attempt to balance covariates between experimental groups. Using multivariable modeling, the characteristics of a cohort are used to calculate the probability of receiving the intervention. This probability is the propensity score.

Le caratteristiche della coorte vengono usate per calcolare la probabilità di (*propensità* a) ricevere l'uno o l'altro dei trattamenti a confronto. Tale probabilità è espressa dal *propensity score*.

Comparative Effectiveness of Gemcitabine Plus Cisplatin Versus Methotrexate, Vinblastine, Doxorubicin, Plus Cisplatin as Neoadjuvant Therapy for Muscle-Invasive Bladder Cancer

Matthew D. Galsky, MD[1†]; Sumanta K. Pal, MD[2†]; Simon Chowdhury, MRCP[3]; Lauren C. Harshman, MD[4]; Simon J. Crabb, MRCP[5]; Yu-Ning Wong, MD[6]; Evan Y. Yu, MD[7]; Thomas Powles, MRCP[8]; Erin L. Moshier, PhD[9]; Sylvain Ladoire, MD[10]; Syed A. Hussain, MD[11]; Neeraj Agarwal, MD[12]; Ulka N. Vaishampayan, MD[13]; Federica Recine, MD[14]; Dominik Berthold, MD[15]; Andrea Necchi, MD[16]; Christine Theodore, MD[17]; Matthew I. Milowsky, MD[18]; Joaquim Bellmunt, MD[4]; and Jonathan E. Rosenberg, MD[19]; for the Retrospective International Study of Cancers of the Urothelial Tract (RISC) Investigators

Cancer **2015;121:2586-93.**

Logistic regression was used to compute propensity scores as the predicted probabilities of patients being assigned to MVAC versus GC given their age, calculated creatinine clearance, number of cycles of chemotherapy received, pure versus mixed transitional cell carcinoma histology, Eastern Cooperative Oncology Group performance status, year of diagnosis, cT-classification, and sex. These propensity scores were then included in a new logistic regression model, which was used to estimate an adjusted odds ratio comparing the odds of attaining a pCR for patients who received MVAC versus GC.

Con il Patrocinio di

Aiom

STUDI CLINICI: METODOLOGIA

Coordinatore:
Dr.ssa Stefania Gori

Evento ECM MODULO 1
(formazione di base)
"A good foundation"

NEGRAR
22-23 Gennaio 2016
Centro Formazione
Ospedale Sacro Cuore
Don Calabria

Riflessioni e Sintesi

WHAT?

Cosa è emerso di particolarmente saliente e rilevante?

(indicare almeno 2 risposte condivise)

SO WHAT?

Perché le cose emerse sono così rilevanti?

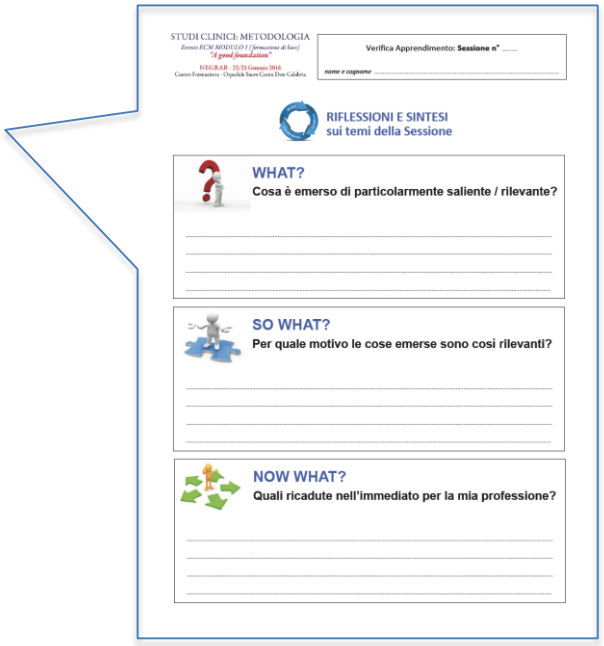
(indicare almeno 2 risposte condivise)

NOW WHAT?

Quali ricadute nell'immediato per la mia professione?

(indicare almeno 2 risposte condivise)

1. Riflettete da soli per 10 min.



WHAT?

Cosa è emerso di particolarmente saliente e rilevante?

(indicare almeno 2 risposte condivise)

SO WHAT?

Perché le cose emerse sono così rilevanti?

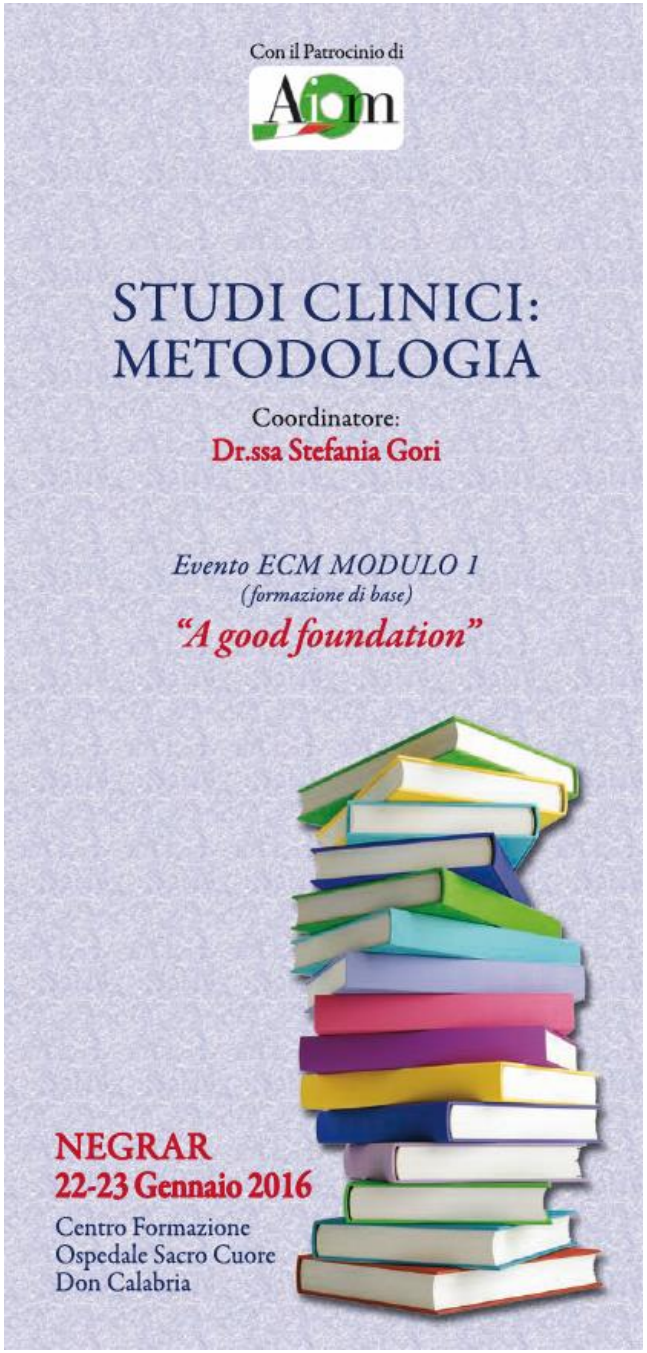
(indicare almeno 2 risposte condivise)

NOW WHAT?

Quali ricadute nell'immediato per la mia professione?

(indicare almeno 2 risposte condivise)

1. Riflettete da soli per 10 min.
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



Venerdì 22 gennaio 2016

- Plausibilità e opportunità dello studio
  - ✓ criteri FINER
- Obiettivi (primario e secondari)
  - ✓ strutturazione sec. P.I.C.O.
- **Disegno dello studio**
  - ✓ tipologie di disegno di studio
  - ✓ **procedure di randomizzazione**
  - ✓ **scelta del braccio di controllo**
- Endpoints (primario e secondari)
  - ✓ endpoints surrogati
  - ✓ PROs
- Selezione dei pazienti
  - ✓ criteri restrittivi Vs inclusivi
  - ✓ conseguenze su trasferibilità e precisione delle evidenze

RANDOMIZZAZIONE

Assegnazione casuale dei pazienti al gruppo sperimentale o di controllo, al fine di assicurare che tutti i fattori prognostici - noti e sconosciuti - si distribuiscano omogeneamente nei due gruppi.

Tutti i requisiti della randomizzazione hanno lo scopo di assicurare che il **processo con cui vengono creati i due gruppi a confronto segua le leggi del caso**, e che **nessun fattore possa interferire** con la sua casualità.

Lachin, 2000

SOURCES OF BIAS IN CLINICAL TRIALS

Type of bias	Description	
Selection bias.	Systematic differences between baseline characteristics of the groups that are compared.	• Sequence generation. • Allocation concealment.
Performance bias.	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.	• Blinding of participants and personnel. • Other potential threats to validity.
Detection bias.	Systematic differences between groups in how outcomes are determined.	• Blinding of outcome assessment. • Other potential threats to validity.
Attrition bias.	Systematic differences between groups in withdrawals from a study.	• Incomplete outcome data
Reporting bias.	Systematic differences between reported and unreported findings.	• Selective outcome reporting

Cochrane Handbook for Systematic Reviews of Interventions

Version 5.1.0

RANDOMIZZAZIONE A BLOCCHI

- La sequenza totale delle assegnazioni previste viene divisa in un certo numero di blocchi successivi.
- Il blocco rappresenta un gruppo di assegnazioni all'interno del quale vi è bilanciamento nel numero di pazienti assegnati ai due trattamenti, in modo da rispettare il rapporto di assegnazione previsto.
- I blocchi dovrebbero essere di dimensione variabile, in dipendenza dalle dimensioni campionarie e dal numero di strati)
  - es. blocco di 4: ABAB
  - es. blocco di 6: ABABAB
  - es. blocco di 8: ABABABAB

RANDOMIZZAZIONE A BLOCCHI

- ✓ Se n = 4 (dimensione del blocco)
- ✓ Se x = 2 (numero dei trattamenti)
- ✓ Se A:B = 1:1 (rapporto di assegnazione)

Quante (e quali) sono le possibili permutazioni?

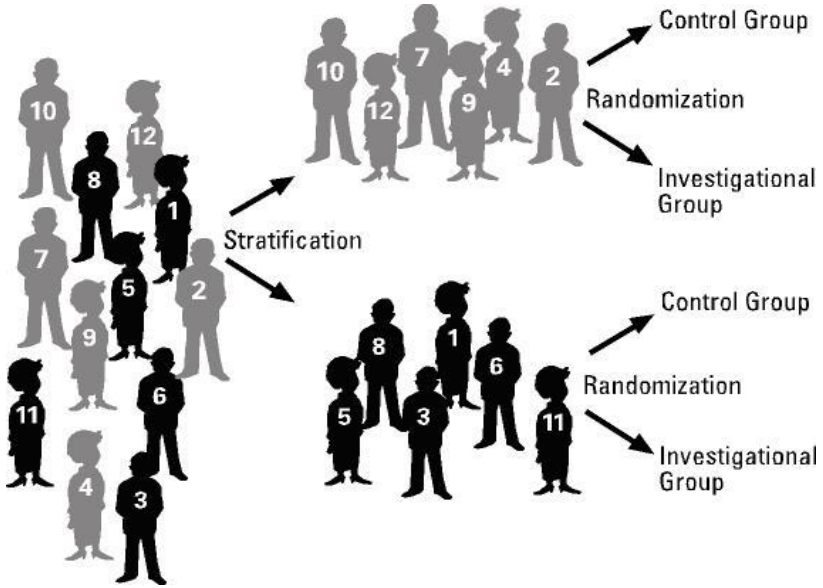
$$\frac{n!}{x!\,(n-x!)} = \frac{4!}{2!\,2!} = 6$$

AABB
ABAB
BABA
ABBA
BAAB
BBAA

RANDOMIZZAZIONE STRATIFICATA

Allestimento di liste di randomizzazione separate per una o più caratteristiche pre-trattamento:

- ✓ misura atta a evitare sbilanciamenti fra i trattamenti a confronto per specifici fattori prognostici;
- ✓ possibili vantaggi di tipo gestionale e organizzativo (es. stratificazione per Centro);
- ✓ considerare solo fattori di stratificazione oggettivamente definibili.



RANDOMIZZAZIONE STRATIFICATA

Il numero di liste random che si viene a formare con la stratificazione è uguale al prodotto del numero degli strati di ogni fattore di stratificazione:

RAPID axSpA

- ✓ Site * 104
- ✓ mNY status * 2
- ✓ Prior TNF inhibition * 2

416 Liste di Randomizzazione

(325 pazienti)

RAPID PsA

- ✓ Site * 92
- ✓ Prior TNF inhibitor use * 2

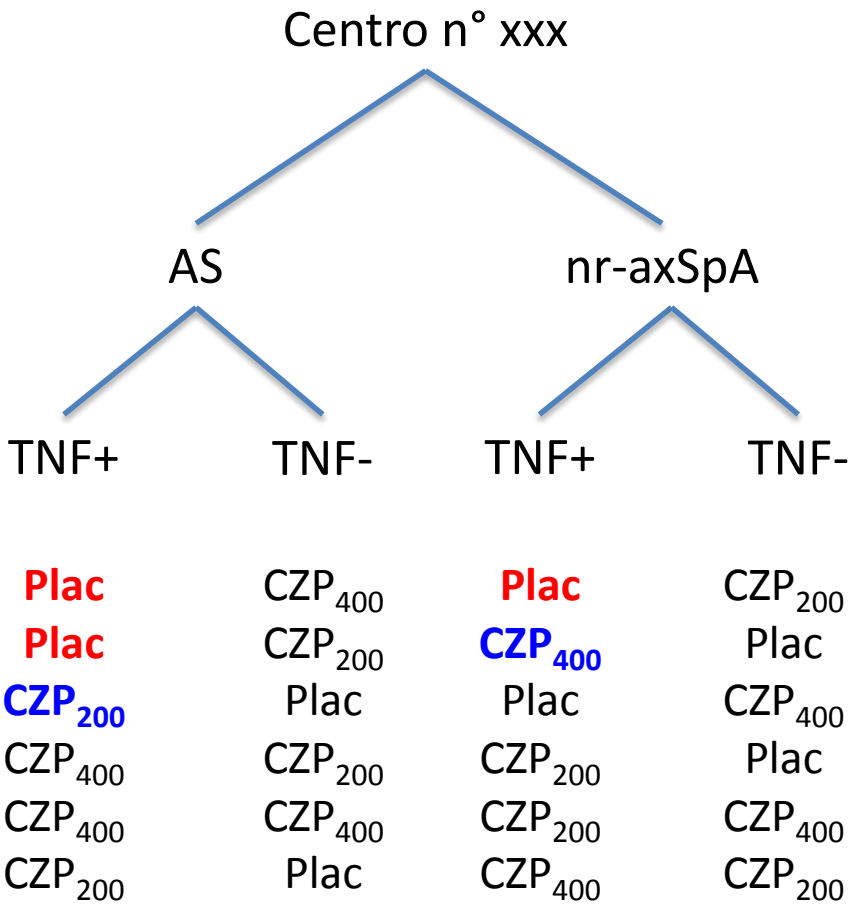
184 Liste di Randomizzazione

(409 pazienti)

Attenzione alla *overstratification* !

OVERSTRATIFICATION IN RAPID axSpA?

Possibile Scenario (potrebbe valere anche l'ipotesi opposta)



(alcune delle possibili permutazioni del *blocco* di 6)

Nel Centro n° xxx sono stati arruolati 5 pazienti con precedente esposizione a TNFi:

- ✓ di 3 pazienti con AS, 2 sono stati assegnati a Plac e 1 a CZP_{200}
- ✓ di 2 pazienti con nr-axSpA, 1 è stato assegnato a Plac e 1 a CZP_{400}

Gli strati TNF+ hanno un arruolamento non sufficiente a garantire il riempimento del *blocco* di 6 pazienti

MASCHERAMENTO

- **Insieme delle procedure atte a prevenire distorsioni dovute al fatto che il Paziente, il Medico o il Valutatore sono a conoscenza del trattamento ricevuto dal Paziente:**
  - ***Paziente = singolo cieco***
  - ***Paziente + Medico = doppio cieco***
  - ***Paziente + Medico + Valutatore = triplo cieco***
- **Necessità connessa agli obiettivi dello studio e al tipo di endpoint utilizzato**

Less Hypoglycemia With Insulin Glargine in Intensive Insulin Therapy for Type 1 Diabetes

ROBERT E. RATNER, MD
IRL B. HIRSCH, MD
JAMES L. NEIFING, MD
THOMAS E. MECCA, PHD
CRAIG A. WILSON, PHD
SATISH K. GARG, MD

FOR THE U.S. STUDY GROUP OF INSULIN GLARGINE IN TYPE 1 DIABETES

Diabetes Care 23:639–643, 2000

A double-blind design was not feasible because insulin glargine is a clear solution and is distinguishable from cloudy NPH insulin.

OPPORTUNITA' DEL MASCHERAMENTO

	paziente	*medico*	*valutatore*
Decesso (per ogni causa)	**no**	**no**	**no**
Decesso per causa specifica	**no**	**no**	**si**
Recidiva, progressione	**no**	**no(?)**	**si**
Risposta clinica	**no (?)**	**no(?)**	**si**
Risposta soggettiva	**si**	**si**	**si**
Dolore	**si**	**si**	**si**
Stato psichico	**si**	**si**	**si**

Randomized Trial of Oral Teriflunomide for Relapsing Multiple Sclerosis

Paul O'Connor, M.D., Jerry S. Wolinsky, M.D., Christian Confavreux, M.D., Giancarlo Comi, M.D., Ludwig Kappos, M.D., Tomas P. Olsson, M.D., Ph.D., Hadj Benzerdjeb, M.D., Philippe Truffinet, M.D., Lin Wang, Ph.D., Aaron Miller, M.D., and Mark S. Freedman, M.D., for the TEMSO Trial Group*

N Engl J Med 2011;365:1293-303

The primary objective of the study was to determine the efficacy of teriflunomide in reducing the annualized relapse rate (defined as the number of confirmed relapses per patient-year).

Both treating and examining neurologists were unaware of treatment assignments.

Imaging data were collected at the MRI facilities of the participating clinical sites and sent to the central MRI Analysis Center in Houston for processing and data extraction.

SOURCES OF BIAS IN CLINICAL TRIALS

Type of bias	Description	
Selection bias.	Systematic differences between baseline characteristics of the groups that are compared.	• Sequence generation. • Allocation concealment.
Performance bias.	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.	• Blinding of participants and personnel. • Other potential threats to validity.
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If no evaluator blinding was performed…

… was he (totally) **unbiased** when evaluating the scan?

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Selection bias.	Systematic differences between baseline characteristics of the groups that are compared.	• Sequence generation. • Allocation concealment.
Performance bias.	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.	• Blinding of participants and personnel. • Other potential threats to validity.
Detection bias.	Systematic differences between groups in how outcomes are determined.	• Blinding of outcome assessment. • Other potential threats to validity.
Attrition bias.	Systematic differences between groups in withdrawals from a study.	• Incomplete outcome data
Reporting bias.	Systematic differences between reported and unreported findings.	• Selective outcome reporting

Cochrane Handbook for Systematic Reviews of Interventions

Version 5.1.0

If no patient blinding was performed…

… were they **unbiased** when filling the QoL questionnaire?

Choice of Control Group

- The selection of an appropriate control group is a critical decision which impacts on the scientific validity and ethical acceptability of a clinical investigation.
- The proper control group allows for discrimination between patient outcomes caused by the test treatment, and outcomes caused by other factors such as the natural progression of the disease, observer or patient expectations, or other treatments.

EFFICACIA E GRUPPO DI CONTROLLO

- **Studio di superiorità**
  - *L'uso del nuovo farmaco comporta un beneficio clinico per i pazienti? (controllo = placebo o nulla)*
  - *Il nuovo farmaco è più efficace di altri farmaci? (controllo = il miglior trattamento disponibile)*
- **Studio di non inferiorità**
  - *Cosa siamo disposti a "perdere" in cambio di minori effetti collaterali (disagi, costi)? (controllo = il miglior trattamento disponibile)*

Health Authority Guidelines

- US Regulations require the establishment of safety and efficacy
  - Guideline for control group:
    - The standard regimen should have a well-characterized clinical benefit (survival benefit)
- EMEA
  - Reference therapy should be selected from the best available, evidence-based therapeutic options
    - Widely used, but not necessarily licensed regimen with a favourable benefit-risk convincingly documented through randomised trials and at least as good as alternative evidence-based treatment options

S.D. Averbuch, ASCO 2008

Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract

Joaqui… …ristine Théodore, Tomasz Demkov, Boris Komyakov, Lisa Sengelov, Gedske Daugaard, Ar… …rles, Agnieszka Jagiello-Gruszfeld, Oleg Karyakin, François-Michel Delgado, …c Winquist, Nassim Morsli, Yacine Salhi, Stéphane Culine, and Hans von der Maase

…54-4461.

Untreated metastatic TCCU is associated with a median survival time rarely exceeding 3 to 6 months; it is a chemotherapy-sensitive tumor and cisplatin-based chemotherapy is the standard treatment,[4-7] without an approved or established option for second-line treatment.[8,9]

BSC
n = 108
98
10 (9.3%)
4.3
(3.8 to 5.4)
…1 to 0.99)
…403

Overall S…
0.2
0

Second-line therapy in bladder cancer

Mark Bachner and Maria De Santis

Current Opinion in Urology 2009, 19:533–539

So far no standard therapy has been established for pretreated patients with transitional cell carcinoma.

Health Authority Guidelines

- US Regulations require the establishment of

Considering Usual Medical Care in Clinical Trial Design

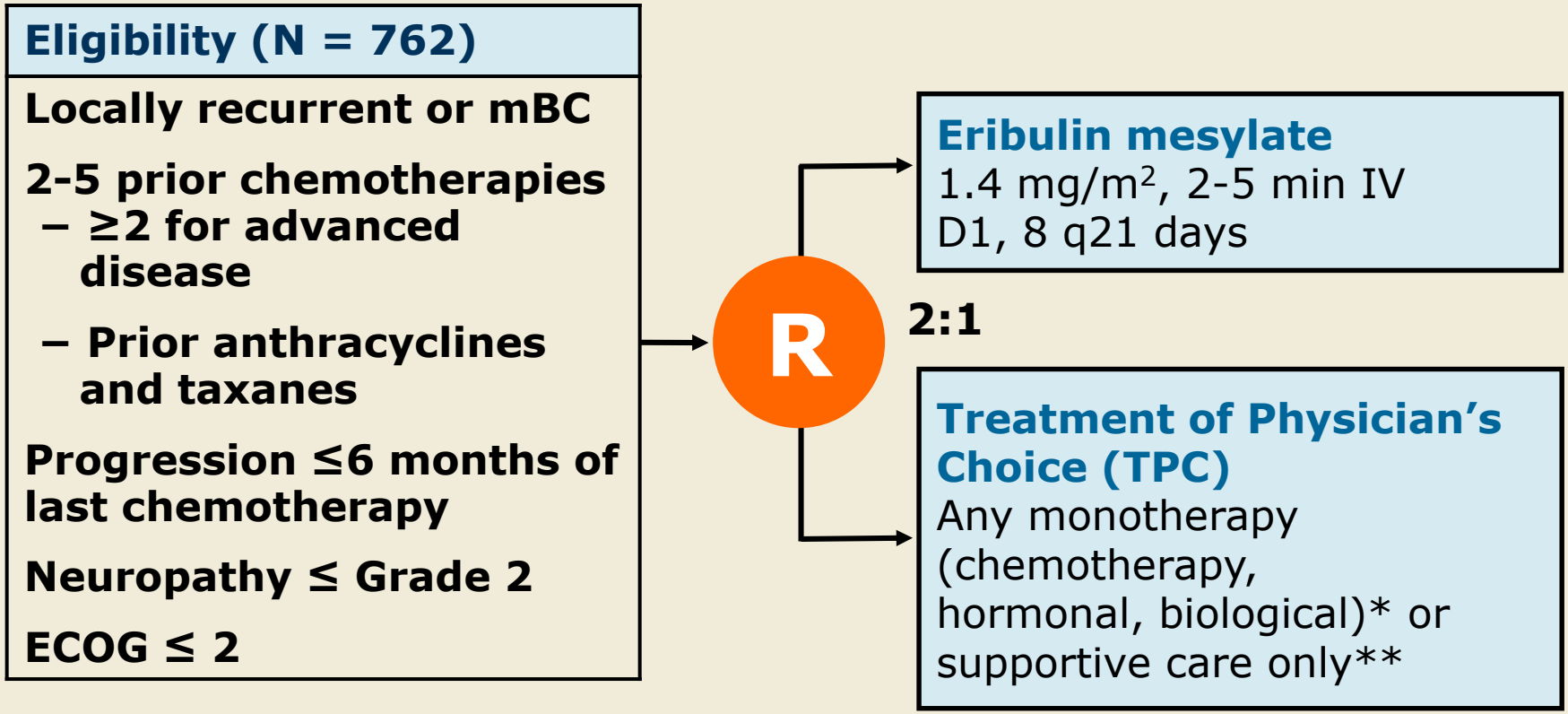
Liza Dawson[1]*, Deborah A. Zarin[2], Ezekiel J. Emanuel[3], Lawrence M. Friedman[4], Bimal Chaudhari[5], Steven N. Goodman[6]

PLoS Med 6(9): e1000111. doi:10.1371/journal.pmed.1000111

- EMEA
  - Reference therapy should be selected from the best available, evidence-based therapeutic options
    - Widely used, but not necessarily licensed regimen with a favourable benefit-risk convincingly documented through randomised trials and at least as good as alternative evidence-based treatment options

S.D. Averbuch, ASCO 2008

EMBRACE Study Design



* Approved for cancer treatment

** Or palliative treatment or radiotherapy according to local practice

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

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

Ezetimibe was utilized as the comparator in this study as it is one of the options recommended for treating patients with statin intolerance [6].

The primary objective of this study was to evaluate the efficacy and safety of alirocumab monotherapy compared with ezetimibe in patients with hypercholesterolemia and at moderate cardiovascular (CV) risk (i.e. a 10-year risk of fatal CV events ≥1% and <5%) [5], who were not receiving statin or other lipid-lowering therapy.


Study Design
Lo standard erano le citochine…
C'era già il Sorafenib…
anced RCC
)
easurable disease
COG PS 0 or 1
Rx-naive or 1 prior cytokine
Stratification
• ECOG PS: 0 vs. 1
• Prior nephrectomy: yes vs. no
• Rx-naive vs. 1 prior cytokine
Randomization 2:1
Pazopanib 800 mg qd (n = 290)
atching Placebo
Option to receive pazopa
JOURNAL OF THE ROYAL SOCIETY OF MEDICINE Volume 88 October 1995
Equipoise and the ethics of randomization
Richard J Lilford MRCOG MRCP MFPHM[1] Jennifer Jackson MA[2]
Equipoise is the point where there is no preference between treatments, i.e. it is thought equally likely that treatment A or B will turn out to be superior.

National Multiple Sclerosis Society

Expert Opinion Paper

National Medical Advisory Board of the National Multiple Sclerosis Society

Treatment Recommendations for Clinicians

Changing Therapy in Relapsing Multiple Sclerosis: Considerations and Recommendations of a Task Force of the National Multiple Sclerosis Society

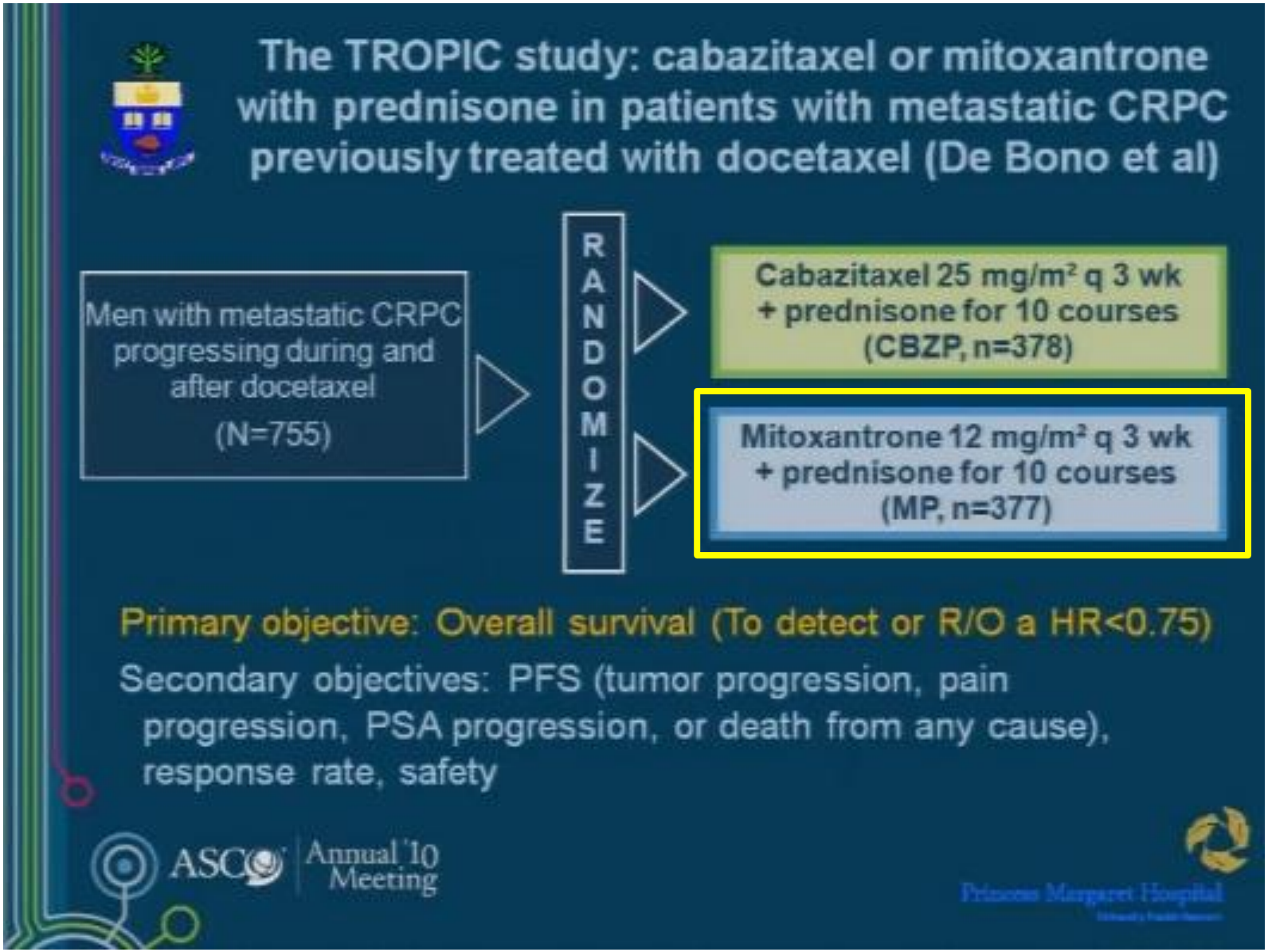
- There are no direct comparative data to allow a fully informed choice of the best immunomodulatory drug class (interferon beta or glatiramer acetate) with which to initiate therapy in relapsing forms of MS.
- Higher-dosed, more frequently administered formulations of interferon beta may provide better short-term clinical efficacy than lower, less frequently dosed formulations of interferon beta in relapsing MS.[8,9]

Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis

Robert J. Fox, M.D., David H. Miller, M.D., J. Theodore Phillips, M.D., Ph.D., Michael Hutchinson, F.R.C.P., Eva Havrdova, M.D., Mariko Kita, M.D., Minhua Yang, M.S., Kartik Raghupathi, M.S., Mark Novas, M.D., Marianne T. Sweetser, M.D., Ph.D., Vissia Viglietta, M.D., Ph.D., and Katherine T. Dawson, M.D., for the CONFIRM Study Investigators*

N Engl J Med 2012;367:1087-97.

Here, we report the results of the Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis (CONFIRM) trial, a randomized, multicenter, double-blind, 2-year study evaluating the efficacy and safety of BG-12, at a dose of 240 mg two or three times per day, versus placebo in patients with relapsing–remitting multiple sclerosis.

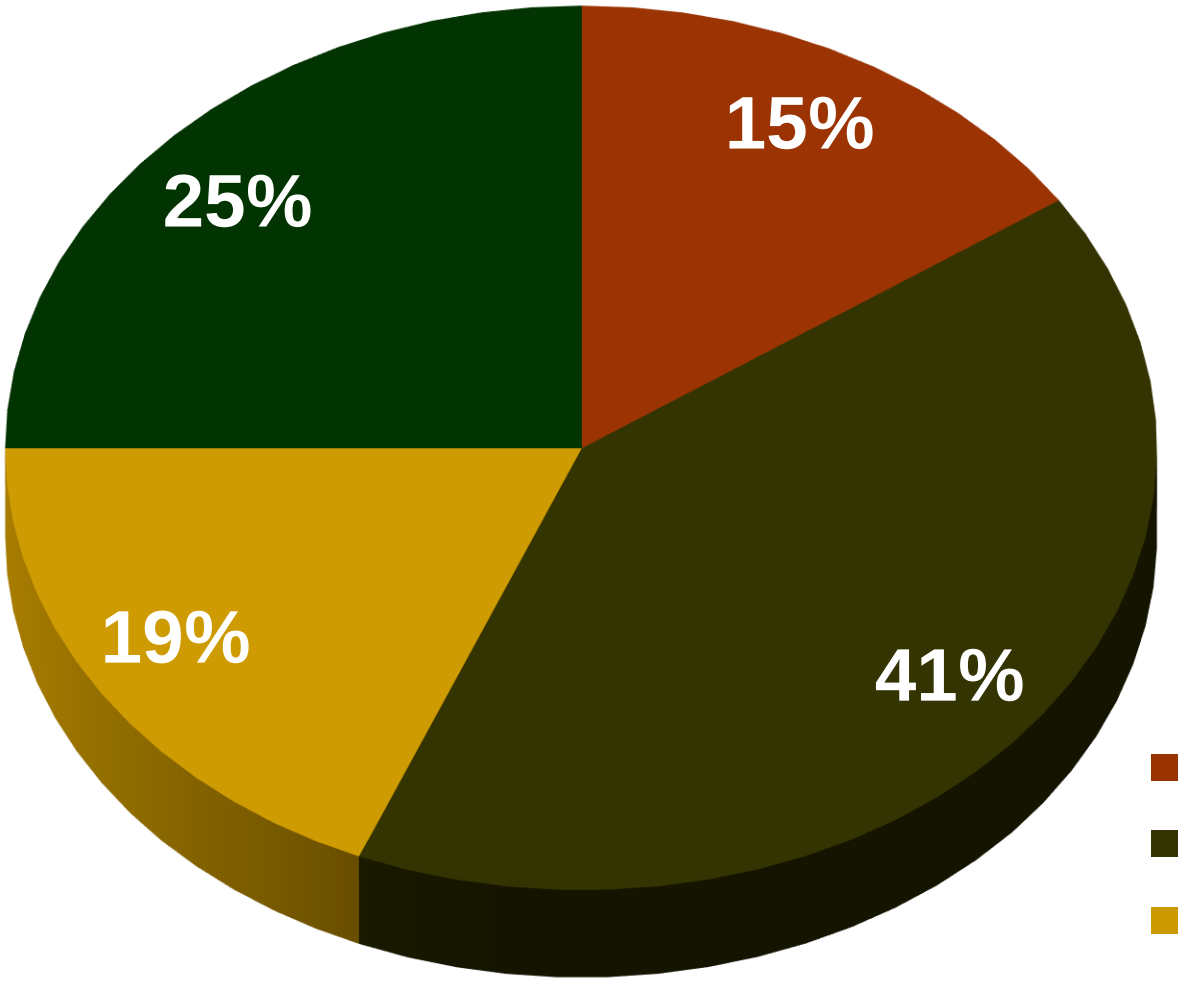


I Tannock, ASCO 2010

Important questions re study design

1. Why cabazitaxel (XRP6258)?
   - Semi-synthetic taxoid
   - More potent than docetaxel
   - Active in MDR+ cells, and in cells resistant to docetaxel
   - Dose limiting toxicity is neutropenia (but also neuropathy)
2. Is mitoxantrone the appropriate control?
   - No FDA-approved treatment after docetaxel
   - Standard practice in fit patients progressing after docetaxel is to give further treatment (mitoxantrone, further docetaxel, other chemotherapy, 3rd line hormonal agents)

Trattamento a progressione dopo 1a linea con Docetaxel



Cabazitaxel

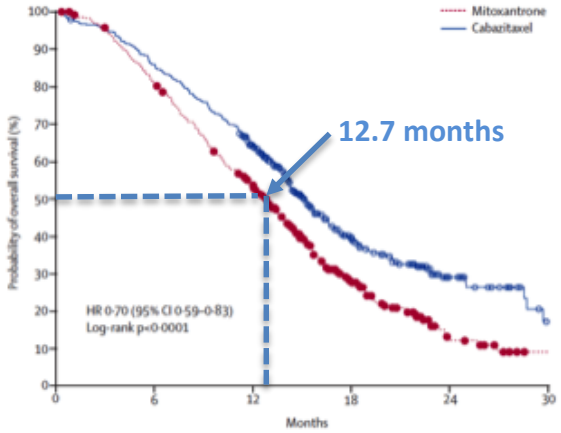
mHRPC patients who progressed during or after treatment with a Taxotere-containing regimen
N = 755

STRATIFICATION
ECOG PS: 0, 1 vs 2
Measurable vs non-measurable disease

Randomise

Jevtana 25 mg/m² q 3 wk + oral prednisone
10 mg daily for 10 cycles
(n = 378)

Mitoxantrone 12 mg/m² q 3 wk + oral prednisone
10 mg daily for 10 cycles
(n = 377)



Abiraterone

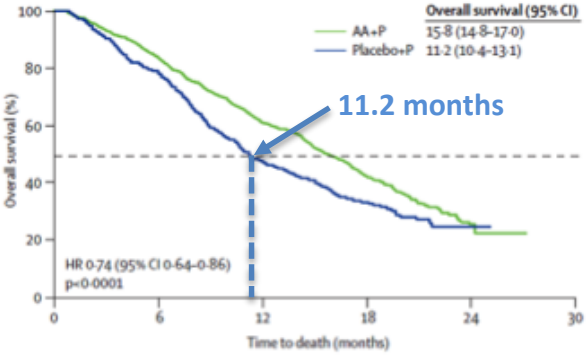
mCRPC
(n = 1195)

ECOG PS ≤2
Bone or lymph node metastases

RANDOMISE 2:1

Abiraterone acetate, 1000 mg/day + prednisone, 5 mg twice daily

Placebo + prednisone, 5 mg twice daily



Enzalutamide

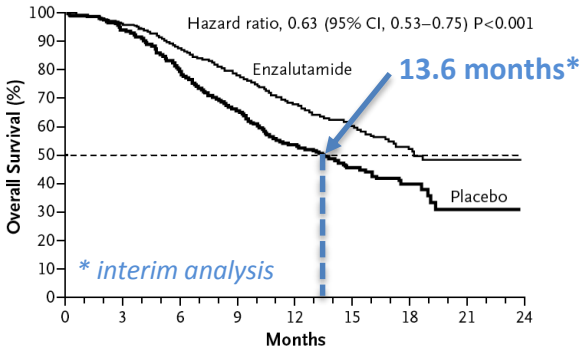
mCRPC
(n = ~1170)

ECOG PS ≤2

RANDOMISE 2:1

MDV3100 160 mg QD (n = 780)

Placebo QD (n = 390)



Placebo/No Tx Arms In Absence Of Effective Therapy

- Control subjects typically not worse off than they would be outside the trial
- No-treatment controls acceptable when:
  - Alternative designs inadequate
  - Risks minimized and benefits maximized, *while ensuring answer to study question*
  - Fastidious attention to informed consent

JCO 26:1371, 2008

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

Randomised placebo-controlled trials to assess clinical outcomes specifically in familial hypercholesterolaemia have not been done, because of the ethical considerations of denying effective LDL-C lowering drugs to these very-high-risk patients.

Con il Patrocinio di

Aiom

STUDI CLINICI: METODOLOGIA

Coordinatore:
Dr.ssa Stefania Gori

Evento ECM MODULO 1
(formazione di base)
"A good foundation"

NEGRAR
22-23 Gennaio 2016
Centro Formazione
Ospedale Sacro Cuore
Don Calabria

Riflessioni e Sintesi

WHAT?

Cosa è emerso di particolarmente saliente e rilevante?

(indicare almeno 2 risposte condivise)

SO WHAT?

Perché le cose emerse sono così rilevanti?

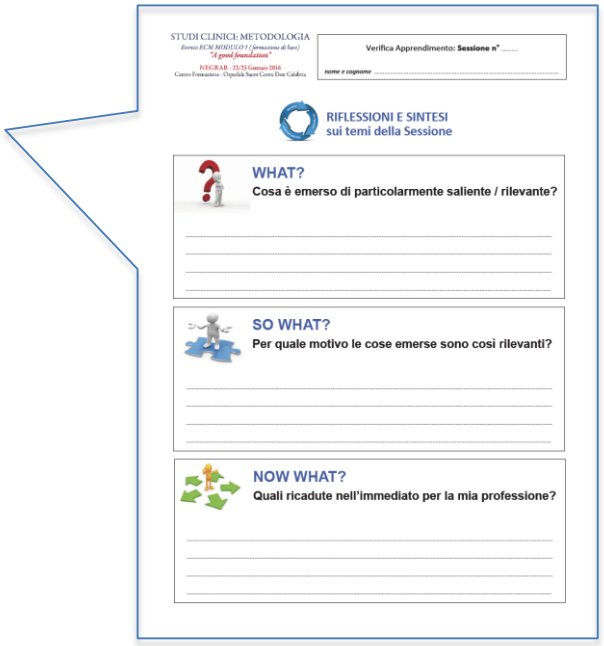
(indicare almeno 2 risposte condivise)

NOW WHAT?

Quali ricadute nell'immediato per la mia professione?

(indicare almeno 2 risposte condivise)

1. Riflettete da soli per 10 min.



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(indicare almeno 2 risposte condivise)

1. Riflettete da soli per 10 min.
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