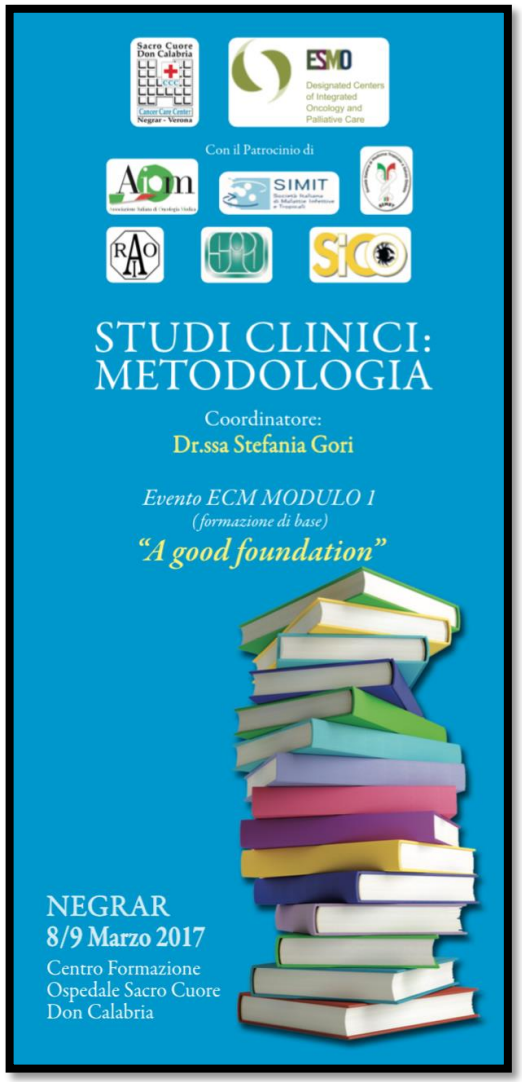
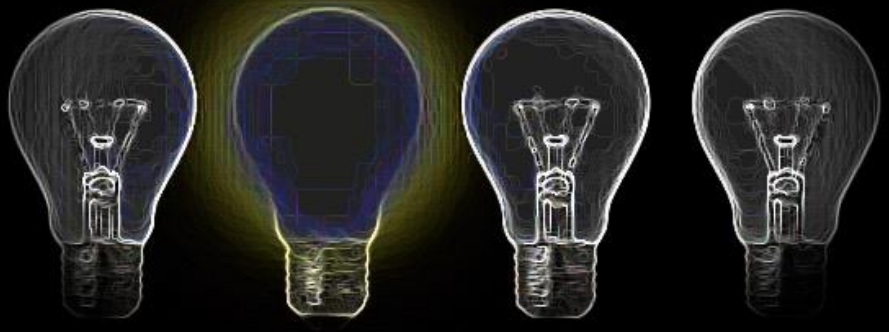


STUDI CLINICI: METODOLOGIA

A good foundation

Marta Bonotto
Udine


VENI!
VISNE LINGUAM
LATINAM
DISCĔRE?



STUDI CLINICI: METODOLOGIA

Il quesito come
primum movens

Quesito cui gli sperimentatori sono più interessati a rispondere, e al quale lo studio vuole dare una risposta

Quesito cui gli sperimentatori sono più interessati a rispondere, e al quale lo studio vuole dare una risposta

OBIETTIVO PRIMARIO

Quesito cui gli sperimentatori sono più interessati a rispondere, e al quale lo studio vuole dare una risposta

OBIETTIVO PRIMARIO

OBIETTIVI SECONDARI

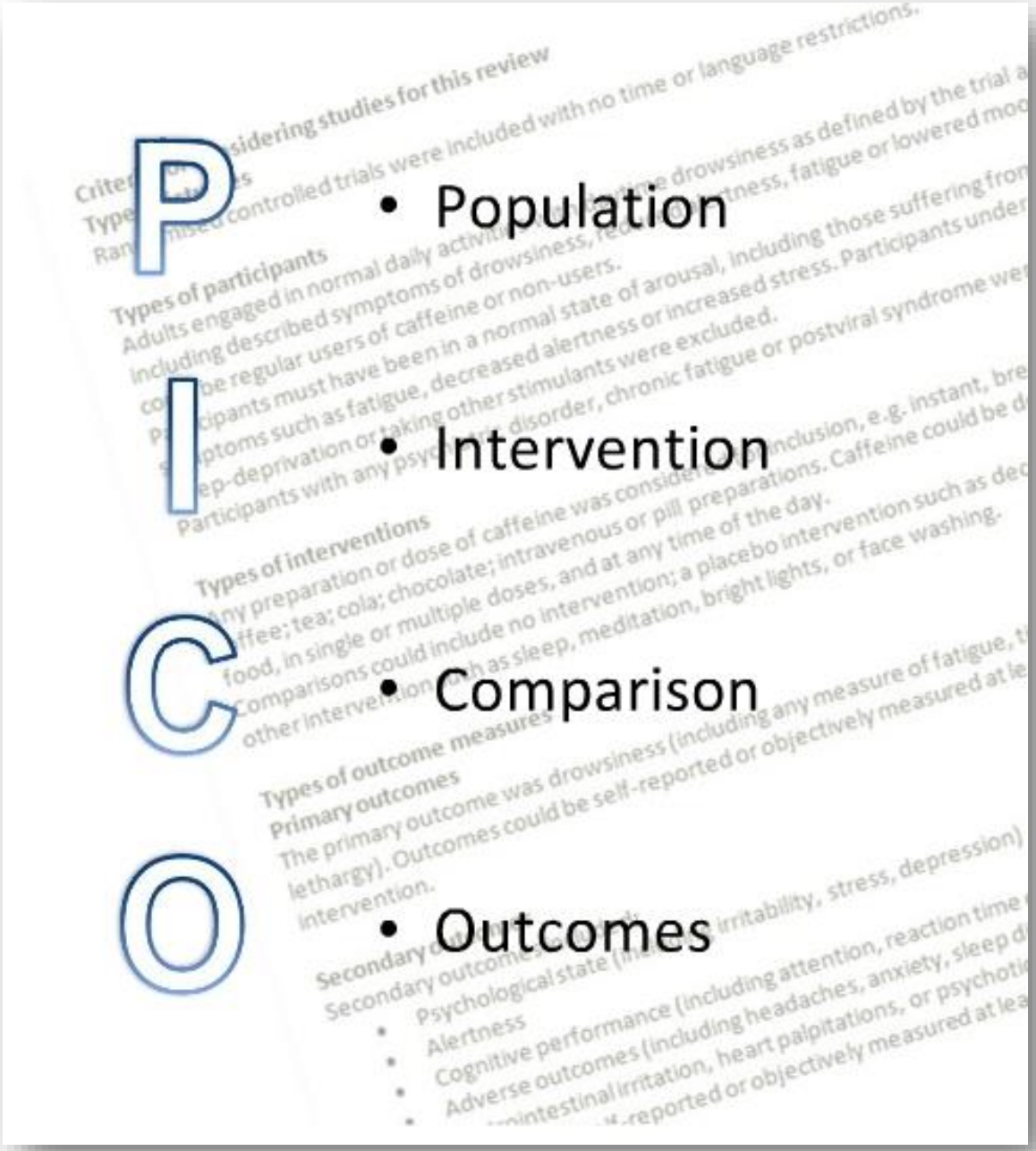
altri quesiti di interesse, in qualche modo correlati al quesito primario

Il quesito come *primum movens*

Quesito di ricerca

L'utilizzo di un percorso di cure riabilitative di tipo multidisciplinare nell'utente anziano con frattura del femore può ridurre l'incidenza dei tassi di mortalità e morbilità, diminuire i tempi di degenza e il rischio di riammissioni e migliorare la performance nelle attività di vita quotidiana?

GRADE



P
- Population

I
- Intervention

C
- Comparison

O
- Outcomes

Il quesito come *primum movens*

Metodologia PICO		
P	*patient* (paziente)	età superiore ai 65 anni con frattura del femore
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N Engl J Med 2017;376:826-35. DOI: 10.1056/NEJMoa1606490

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anti–Interleukin-31 Receptor A Antibody for Atopic Dermatitis

Thomas Ruzicka, M.D., Jon M. Hanifin, M.D., Masutaka Furue, M.D., Ph.D., Grazyna Pulka, M.D., Izabela Mlynarczyk, M.D., Andreas Wollenberg, M.D., Ryszard Galus, M.D., Ph.D., Takafumi Etoh, M.D., Ryosuke Mihara, M.S., Hiroki Yoshida, M.S., Jonathan Stewart, M.B., Ch.B., and Kenji Kabashima, M.D., Ph.D., for the XCIMA Study Group*

From the Department of Dermatology and Allergology, Ludwig Maximilian University, Munich, Germany (T.R., A.W.); the Department of Dermatology, Oregon Health and Science University, Portland (J.M.H.); the Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka (M.F.), Tokyo Teishin Hospital (T.E.) and Chugai Pharmaceutical (R.M., H.Y.), Tokyo, the Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto (K.K.), and Precursory Research for Embryonic Science and Technology, Japan Science and Technology Agency, Saitama (K.K.) — all in Japan; Jagiellonian University School of Medicine, Krakow (G.P.), Academic Health, Dermatology Clinic, Rzeszow (I.M.), and the Department of Histology and Embryology, Center for Biostructure, Medical University of Warsaw, Warsaw (R.G.) — all in Poland; and Chugai

ABSTRACT

BACKGROUND

Interleukin-31 may play a role in the pathobiologic mechanism of atopic dermatitis and pruritus. We wanted to assess the efficacy and safety of nemolizumab (CIM331), a humanized antibody against interleukin-31 receptor A, in the treatment of atopic dermatitis.

METHODS

In this phase 2, randomized, double-blind, placebo-controlled, 12-week trial, we assigned adults with moderate-to-severe atopic dermatitis that was inadequately controlled by topical treatments to receive subcutaneous nemolizumab (at a dose of 0.1 mg, 0.5 mg, or 2.0 mg per kilogram of body weight) or placebo every 4 weeks or an exploratory dose of 2.0 mg of nemolizumab per kilogram every 8 weeks. The primary end point was the percentage improvement from baseline in the score on the pruritus visual-analogue scale (on which a negative change indicates improvement) at week 12. Secondary end points included changes in the score on the Eczema Area and Severity Index (EASI, on which a negative change indicates improvement), and body-surface area of atopic dermatitis.

RESULTS

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RESULTS

Of 264 patients who underwent randomization, 216 (82%) completed the study. At

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiometabolic Risks and Severity of Obesity in Children and Young Adults

Asheley C. Skinner, Ph.D., Eliana M. Perrin, M.D., M.P.H., Leslie A. Moss, M.H.A., C.H.E.S., and Joseph A. Skelton, M.D.

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The prevalence of severe obesity among children and young adults has increased over the past decade. Although the prevalence of cardiometabolic risk factors is relatively low among children and young adults who are overweight or obese, those with more severe forms of obesity may be at greater risk.

METHODS

We performed a cross-sectional analysis of data from overweight or obese children and young adults 3 to 19 years of age who were included in the National Health and Nutrition Examination Survey from 1999 through 2012 to assess the prevalence of multiple cardiometabolic risk factors according to the severity of obesity. Weight status was classified on the basis of measured height and weight. We used standard definitions of abnormal values for total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, triglycerides, blood pressure, glycated hemoglobin, and fasting glucose and report the prevalence of abnormal values in children and young adults according to weight status.

RESULTS

From the Department of Pediatrics, Division of General Pediatrics and Adolescent Medicine, School of Medicine (A.C.S., E.M.P.), Department of Health Policy and Management, Gillings School of Global Public Health (A.C.S.), and Injury Prevention Research Center (L.A.M.), University of North Carolina at Chapel Hill, Chapel Hill, and the Department of Pediatrics, Wake Forest School of Medicine, and Brenner FIT (Families in Training), Brenner Children's Hospital, Winston-Salem (J.A.S.) — all in North Carolina. Address reprint requests to Dr. Skinner at the Department of Pediatrics, University of North Carolina at Chapel Hill School of Medicine, 231 MacNider, 229B, CB 7225, Chapel Hill, NC 27599, or at asheley@unc.edu.

N Engl J Med 2015;373:1307-17.
DOI: 10.1056/NEJMoa1502821
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Perché la P ?

Il quesito come *primum movens*

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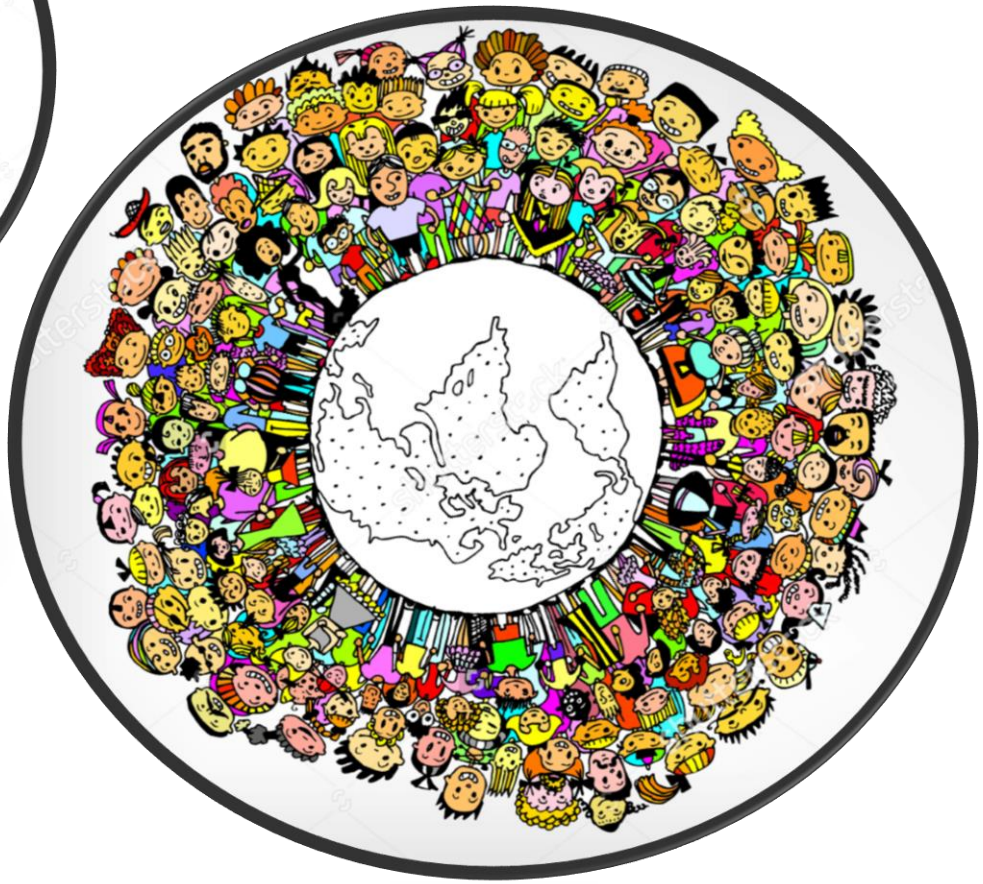
CHINA


CHINA



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

PANCREOX: A Randomized Phase III Study of 5-Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy

Sharlene Gill, Yoo-Joung Ko, Christine Cripps, Annie Beaudoin, Sukhbinder Dhesy-Thind, Muhammad Zulfiqar, Pawel Zalewski, Thuan Do, Pablo Cano, Wendy Yin Han Lam, Scot Dowden, Helene Grassin, John Stewart, and Malcolm Moore

Sharlene Gill and Malcolm Moore, BC Cancer Agency, Vancouver; Muhammad Zulfiqar, BC Cancer Agency, Abbotsford; Thuan Do, BC Cancer Agency, Surrey; Wendy Yin Han Lam, Burnaby Hospital Cancer Centre, Burnaby, British Columbia; Yoo-Joung Ko, Sunnybrook Health Sciences Centre; Malcolm Moore, Princess Margaret Hospital, Toronto; Christine Cripps, Ottawa Hospital Cancer Centre, Ottawa; Sukhbinder Dhesy-Thind, Juravinski Cancer Centre, Hamilton; Pawel Zalewski, RSM Durham Regional Cancer Centre, Oshawa; Pablo Cano, Sudbury Regional Hospital, Sudbury, Ontario; Annie Beaudoin, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke; Helene Grassin and John Stewart, Sanofi Canada, Laval, Quebec; and Scot Dowden, Alberta Health Service, Calgary, Alberta, Canada.

Published online ahead of print at www.jco.org on September 12, 2016.

Supported by Sanofi Canada.

Presented in part at the 50th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL May 30-June 3, 2014.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT01121848.

Corresponding author: Sharlene Gill, MD, MPH, British Columbia Cancer Agency,

ABSTRACT

Purpose

The standard of care for second-line therapy in patients with advanced pancreatic cancer after gemcitabine-based therapy is not clearly defined. The CONKO-003 phase III study reported a survival benefit with second-line fluorouracil (FU) and oxaliplatin using the oxaliplatin, folinic acid, and FU (OFF) regimen.[1] PANCREOX was a phase III multicenter trial to evaluate the benefit of FU and oxaliplatin administered as modified FOLFOX6 (mFOLFOX6; infusional fluorouracil, leucovorin, and oxaliplatin) versus infusional FU/leucovorin (LV) in this setting.

Patients and Methods

Patients with confirmed advanced pancreatic cancer who were previously treated with gemcitabine therapy and with an Eastern Cooperative Oncology Group performance status of 0-2 were eligible. A total of 108 patients were randomly assigned to receive biweekly mFOLFOX6 or infusional FU/LV until progression. Progression-free survival (PFS) was the primary end point.

Results

Baseline patient characteristics were similar in both arms. No difference was observed in PFS (median, 3.1 months *v* 2.9 months; $P = .99$). Overall survival (OS) was inferior in patients assigned to mFOLFOX6 (median, 6.1 months *v* 9.9 months; $P = .02$). Increased toxicity was observed with the addition of oxaliplatin, with grade 3/4 adverse events occurring in 63% of patients who received mFOLFOX6 and 11% of those who received FU/LV. More patients in the mFOLFOX6 arm withdrew from study due to adverse events than in the FU/LV arm (20% *v* 2%), whereas the use of post-progression therapy was significantly higher in the FU/LV arm (25% *v* 7%; $P = .015$). No significant differences were observed in time to deterioration on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 global health scale.

Conclusion

No benefit was observed with the addition of oxaliplatin, administered as mFOLFOX6, versus infusional FU/LV in patients with advanced pancreatic cancer previously treated with first-line gemcitabine.

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VOLUME 34 · NUMBER 23 · AUGUST 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Davendra P.S. Sohal and Alok A. Khorana, Cleveland Clinic, Cleveland, OH; Pamela B. Mangu, American Society of Clinical

Davendra P.S. Sohal, Pamela B. Mangu, Alok A. Khorana, Manish A. Shah, Philip A. Philip, Eileen M. O'Reilly, Hope E. Uronis, Ramesh K. Ramanathan, Christopher H. Crane, Anitra Engebretson, Joseph T. Ruggiero, Mehmet S. Copur, Michelle Lau, Susan Urba, and Daniel Laheru

Clinical Question 2: What Is the Appropriate First-Line Treatment of Patients With Metastatic Pancreatic Cancer?

Recommendation 2.1. Leucovorin, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) is recommended for patients who meet all of the following criteria: ECOG PS 0 to 1, favorable comorbidity profile, patient preference and support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.2. Gemcitabine plus nanoparticle albumin-bound (NAB) -paclitaxel is recommended for patients who meet all of the following criteria: ECOG PS 0 to 1, relatively favorable comorbidity profile, and patient preference and support system for relatively aggressive medical therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.3. Gemcitabine alone is recommended for patients who have either an ECOG PS 2 or a comorbidity profile that precludes more-aggressive regimens and who wish to pursue cancer-directed therapy. The addition of either capecitabine or erlotinib to gemcitabine may be offered in this setting (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

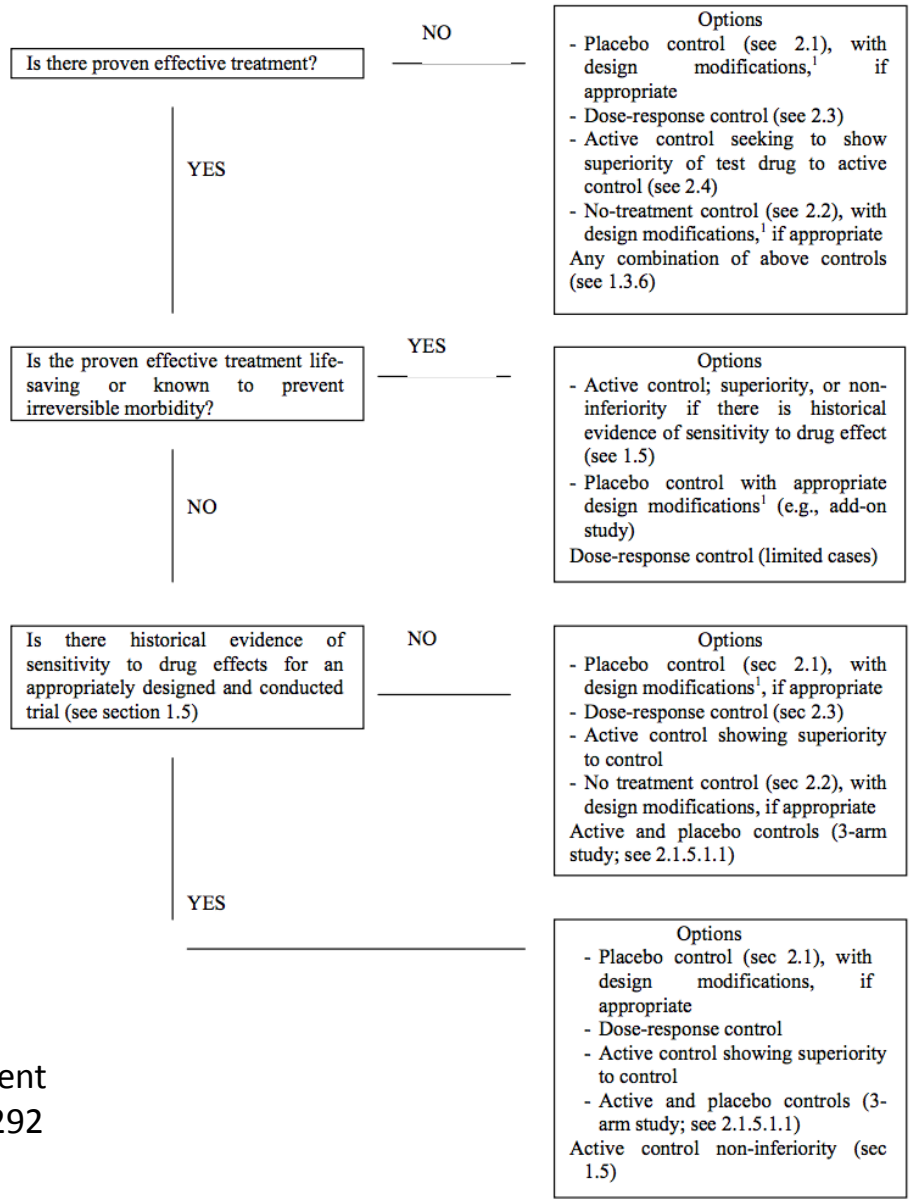
Recommendation 2.4. Patients with an ECOG PS > 2 or with

Perché la C ?

Perché la C ?

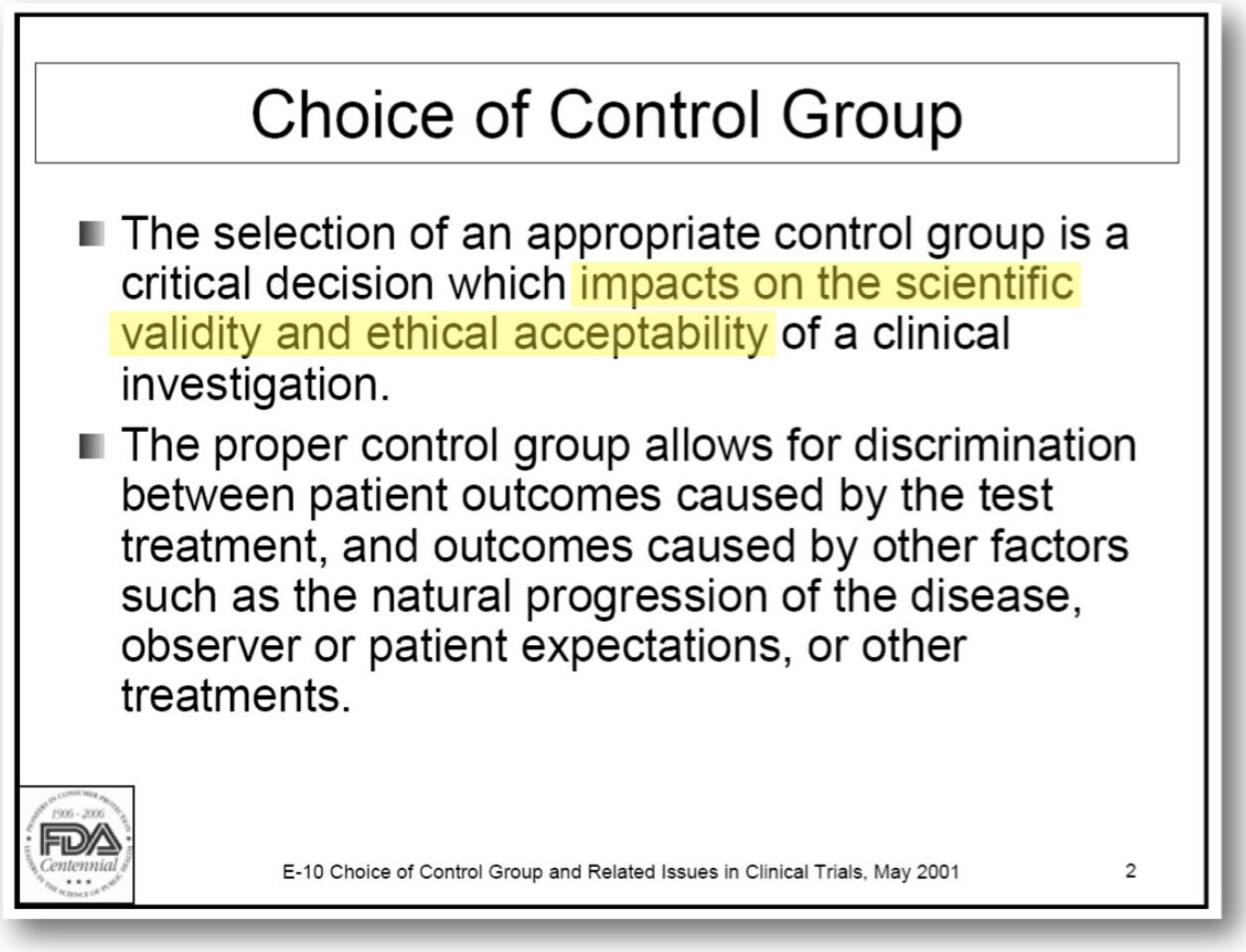
FIGURE 1: CHOOSING THE CONCURRENT CONTROL FOR DEMONSTRATING EFFICACY

This figure shows the basic logic for choosing the control group; the decision may depend on the available drugs or medical practices in the specific region.



http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002925.pdf

Perché la C ?



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.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiometabolic Risks and Severity of Obesity in Children and Young Adults

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ABSTRACT

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The prevalence of severe obesity among children and young adults has increased over the past decade. Although the prevalence of cardiometabolic risk factors is relatively low among children and young adults who are overweight or obese, those with more severe forms of obesity may be at greater risk.

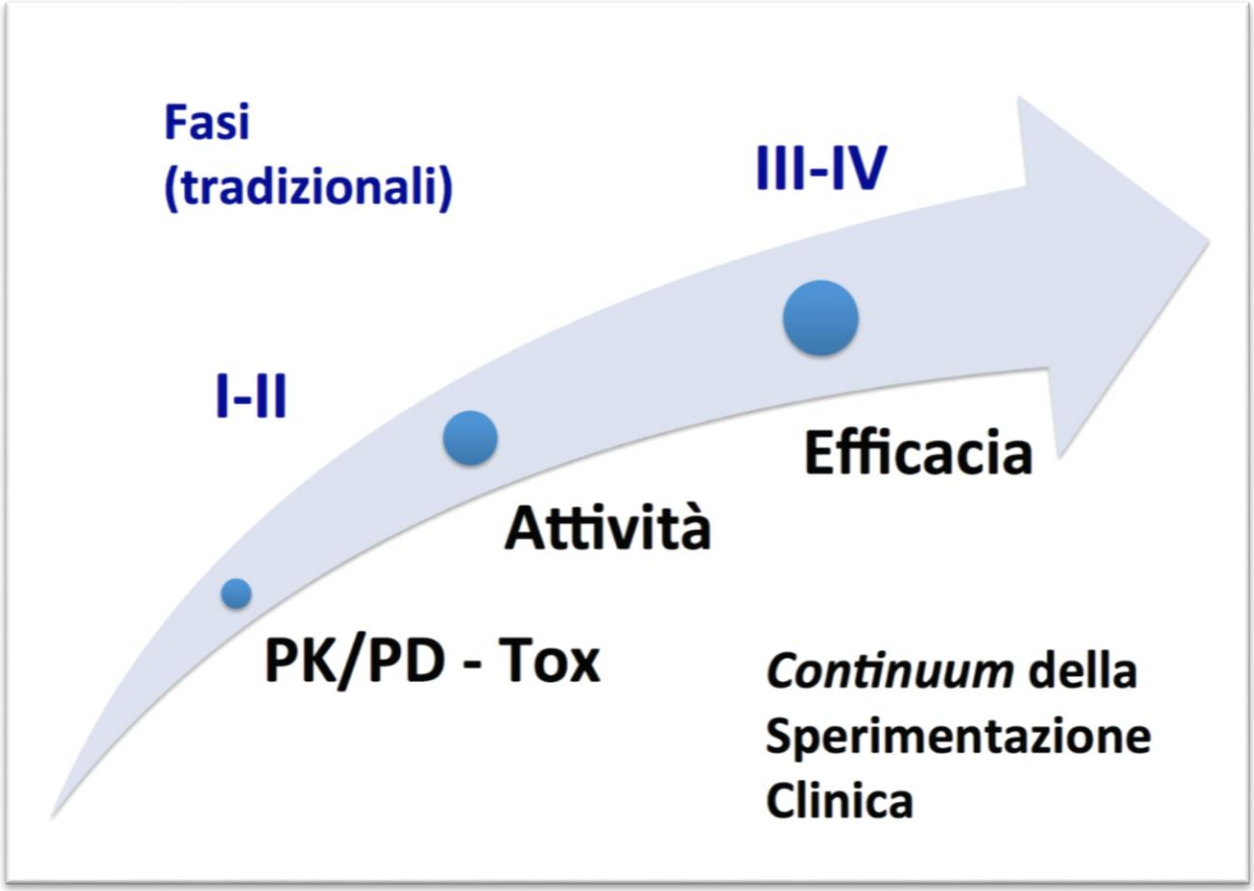
Table 1. Definitions of Abnormal Values for Risk-Factor Variables.*

Variable	Age Range	No. of Participants Evaluated	Definition of Abnormal Value
	yr		
Total cholesterol	3–19	6876	≥200 mg/dl
HDL cholesterol	3–19	6873	<35 mg/dl
Systolic BP	8–19	6412	≥95th percentile
Diastolic BP	8–19	6412	≥95th percentile
LDL cholesterol	3–19	2464	≥130 mg/dl
Triglycerides	3–19	2537	≥150 mg/dl
Glycated hemoglobin	12–19	4237	>5.7%
Glucose	12–19	1991	≥100 mg/dl

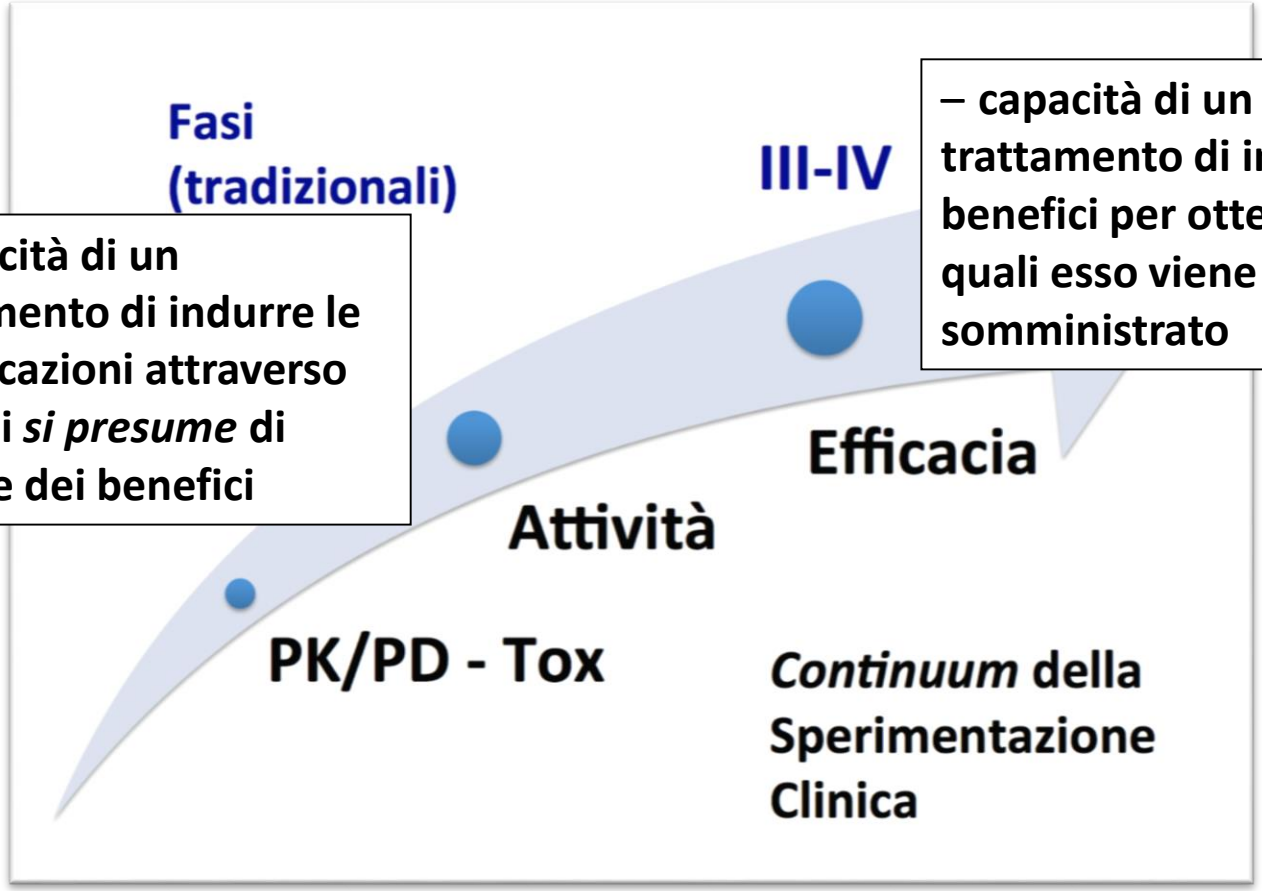
Table 4. Risk Ratios for Cardiovascular Risk Factors by Sex and Weight Category.*

Risk-Factor Variable and Weight Category	All Participants		Female Participants		Male Participants	
	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value
Total cholesterol						
Overweight	0.70 (0.58–0.85)	<0.001	0.79 (0.58–1.07)	0.12	0.63 (0.49–0.82)	<0.001
Class I obesity	Reference		Reference		Reference	
Class II obesity	1.12 (0.88–1.45)	0.34	1.17 (0.78–1.77)	0.45	1.09 (0.78–1.54)	0.60
Class III obesity	1.29 (0.92–1.80)	0.14	1.08 (0.56–2.00)	0.80	1.41 (0.93–2.15)	0.10
HDL cholesterol						
Overweight	0.55 (0.44–0.69)	<0.001	0.46 (0.33–0.65)	<0.001	0.60 (0.43–0.85)	0.004
Class I obesity	Reference		Reference		Reference	
Class II obesity	1.65 (1.31–2.01)	<0.001	1.06 (0.70–1.60)	0.78	2.00 (1.45–2.74)	<0.001
Class III obesity	1.89 (1.35–2.66)	<0.001	1.19 (0.66–2.12)	0.56	2.36 (1.55–3.58)	<0.001
LDL cholesterol						
Overweight	0.67 (0.48–0.93)	0.02	0.66 (0.41–1.06)	0.08	0.69 (0.42–1.12)	0.13
Class I obesity	Reference		Reference		Reference	
Class II obesity	0.92 (0.57–1.48)	0.19	1.04 (0.51–2.18)	0.90	0.80 (0.42–1.52)	0.50
Class III obesity	0.79 (0.44–1.43)	0.59	0.85 (0.38–1.89)	0.68	0.75 (0.32–1.78)	0.51

Quale O?


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

Quale O?


Fasi
(tradizionali)
III-IV
– capacità di un trattamento di indurre le modificazioni attraverso le quali *si presume* di indurre dei benefici
– capacità di un trattamento di indurre i benefici per ottenere i quali esso viene somministrato
Efficacia
Attività
PK/PD - Tox
Continuum della Sperimentazione Clinica

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

trattamento	*attività*	*efficacia*
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OBIETTIVO PRIMARIO

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altri quesiti di interesse, in qualche modo correlati al quesito primario

Il quesito come *primum movens*

Metodologia PICO

P	*patient* (paziente)	età superiore ai 65 anni con frattura del femore
I	*intervention* (intervento)	percorso di riabilitazione multidisciplinare
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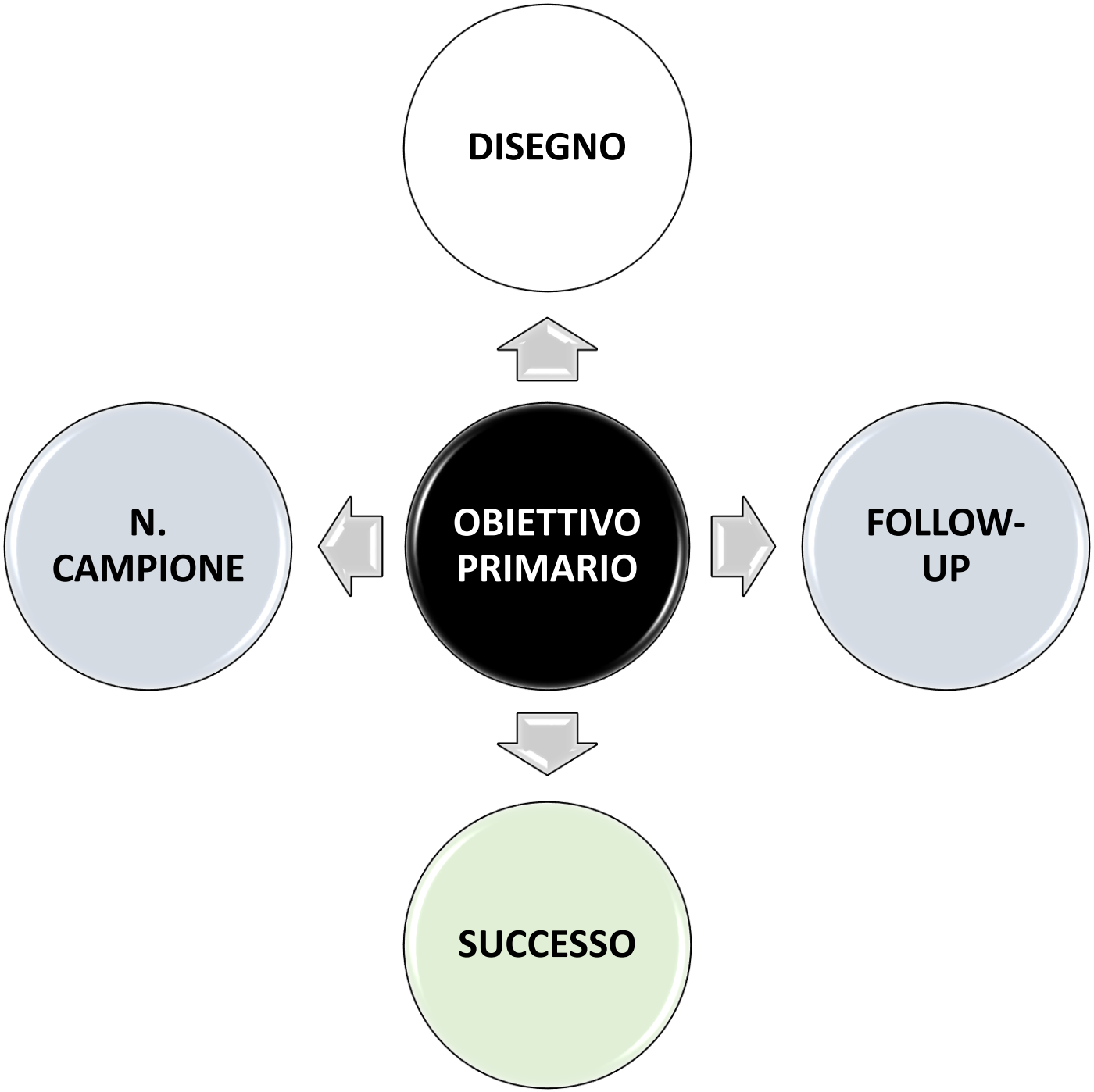
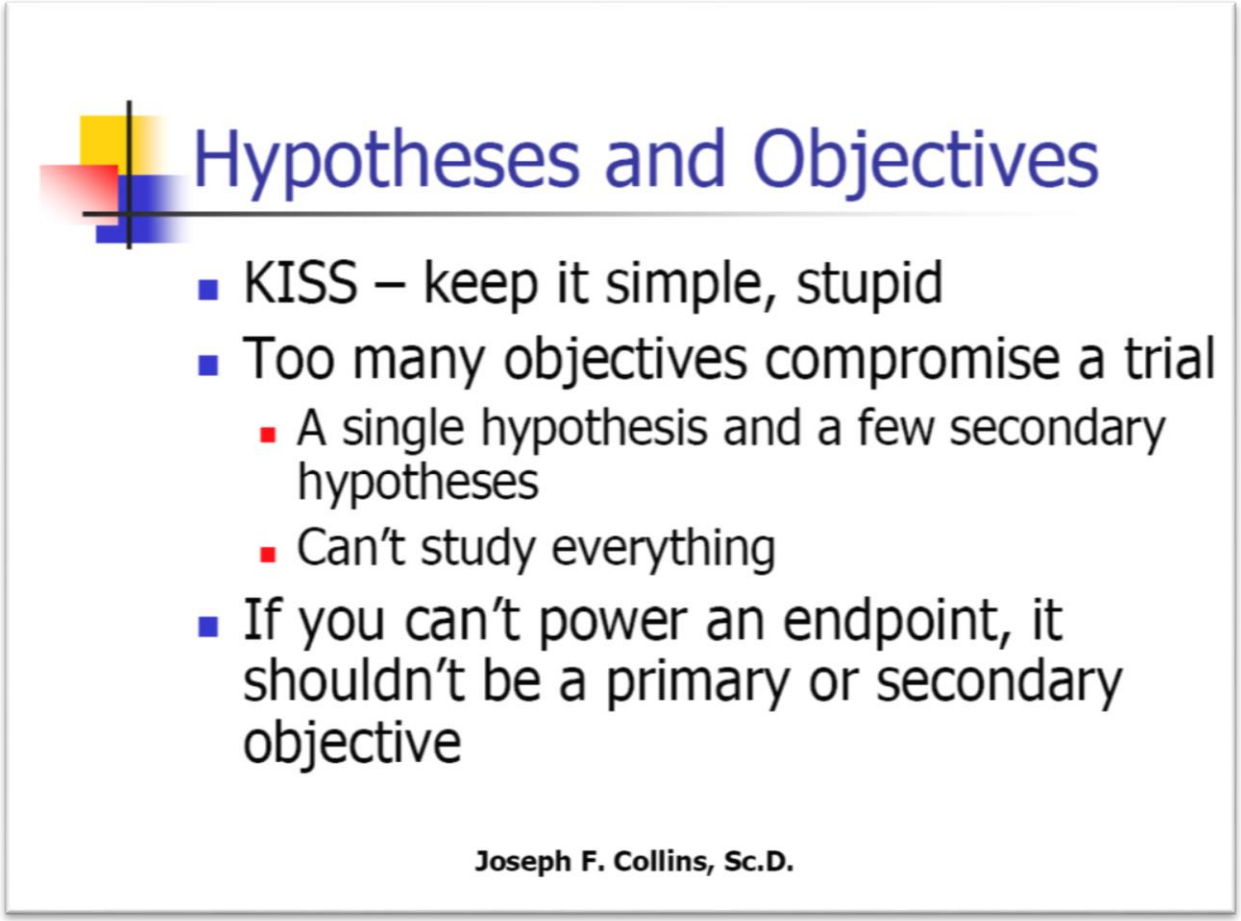

DISEGNO
N. CAMPIONE
OBIETTIVO PRIMARIO
FOLLOW-UP
SUCCESSO

OBIETTIVO


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
Joseph F. Collins, Sc.D.

OBIETTIVO

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

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

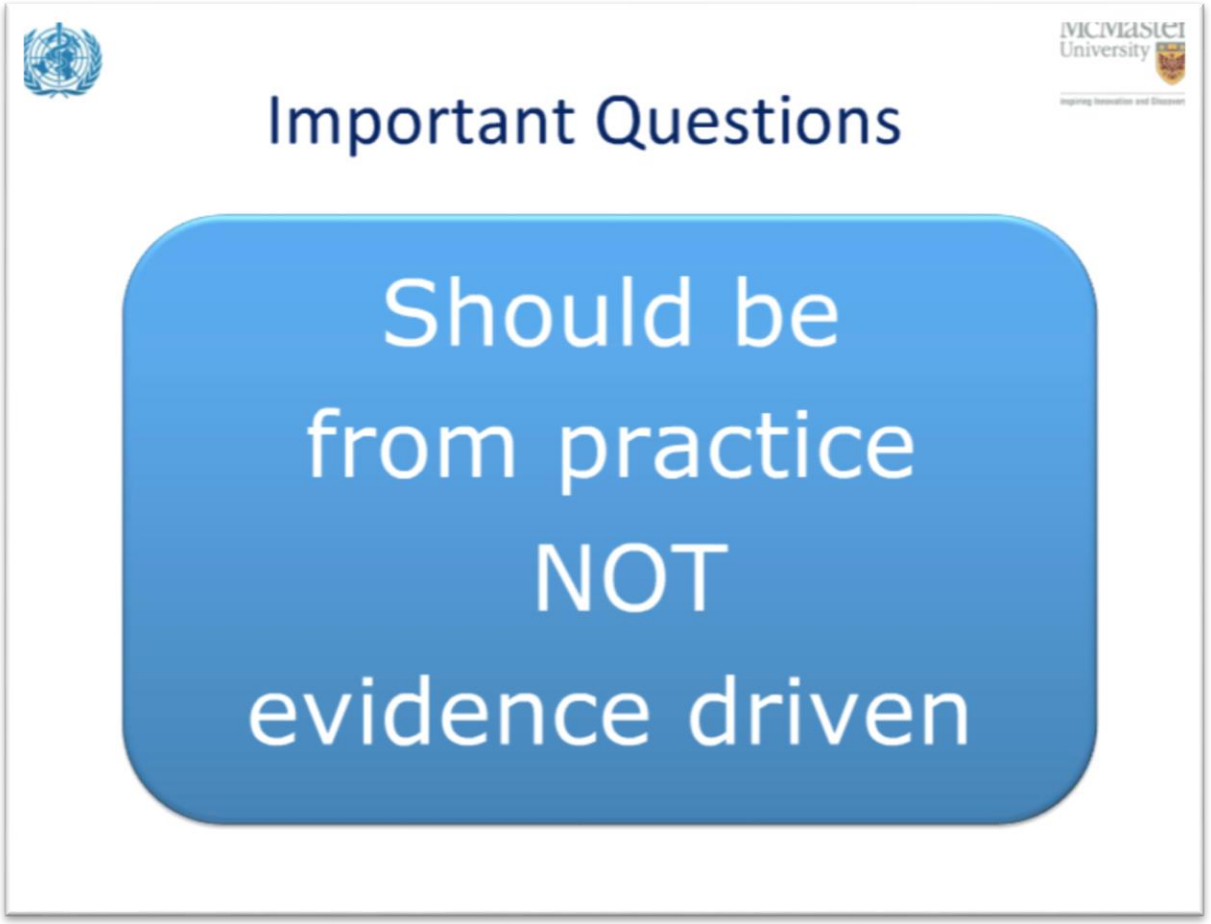
STUDI CLINICI: METODOLOGIA

Plausibilità e rilevanza dello studio

RAZIONALE

RAZIONALE

Fattori da considerare sull'opportunità di una sperimentazione clinica



Fattori da considerare sull'opportunità di una sperimentazione clinica

1) Gravità dell'affezione/problema

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

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.

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.

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.

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.

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

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N Engl J Med 2012;366:109-19

Gravità dell'affezione/problema

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.

Efficacia delle terapie disponibili

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.

Tossicità (scomodità) delle terapie disponibili rispetto a quelle alternative

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④

Presumibile superiorità delle terapie sperimentali

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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 ③ least 3 months.[2] Although effective, this regimen 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.

Tossicità (scomodità) delle terapie disponibili rispetto a quelle alternative

E QUI?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiometabolic Risks and Severity of Obesity in Children and Young Adults

Asheley C. Skinner, Ph.D., Eliana M. Perrin, M.D., M.P.H., Leslie A. Moss, M.H.A., C.H.E.S., and Joseph A. Skelton, M.D.

ABSTRACT

BACKGROUND

The prevalence of severe obesity among children and young adults has increased over the past decade. Although the prevalence of cardiometabolic risk factors is relatively low among children and young adults who are overweight or obese, those with more severe forms of obesity may be at greater risk.

METHODS

We performed a cross-sectional analysis of data from overweight or obese children and young adults 3 to 19 years of age who were included in the National Health and Nutrition Examination Survey from 1999 through 2012 to assess the prevalence of multiple cardiometabolic risk factors according to the severity of obesity. Weight status was classified on the basis of measured height and weight. We used standard definitions of abnormal values for total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, triglycerides, blood pressure, glycated hemoglobin, and fasting glucose and report the prevalence of abnormal values in children and young adults according to weight status.

THE PREVALENCE OF SEVERE OBESITY among children and young adults has increased in recent years[1] and has led to a heightened awareness and concern about the cardiovascular and metabolic health of persons in this age group. In 1999–2004, almost 4% of children and young adults in the United States 2 to 19 years of age were classified as having severe obesity,[2] and as recently as 2011–2012, the prevalence of severe obesity increased to approximately 6% in this age group[3]; however, the prevalence of cardiometabolic risk factors accompanying severe obesity in these children and young adults is unclear.

Cardiometabolic risk factors are more prevalent among overweight or obese children and young adults than among those of healthy weight.[3] However, the use of only a single category for obesity does not take into account the varying severity of obesity. The American Heart Association identified several relatively small studies that showed that more severe forms of obesity were associated with a greater immediate risk of complications related to weight, including abnormal lipid and blood glucose levels and increased blood-pressure levels[4]; however, various definitions of severe obesity were used in these studies. Clearer guidelines now exist to define severe obesity as 120% of the 95th percentile for body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) and to define markedly severe obesity as 140% of the 95th percentile.[1,4] As children approach adulthood, these high percentile curves approximate a BMI of at least 35 for severe obesity (class II obesity) and a BMI of at least 40 for markedly severe obesity (class III obesity).[1] To improve the understanding of the distribution of cardiometabolic risk factors, we examined the prevalence of multiple cardiometabolic risk factors according to the severity of obesity using nationally representative data.

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FATTIBILE

INTERESSANTE

NUOVO

ETICO

RILEVANTE

FATTIBILE

- Ambiente ricettivo
- Valutazione delle tempistiche
- Adeguato campionamento
- Competenza
  - statistiche, cliniche, metodologiche
- Risorse

INTERESSANTE

- **Per la comunità:**
    - **risponde a un bisogno**
- Per i finanziatori (industria, istituzioni ...)
- Personale
    - pubblicazione
- Professionale
    - reputazione, carriera
- Rete scientifica

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fish Oil–Derived Fatty Acids in Pregnancy and Wheeze and Asthma in Offspring

Hans Bisgaard, M.D., D.M.Sc., Jakob Stokholm, M.D., Ph.D., Bo L. Chawes, M.D., Ph.D., D.M.Sc., Nadja H. Vissing, M.D., Ph.D., Elin Bjarnadóttir, M.D., Ann-Marie M. Schoos, M.D., Ph.D., Helene M. Wolsk, M.D., Tine M. Pedersen, M.D., Rebecca K. Vinding, M.D., Sunna Thorsteinsdóttir, M.D., Nilofar V. Følsgaard, M.D., Ph.D., Nadia R. Fink, M.D., Jonathan Thorsen, M.D., Anders G. Pedersen, Ph.D., Johannes Waage, Ph.D., Morten A. Rasmussen, Ph.D., Ken D. Stark, Ph.D., Sjurdur F. Olsen, M.D., D.M.Sc., and Klaus Bønnelykke, M.D., Ph.D.

ABSTRACT

BACKGROUND

Reduced intake of n–3 long-chain polyunsaturated fatty acids (LCPUFAs) may be a contributing factor to the increasing prevalence of wheezing disorders. We assessed the effect of supplementation with n–3 LCPUFAs in pregnant women on the risk of persistent wheeze and asthma in their offspring.

From COPSAC (Copenhagen Prospective Studies on Asthma in Childhood), Herlev and Gentofte Hospital, University of Copenhagen (H.B., J.S., B.L.C., N.H.V., E.B., A.-M.M.S., H.M.W., T.M.P., R.K.V., S.T.,

Nuovo

- Contributo scientifico significativo
- A supporto della letteratura disponibile
- Aumenta il livello di evidenza
- Valida i risultati su un’altra popolazione
- Risultati meglio generalizzabili

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

PANCREOX: A Randomized Phase III Study of 5-Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy

Sharlene Gill, Yoo-Joung Ko, Christine Cripps, Annie Beaudoin, Sukhbinder Dhesy-Thind, Muhammad Zulfiqar, Pawel Zalewski, Thuan Do, Pablo Cano, Wendy Yin Han Lam, Scot Dowden, Helene Grassin, John Stewart, and Malcolm Moore

Sharlene Gill and Malcolm Moore, BC Cancer Agency, Vancouver; Muhammad Zulfiqar, BC Cancer Agency, Abbotsford; Thuan Do, BC Cancer Agency, Surrey; Wendy Yin Han Lam, Burnaby Hospital Cancer Centre, Burnaby, British Columbia; Yoo-Joung Ko, Sunnybrook Health Sciences Centre; Malcolm Moore, Princess Margaret Hospital, Toronto; Christine Cripps, Ottawa Hospital Cancer Centre, Ottawa; Sukhbinder Dhesy-Thind, Juravinski Cancer Centre, Hamilton; Pawel Zalewski, RSM Durham Regional Cancer Centre, Oshawa; Pablo Cano, Sudbury Regional Hospital, Sudbury, Ontario; Annie Beaudoin, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke; Helene Grassin and John Stewart, Sanofi Canada, Laval, Quebec; and Scot Dowden, Alberta Health Service, Calgary, Alberta, Canada.

Published online ahead of print at www.jco.org on September 12, 2016.

Supported by Sanofi Canada.

Presented in part at the 50th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL May 30-June 3, 2014.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT01121848.

Corresponding author: Sharlene Gill, MD, MPH, British Columbia Cancer Agency,

ABSTRACT

Purpose

The standard of care for second-line therapy in patients with advanced pancreatic cancer after gemcitabine-based therapy is not clearly defined. The CONKO-003 phase III study reported a survival benefit with second-line fluorouracil (FU) and oxaliplatin using the oxaliplatin, folinic acid, and FU (OFF) regimen.[1] PANCREOX was a phase III multicenter trial to evaluate the benefit of FU and oxaliplatin administered as modified FOLFOX6 (mFOLFOX6; infusional fluorouracil, leucovorin, and oxaliplatin) versus infusional FU/leucovorin (LV) in this setting.

Patients and Methods

Patients with confirmed advanced pancreatic cancer who were previously treated with gemcitabine therapy and with an Eastern Cooperative Oncology Group performance status of 0-2 were eligible. A total of 108 patients were randomly assigned to receive biweekly mFOLFOX6 or infusional FU/LV until progression. Progression-free survival (PFS) was the primary end point.

Results

Baseline patient characteristics were similar in both arms. No difference was observed in PFS (median, 3.1 months *v* 2.9 months; $P = .99$). Overall survival (OS) was inferior in patients assigned to mFOLFOX6 (median, 6.1 months *v* 9.9 months; $P = .02$). Increased toxicity was observed with the addition of oxaliplatin, with grade 3/4 adverse events occurring in 63% of patients who received mFOLFOX6 and 11% of those who received FU/LV. More patients in the mFOLFOX6 arm withdrew from study due to adverse events than in the FU/LV arm (20% *v* 2%), whereas the use of post-progression therapy was significantly higher in the FU/LV arm (25% *v* 7%; $P = .015$). No significant differences were observed in time to deterioration on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 global health scale.

Conclusion

No benefit was observed with the addition of oxaliplatin, administered as mFOLFOX6, versus infusional FU/LV in patients with advanced pancreatic cancer previously treated with first-line gemcitabine.

J Clin Oncol 34. *© 2016 by American Society of Clinical Oncology*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Persistence of Zika Virus in Body Fluids — Preliminary Report

Gabriela Paz-Bailey, M.D., Ph.D., Eli S. Rosenberg, Ph.D., Kate Doyle, M.P.H., Jorge Munoz-Jordan, Ph.D., Gilberto A. Santiago, Ph.D., Liore Klein, M.S.P.H., Janice Perez-Padilla, M.P.H., Freddy A. Medina, Ph.D., Stephen H. Waterman, M.D., M.P.H., Carlos Garcia Gubern, M.D., Luisa I. Alvarado, M.D., and Tyler M. Sharp, Ph.D.

tion have not been fully described.

Although most ZIKV infections are probably transmitted by infected mosquitoes, ZIKV transmission has been documented through sexual contact,[6] blood transfusion,[7] laboratory exposure,[1] and both intrauterine and intrapartum transmission.[8] ZIKV RNA has been detected in semen,[9] urine,[10] saliva,[11] cerebrospinal fluid,[12] vaginal or cervical secretions,[13,14] and other body fluids.[15-18] Most transmissions through sexual contact have been from men with symptomatic infection to their female partners.[19-21] However, sexual transmission has also occurred from asymptomatic men,[22,23] through male-to-male[24] and female-to-male sex,[25] and possibly through oral sex.[9] Shedding in the female genital tract appears to be rare and of short duration.[13] In contrast, there are reports of prolonged detection of ZIKV RNA in semen, with the longest reported duration of detection up to 188 days after onset.[26,27] Infectious virus has been reported in semen up to 69 days.[28]

A detailed understanding of the dynamics of the early stages of ZIKV infection is needed to inform diagnostic testing algorithms and prevention interventions, since existing evidence is based on case reports and cross-sectional observations, primarily from returning travelers.[29] To estimate the presence and duration of the detection of ZIKV RNA in body fluids and anti–ZIKV IgM antibody among participants with acute ZIKV infection, we established the ZIKV Persistence (ZiPer) cohort study in Puerto Rico, in which we prospectively evaluated multiple concurrently collected specimens from participants. Here, we report the results of the interim analyses to provide timely data that can inform recommendations.

ETICO

- Sicurezza
- **NON sovrastimare i benefici**
- **NON sottostimare i rischi**
- Sicurezza dei dati/confidenzialità
- Reclutare/Acquisizione del consenso

ETICO

ANNALS OF ONCOLOGY

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Article Contents

A need to simplify informed consent documents in cancer clinical trials. A position paper of the ARCAD Group

H. Bleiberg; G. Decoster; A. de Gramont; P. Rougier; A. Sobrero; A. Benson; B. Chibaudel; J.Y. Douillard C. Eng C. Fuchs ... Show more

Ann Oncol mdx050. **DOI:** https://doi.org/10.1093/annonc/mdx050
Published: 13 February 2017 **Article history** ▾

Il nuovo consenso informato? Semplificato e più efficace

Banditi i tecnicismi. Stop ai troppi dettagli incomprensibili. La comunicazione ne gioverebbe e anche la possibilità di scelta indipendente del paziente. La proposta del gruppo ARCAD: un consenso informato più conciso ma parimenti accurato.

Bleiberg H, et al. A need to simplify informed consent documents in cancer clinical trials. A position paper of the ARCAD Group. Ann Oncol 2017, Feb 13, epub ahead of print.

Seguici su...

Diventa follower di

@ONcotwITting

Archivio

I principali limiti dei consensi informati oggi in uso nelle sperimentazioni cliniche sono:

- lunghezza eccessiva
- complessità
- uso smodato di sigle e abbreviazioni
- ridondanze e contraddizioni
- raccomandazioni non sempre supportate da evidenza di alto livello
- dettagli medici non essenziali

A cura di Giuseppe Aprile

Pubblicato Giovedì, 23 Febbraio 2017

Sezione Miscellanea

RILEVANTE

-Migliora l'outcome (efficacia e sicurezza)

-Risponde a un bisogno

-Stimola nuove ricerche

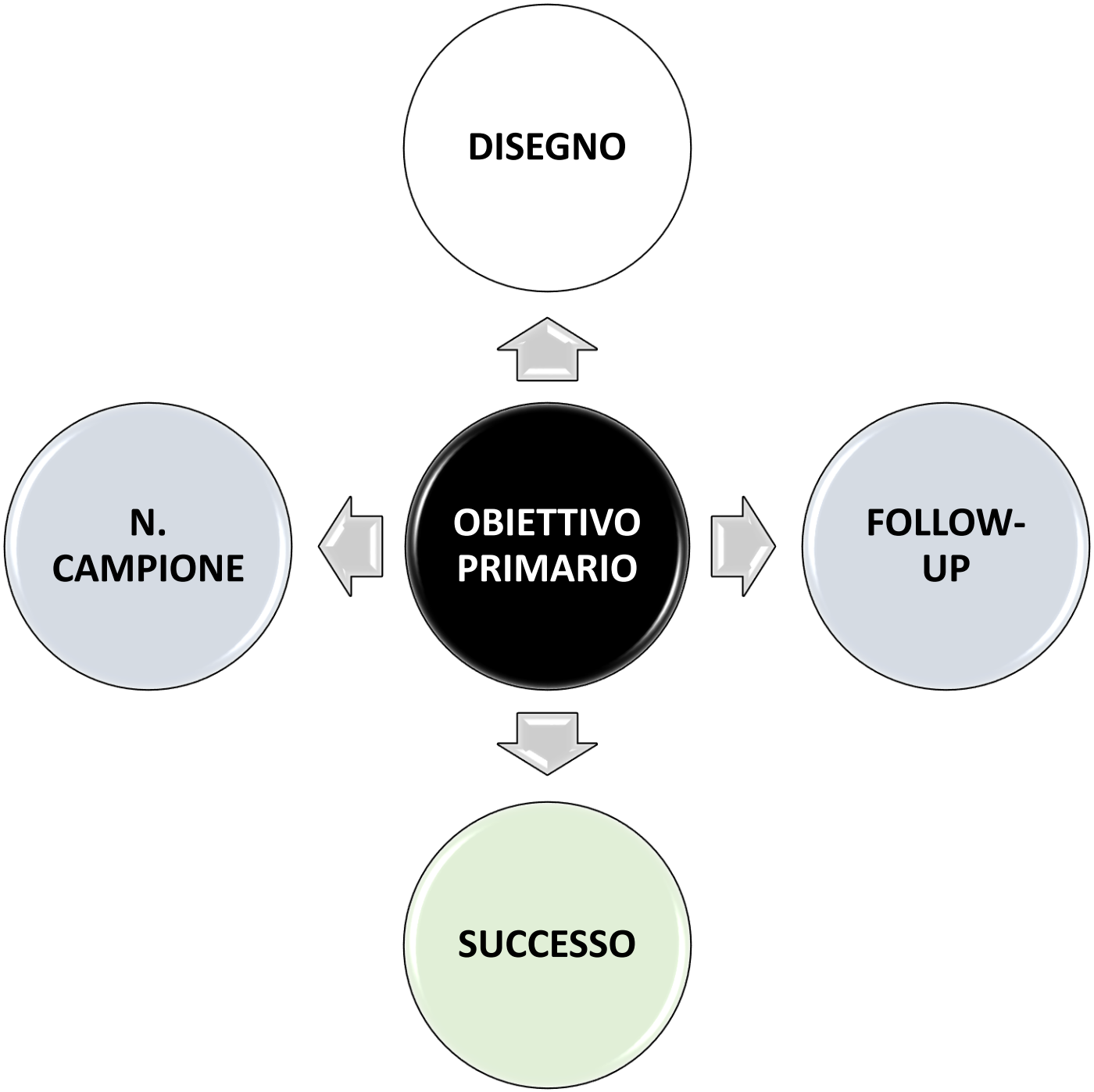
-Influenza lo standard di cura

-Cambia la pratica clinica

STUDI CLINICI: METODOLOGIA

Il disegno dello studio:

Studi osservazionali e studi sperimentali; scelta del braccio di controllo e procedure di randomizzazione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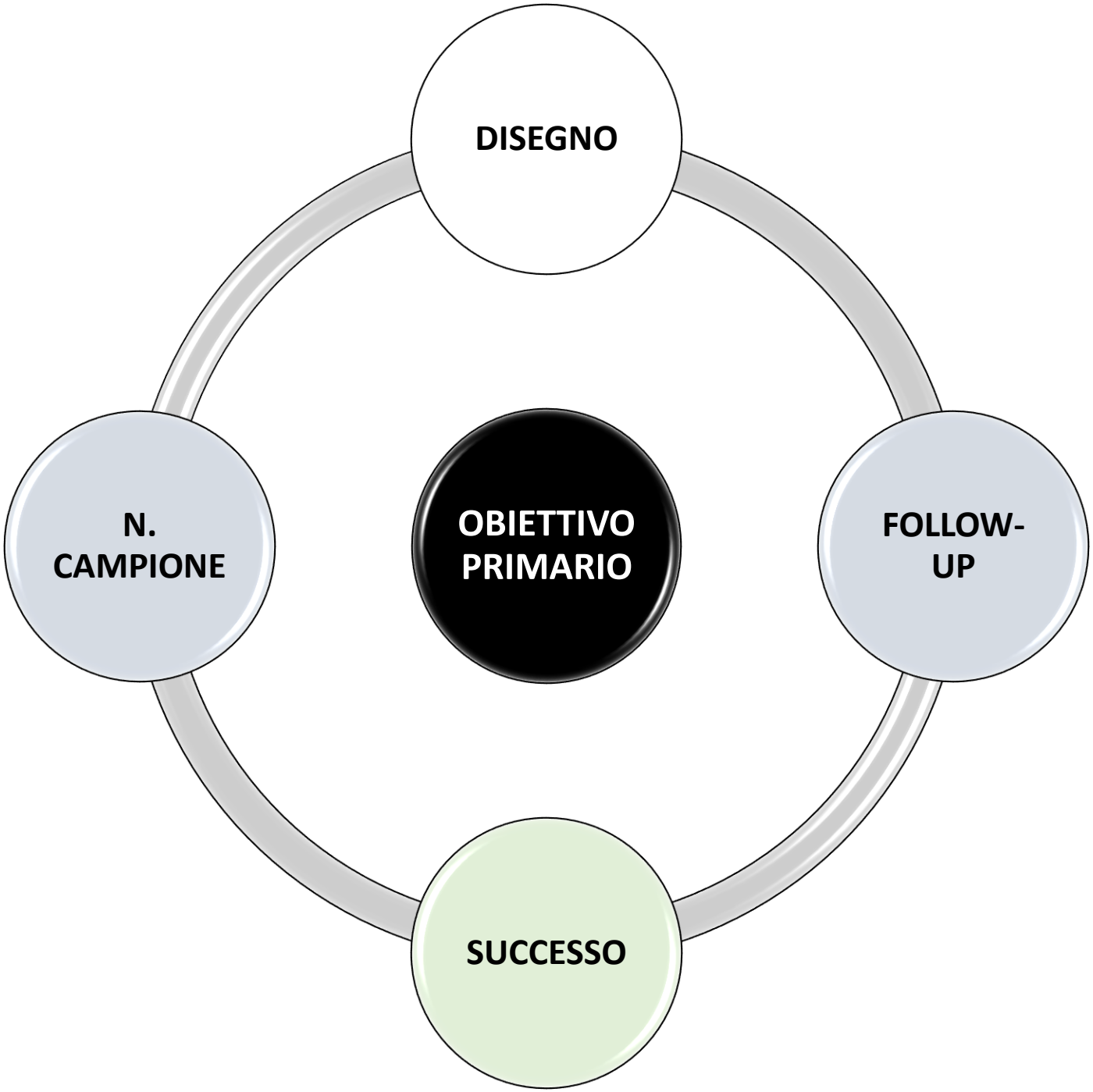
FOLLOW-UP
SUCCESSO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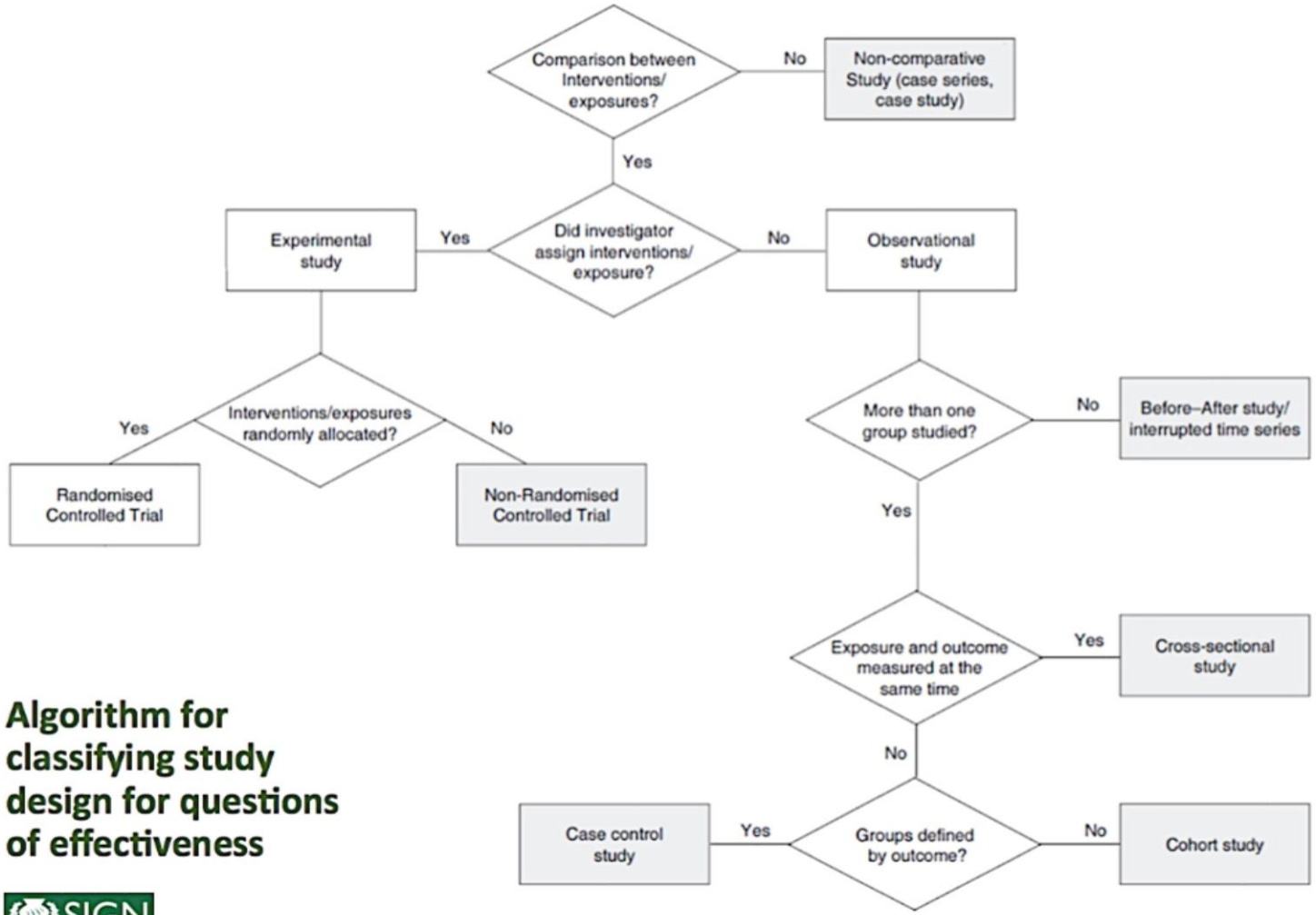
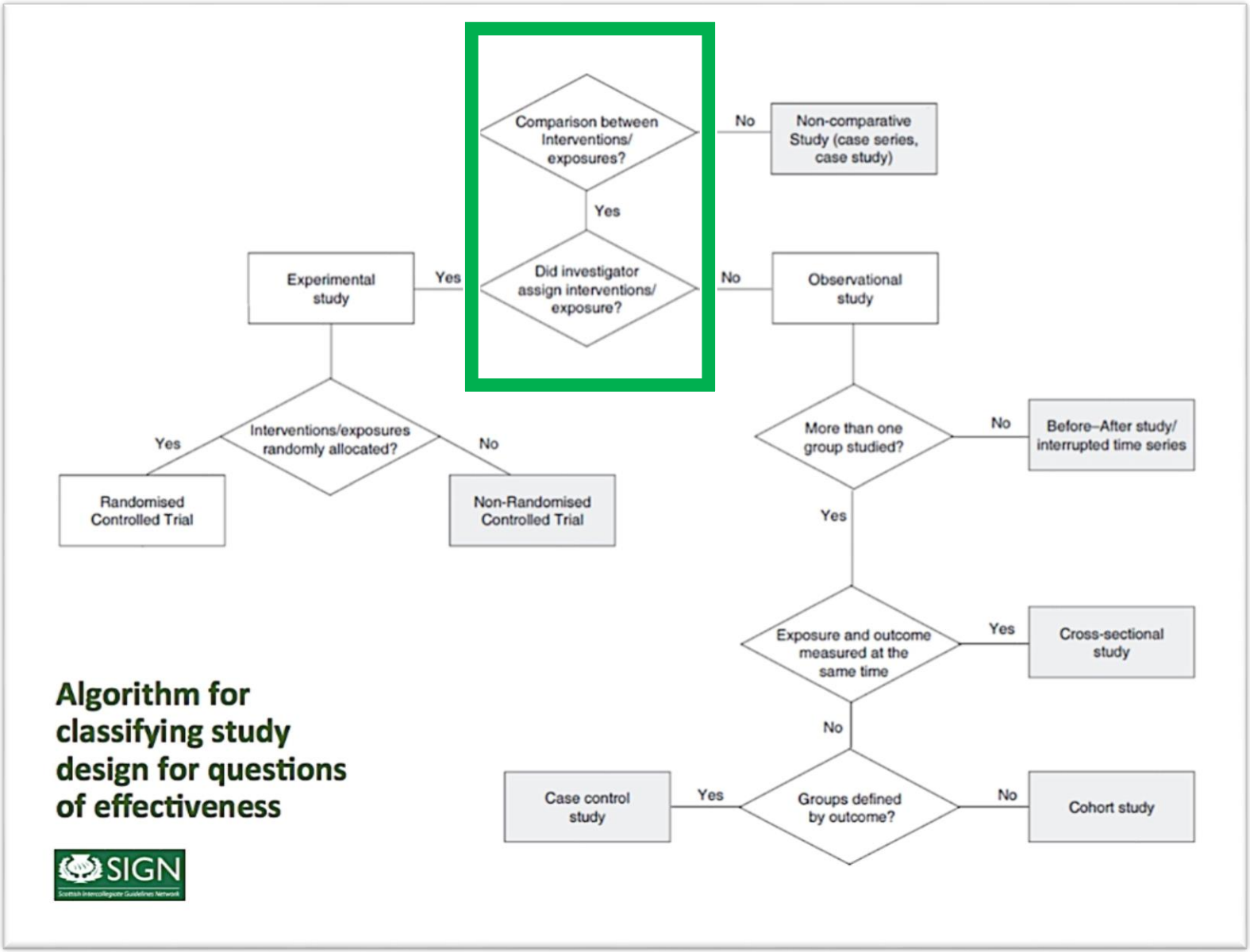

Comparison between Interventions/ exposures?
No
Non-comparative Study (case series, case study)
Yes
Did investigator assign interventions/ exposure?
Yes
Experimental study
No
Observational study
Interventions/exposures randomly allocated?
Yes
No
Randomised Controlled Trial
Non-Randomised Controlled Trial
More than one group studied?
No
Before–After study/ interrupted time series
Yes
Exposure and outcome measured at the same time
Yes
Cross-sectional study
No
Groups defined by outcome?
Yes
Case control study
No
Cohort study
Algorithm for classifying study design for questions of effectiveness
SIGN

DISEGNO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SIGN

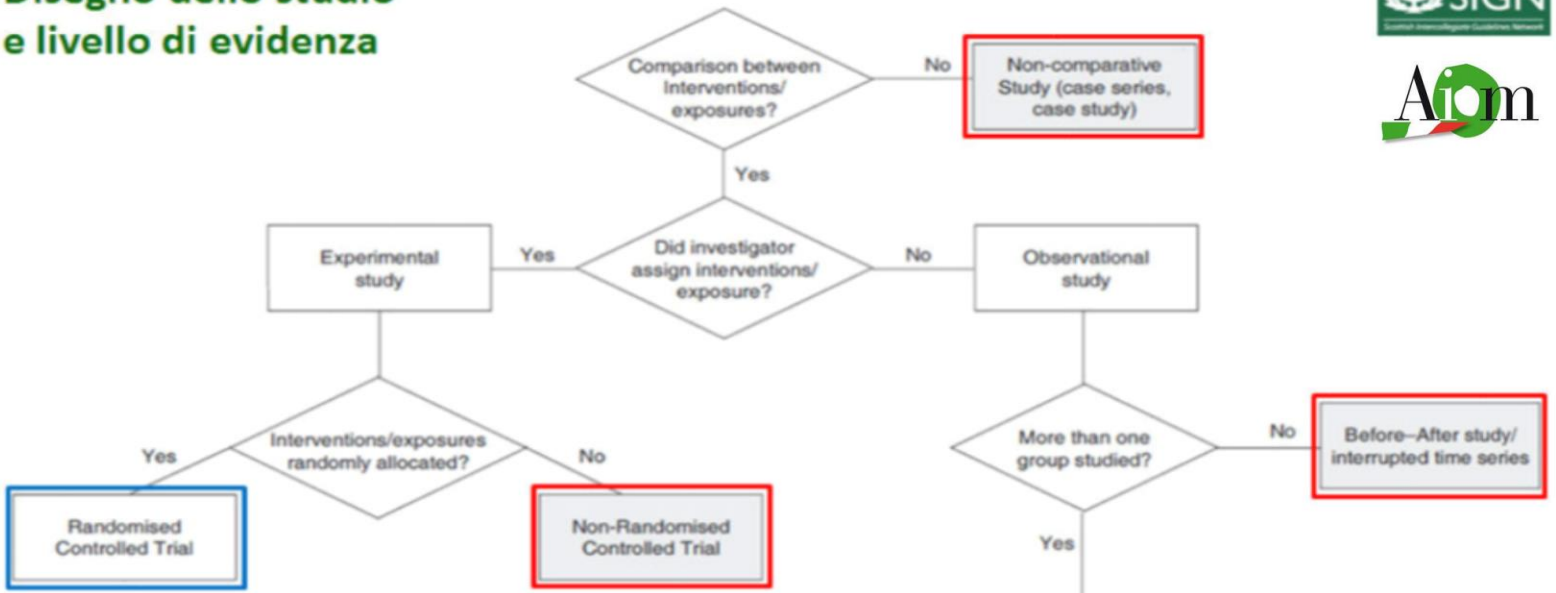
SPERIMENTALE

OSSERVAZIONALE

OSSERVAZIONALE

SPERIMENTALE

Disegno dello studio e livello di evidenza



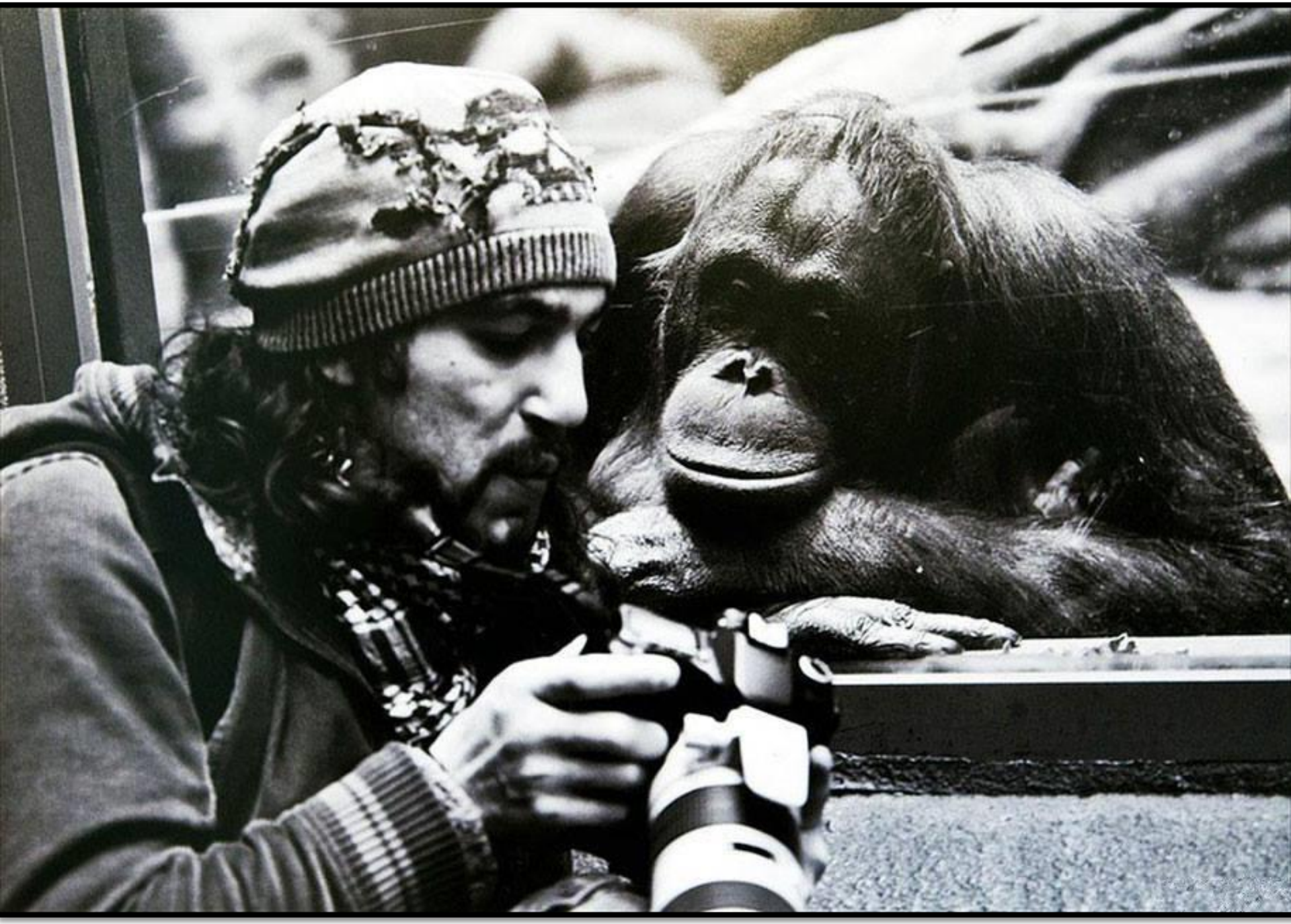
1 = studi randomizzati

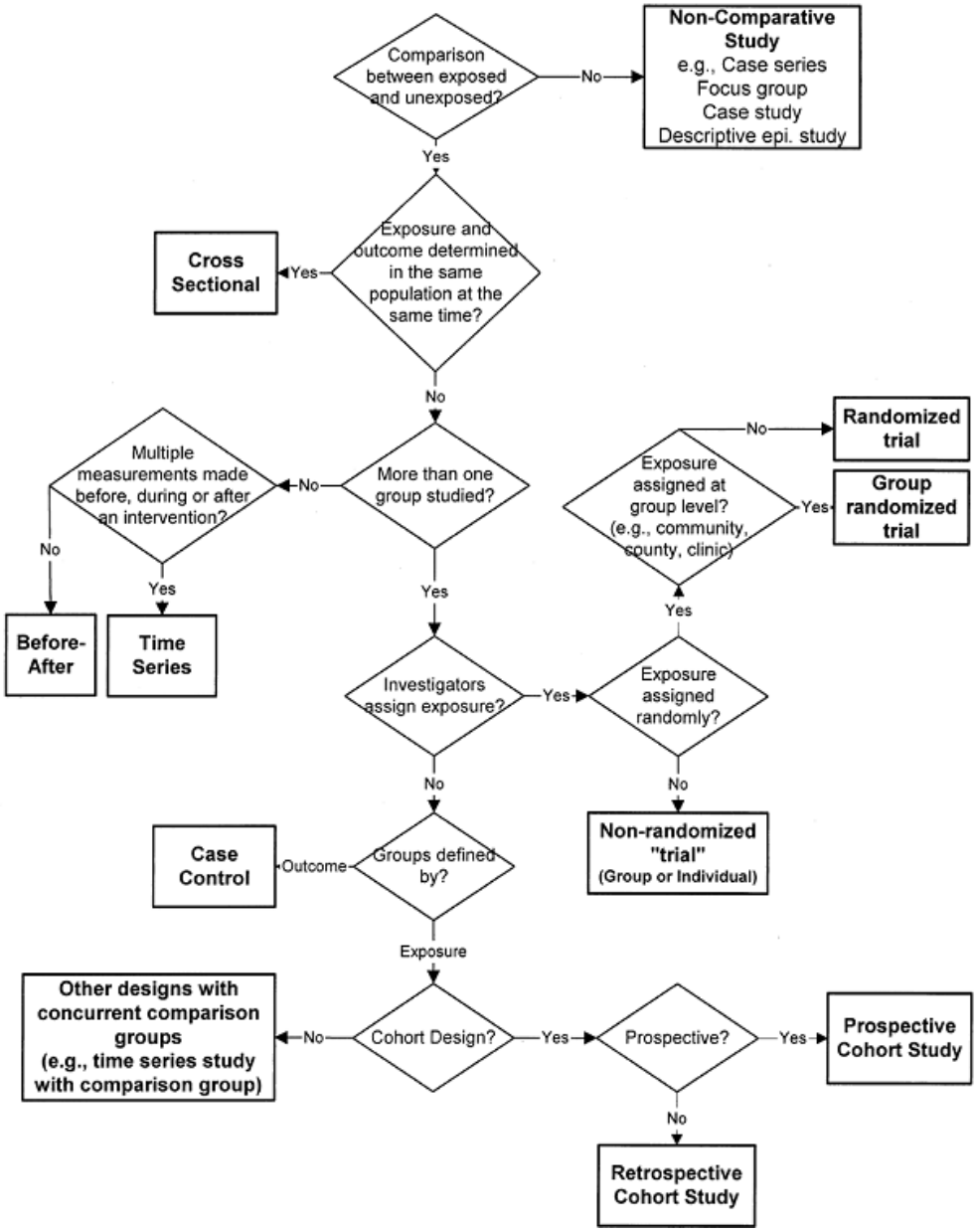
2 = studi di caso-controllo e studi di coorte

3 = serie di casi; studi osservazionali di altro tipo

4 = opinione di esperti

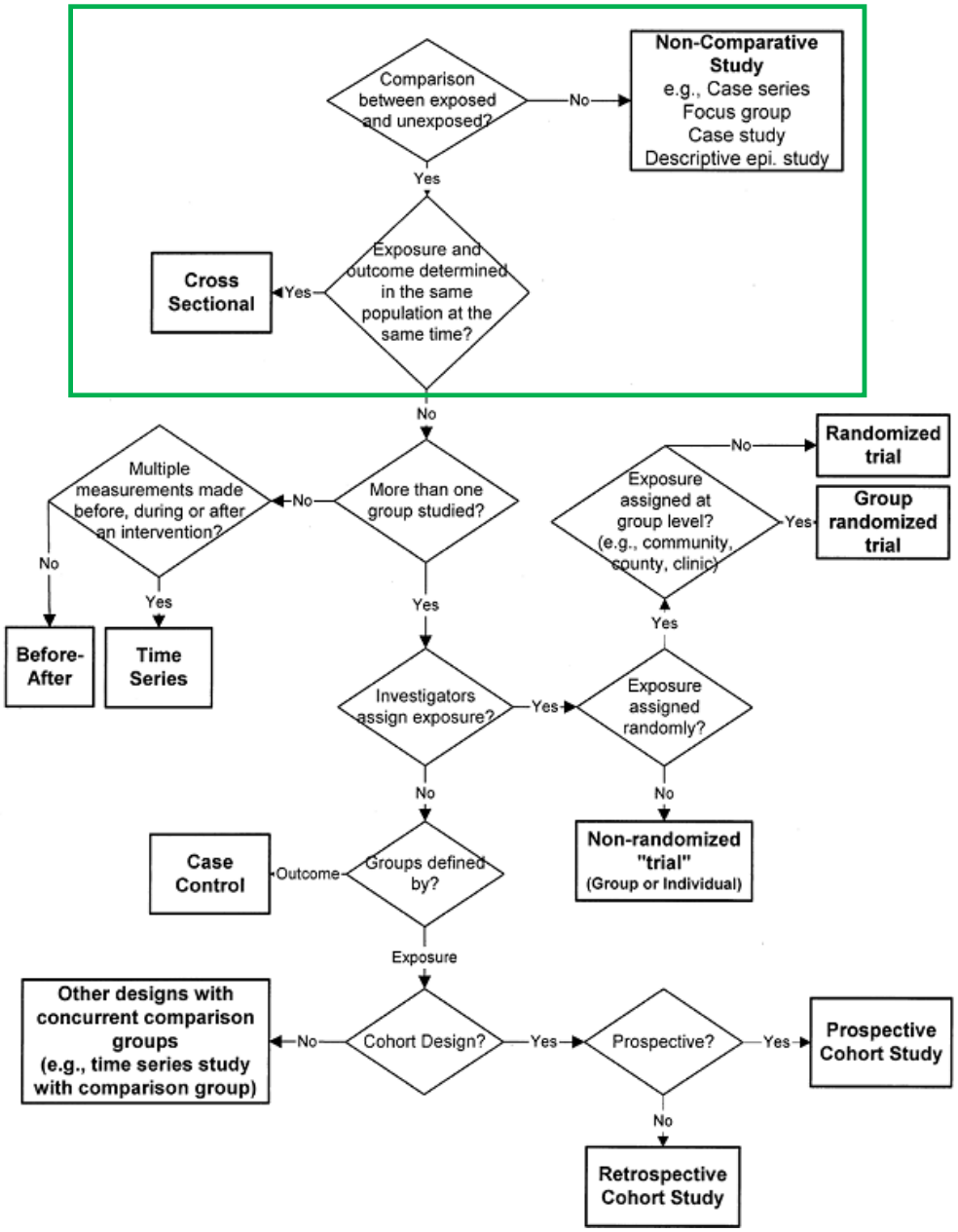
*adattata da SIGN (Algorithm for classifyingstudy design for questions of effectiveness)




Comparison between exposed and unexposed?
No
Non-Comparative Study
e.g., Case series
Focus group
Case study
Descriptive epi. study
Yes
Exposure and outcome determined in the same population at the same time?
Yes
Cross Sectional
No
More than one group studied?
No
Multiple measurements made before, during or after an intervention?
No
Before-After
Yes
Time Series
Yes
Investigators assign exposure?
Yes
Exposure assigned randomly?
No
Randomized trial
Exposure assigned at group level? (e.g., community, county, clinic)
Yes
Group randomized trial
Yes
No
Non-randomized "trial" (Group or Individual)
No
Groups defined by?
Outcome
Case Control
Exposure
Cohort Design?
No
Other designs with concurrent comparison groups (e.g., time series study with comparison group)
Yes
Prospective?
Yes
Prospective Cohort Study
No
Retrospective Cohort Study

STUDI OSSERVAZIONALI

EPIDEMIOLOGICI	**Before-After**	**valutazione del problema prima e dopo un intervento**
	Cross-sectional	**valutazione del problema in una finestra temporale singola e definita**
	Case-control	**indentificazione dei predittori di un determinato outcome**
	Cohort	**identificazione dell'incidenza di un particolare problema nel tempo**
TERAPEUTICI	**Non comparativi**	**valutazione degli outcome dopo/con un determinato trattamento**
	Comparativi	**confronto degli outcome tra gruppi che hanno ricevuto diverso trattamento**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Prospective?
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Prospective Cohort Study
No
Retrospective Cohort Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiometabolic Risks and Severity of Obesity in Children and Young Adults

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RESULTS

From the Department of Pediatrics, Division of General Pediatrics and Adolescent Medicine, School of Medicine (A.C.S., E.M.P.), Department of Health Policy and Management, Gillings School of Global Public Health (A.C.S.), and Injury Prevention Research Center (L.A.M.), University of North Carolina at Chapel Hill, Chapel Hill, and the Department of Pediatrics, Wake Forest School of Medicine, and Brenner FIT (Families in Training), Brenner Children's Hospital, Winston-Salem (J.A.S.) — all in North Carolina. Address reprint requests to Dr. Skinner at the Department of Pediatrics, University of North Carolina at Chapel Hill School of Medicine, 231 MacNider, 229B, CB 7225, Chapel Hill, NC 27599, or at asheley@unc.edu.

N Engl J Med 2015;373:1307-17.
DOI: 10.1056/NEJMoa1502821
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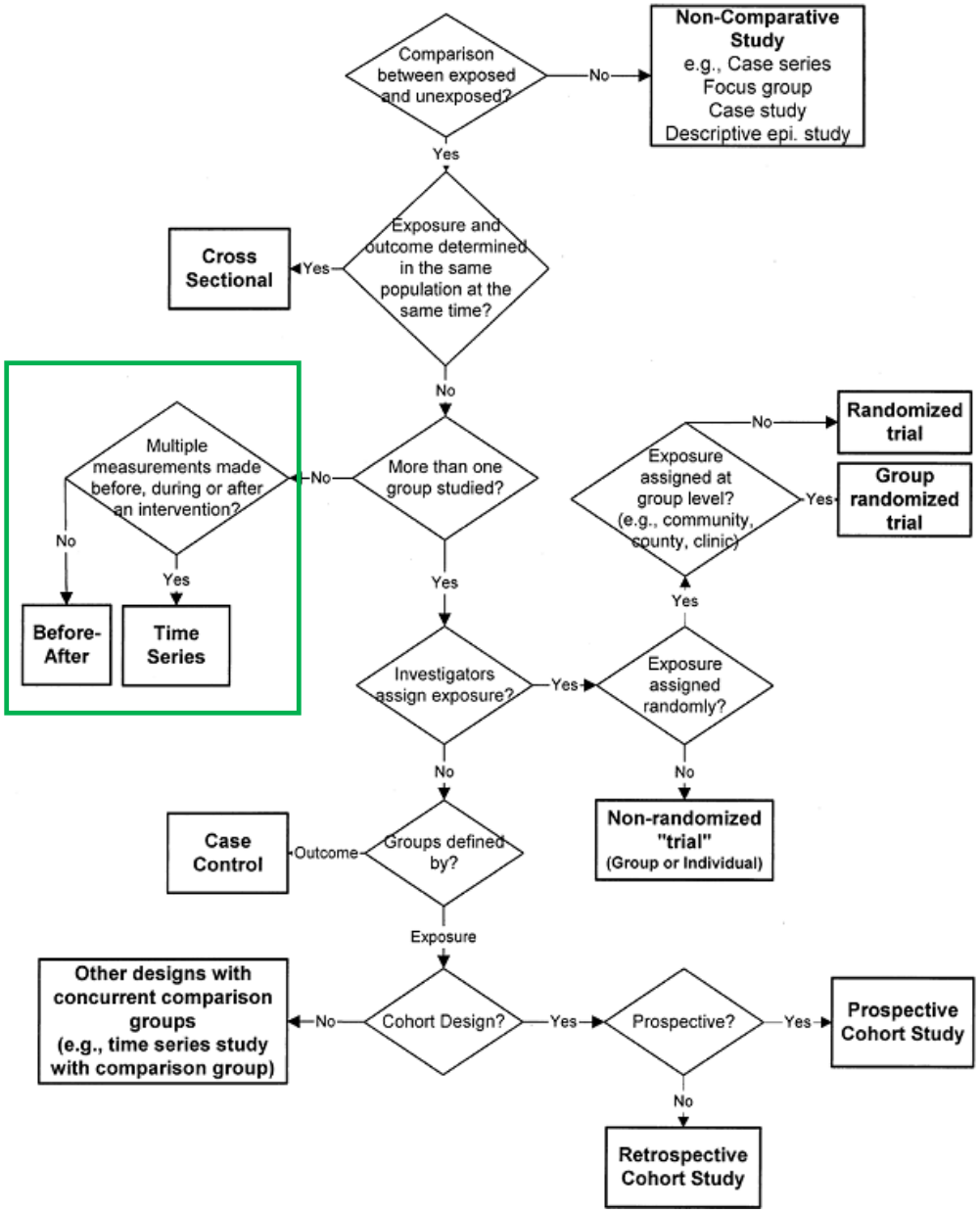
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Cross Sectional
No
More than one group studied?
No
Multiple measurements made before, during or after an intervention?
No
Before-After
Yes
Time Series
Yes
Investigators assign exposure?
Yes
Exposure assigned randomly?
No
Randomized trial
Exposure assigned at group level? (e.g., community, county, clinic)
Yes
Group randomized trial
No
Non-randomized "trial" (Group or Individual)
No
Groups defined by?
Outcome
Case Control
Exposure
Cohort Design?
No
Other designs with concurrent comparison groups (e.g., time series study with comparison group)
Yes
Prospective?
Yes
Prospective Cohort Study
No
Retrospective Cohort Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Functional Status of Elderly Adults before and after Initiation of Dialysis

Manjula Kurella Tamura, M.D., M.P.H., Kenneth E. Covinsky, M.D., M.P.H., Glenn M. Chertow, M.D., M.P.H., Kristine Yaffe, M.D., C. Seth Landefeld, M.D., and Charles E. McCulloch, Ph.D.

ABSTRACT

BACKGROUND

It is unclear whether functional status before dialysis is maintained after the initiation of this therapy in elderly patients with end-stage renal disease (ESRD).

METHODS

Using a national registry of patients undergoing dialysis, which was linked to a national registry of nursing home residents, we identified all 3702 nursing home residents in the United States who were starting treatment with dialysis between June 1998 and October 2000 and for whom at least one measurement of functional status was available before the initiation of dialysis. Functional status was measured by assessing the degree of dependence in seven activities of daily living (on the Minimum Data Set–Activities of Daily Living [MDS–ADL] scale of 0 to 28 points, with higher scores indicating greater functional difficulty).

RESULTS

The median MDS–ADL score increased from 12 during the 3 months before the initiation of dialysis to 16 during the 3 months after the initiation of dialysis. Three months after the initiation of dialysis, functional status had been maintained in 39% of nursing home residents, but by 12 months after the initiation of dialysis, 58% had died and predialysis functional status had been maintained in only 13%. In a ran-

From the Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Palo Alto, CA (M.K.T., G.M.C.); and the Division of Geriatrics, Department of Medicine (K.E.C., C.S.L.), the Departments of Psychiatry and Neurology (K.Y.) and Epidemiology and Biostatistics (K.Y., C.E.M.), University of California San Francisco; and the San Francisco VA Medical Center (K.E.C., K.Y., C.S.L.) — both in San Francisco. Address reprint requests to Dr. Kurella Tamura at the Division of Nephrology, Stanford University School of Medicine, 780 Welch Rd., Suite 106, Palo Alto, CA 94304, or at mktamura@stanford.edu.

N Engl J Med 2009;361:1539-47.
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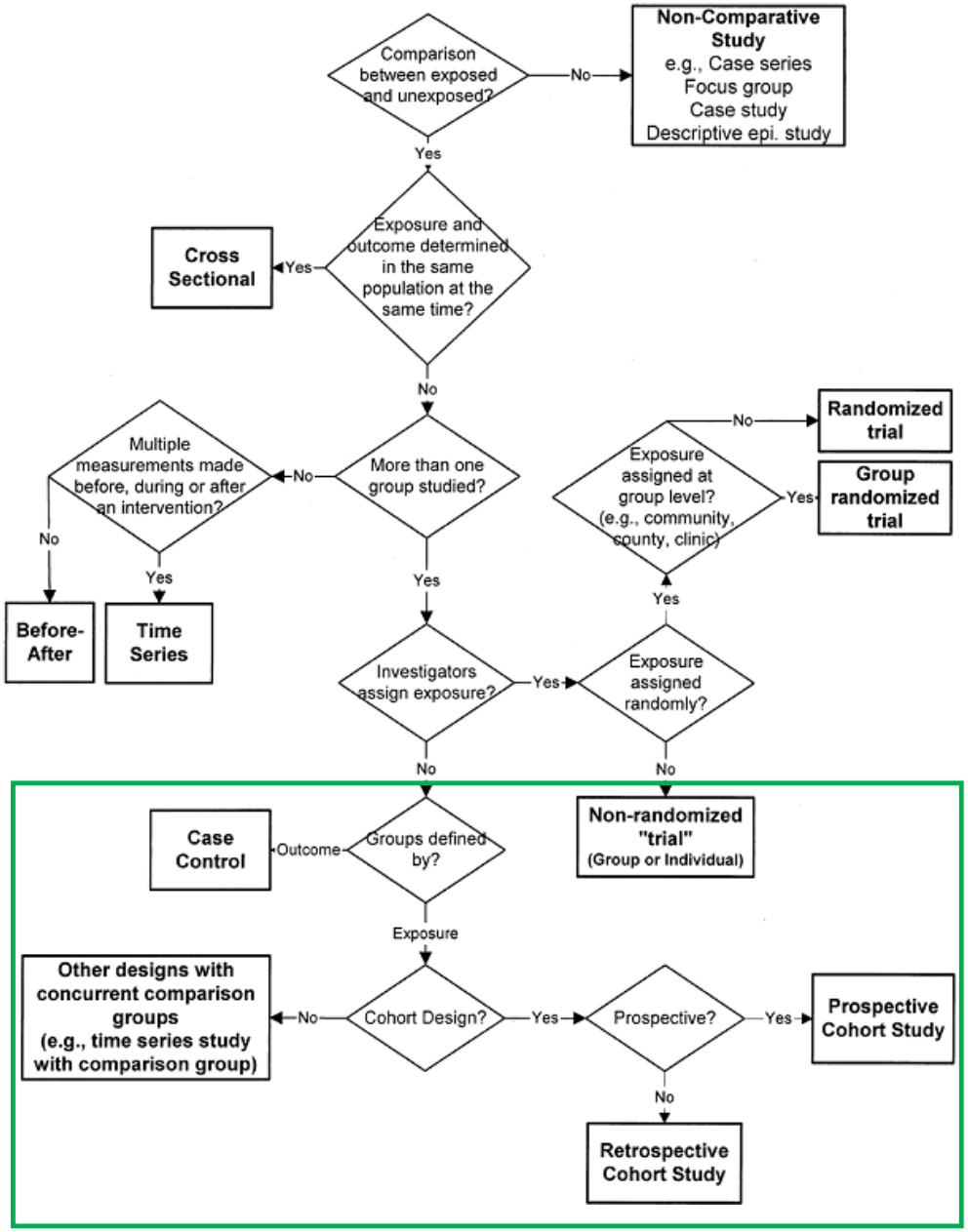
Comparison between exposed and unexposed?
No
Non-Comparative Study
e.g., Case series
Focus group
Case study
Descriptive epi. study
Yes
Exposure and outcome determined in the same population at the same time?
Yes
Cross Sectional
No
More than one group studied?
No
Multiple measurements made before, during or after an intervention?
No
Before-After
Yes
Time Series
Yes
Investigators assign exposure?
Yes
Exposure assigned randomly?
No
Randomized trial
Exposure assigned at group level? (e.g., community, county, clinic)
Yes
Group randomized trial
Yes
No
Non-randomized "trial" (Group or Individual)
Case Control
Outcome
Groups defined by?
Exposure
Other designs with concurrent comparison groups (e.g., time series study with comparison group)
No
Cohort Design?
Yes
Prospective?
Yes
Prospective Cohort Study
No
Retrospective Cohort Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer

Gypsyamber D'Souza, Ph.D., Aimee R. Kreimer, Ph.D., Raphael Viscidi, M.D., Michael Pawlita, M.D., Carole Fakhry, M.D., M.P.H., Wayne M. Koch, M.D., William H. Westra, M.D., and Maura L. Gillison, M.D., Ph.D.

ABSTRACT

BACKGROUND

Substantial molecular evidence suggests a role for human papillomavirus (HPV) in the pathogenesis of oropharyngeal squamous-cell carcinoma, but epidemiologic data have been inconsistent.

METHODS

We performed a hospital-based, case–control study of 100 patients with newly diagnosed oropharyngeal cancer and 200 control patients without cancer to evaluate associations between HPV infection and oropharyngeal cancer. Multivariate logistic-regression models were used for case–control comparisons.

RESULTS

A high lifetime number of vaginal-sex partners (26 or more) was associated with oropharyngeal cancer (odds ratio, 3.1; 95% confidence interval [CI], 1.5 to 6.5), as was a high lifetime number of oral-sex partners (6 or more) (odds ratio, 3.4; 95% CI, 1.3 to 8.8). The degree of association increased with the number of vaginal-sex and oral-sex partners (P values for trend, 0.002 and 0.009, respectively). Oropharyngeal cancer was significantly associated with oral HPV type 16 (HPV-16) infection (odds ratio, 14.6; 95% CI, 6.3 to 36.6), oral infection with any of 37 types of HPV (odds ratio, 12.3; 95% CI, 5.4 to 26.4), and seropositivity for the HPV-16 L1 capsid protein (odds ratio, 32.2; 95% CI, 14.6 to 71.3). HPV-16 DNA was detected in 72% (95% CI, 62 to 81) of 100 paraffin-embedded tumor specimens, and 64% of patients with cancer were seropositive for the HPV-16 oncoprotein E6, E7, or both. HPV-16 L1 seropositivity was highly associated with oropharyngeal cancer among subjects with a history of heavy tobacco and alcohol use (odds ratio, 19.4; 95% CI, 3.3 to 113.9) and among those without such a history (odds ratio, 33.6; 95% CI, 13.3 to 84.8). The association was similarly increased among subjects with oral HPV-16 infection, regardless of their tobacco and alcohol use. By contrast, tobacco and alcohol use increased the association with oropharyngeal cancer primarily among subjects without exposure to HPV-16.

CONCLUSIONS

Oral HPV infection is strongly associated with oropharyngeal cancer among subjects with or without the established risk factors of tobacco and alcohol use.

From the Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health (G.D.); the Departments of Pediatrics (R.V.), Otolaryngology–Head and Neck Surgery (C.F., W.M.K.), and Pathology (W.H.W.), Johns Hopkins Hospital; and the Division of Viral Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University (M.L.G.) — all in Baltimore; the Division of Cancer Prevention, National Cancer Institute, Bethesda, MD (A.R.K.); and the Infection and Cancer Control Program, German Cancer Research Center, Heidelberg, Germany (M.P.). Address reprint requests to Dr. Gillison at Johns Hopkins University, Cancer Research Bldg. I, Rm. 3M 54A, 1650 Orleans St., Baltimore, MD 21231, or to gillima@jhmi.edu.

N Engl J Med 2007;356:1944-56.

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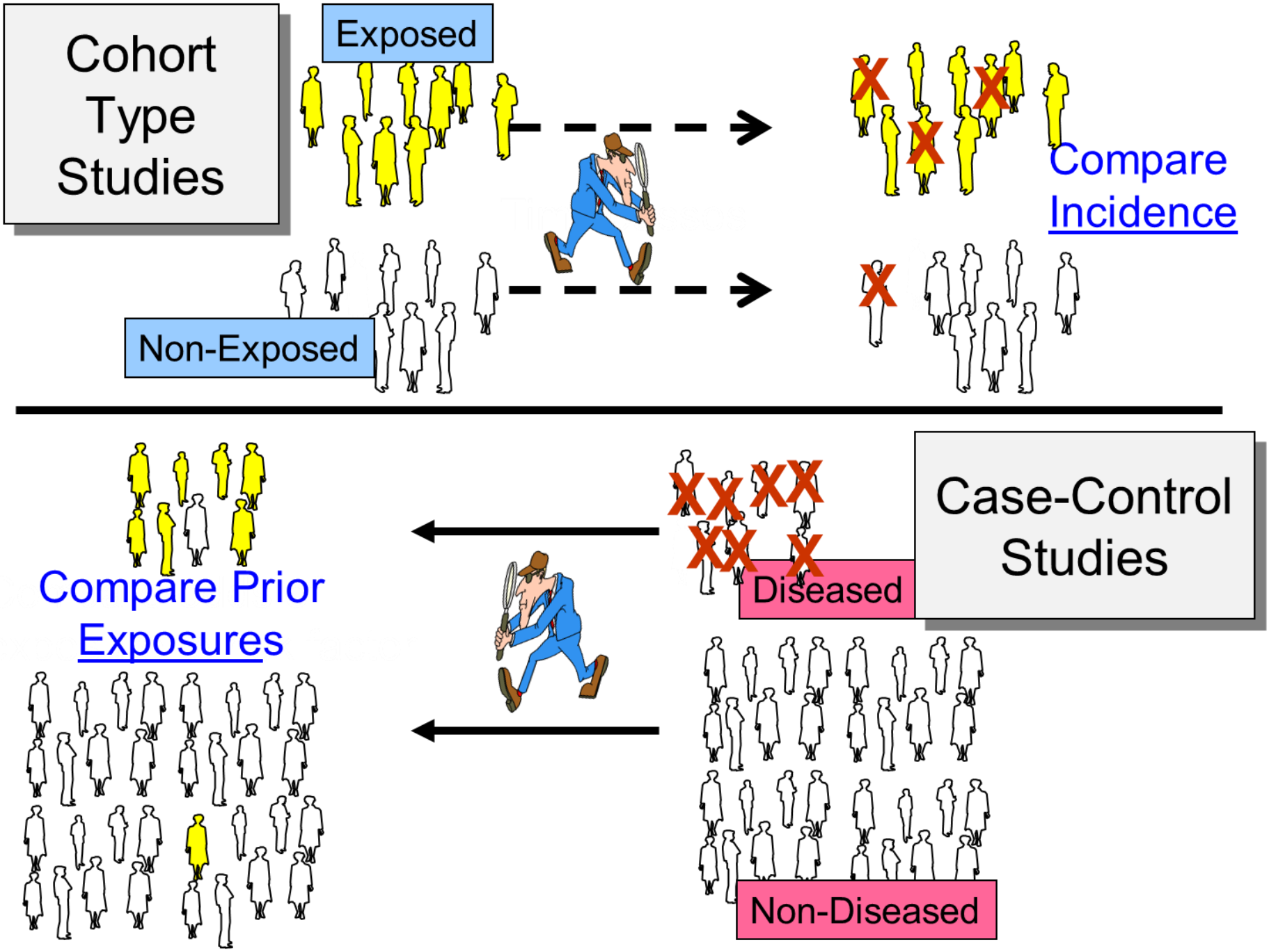
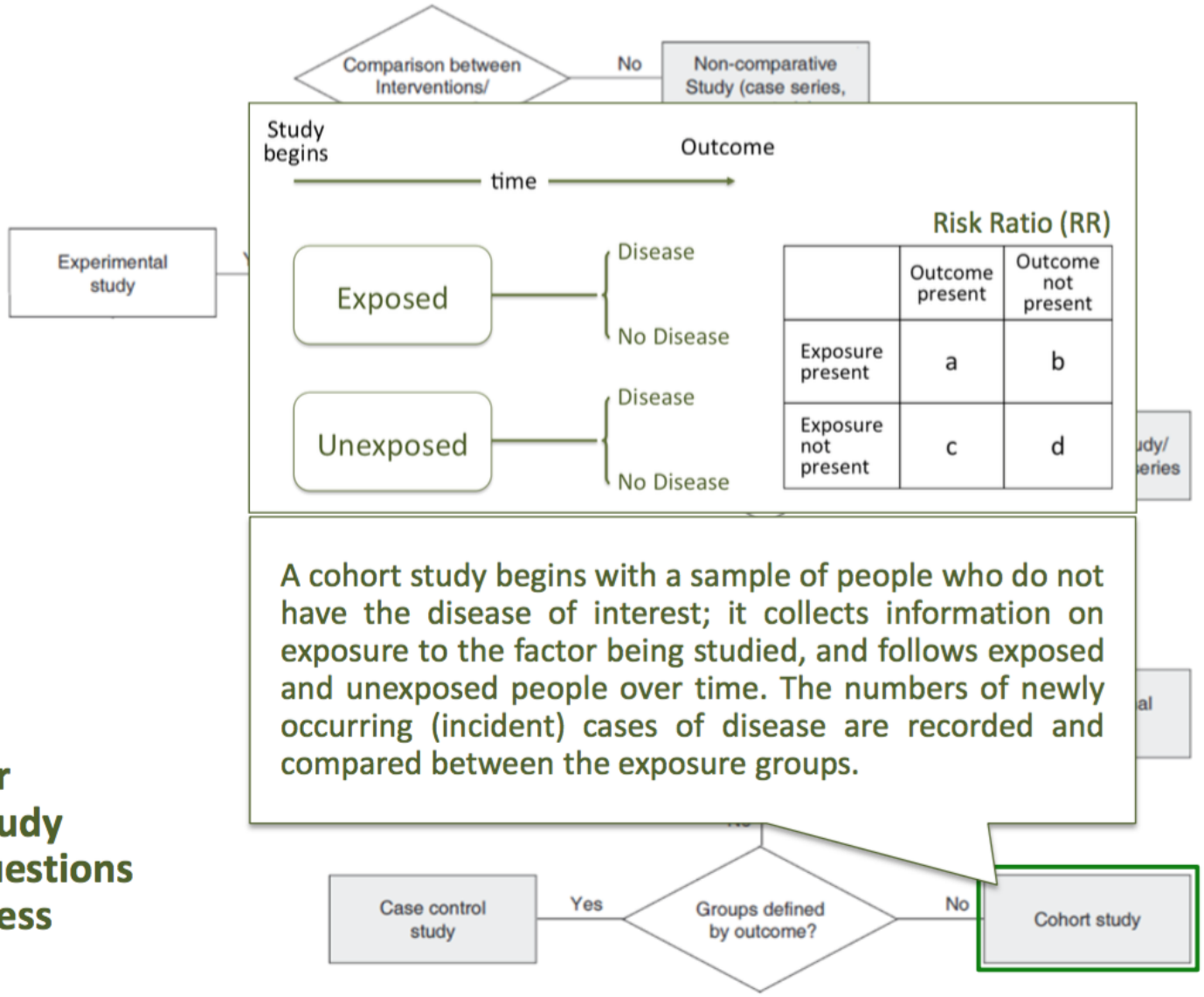
Table 1. Explanatory Variables for Patients with Oropharyngeal Cancer and Control Patients.*

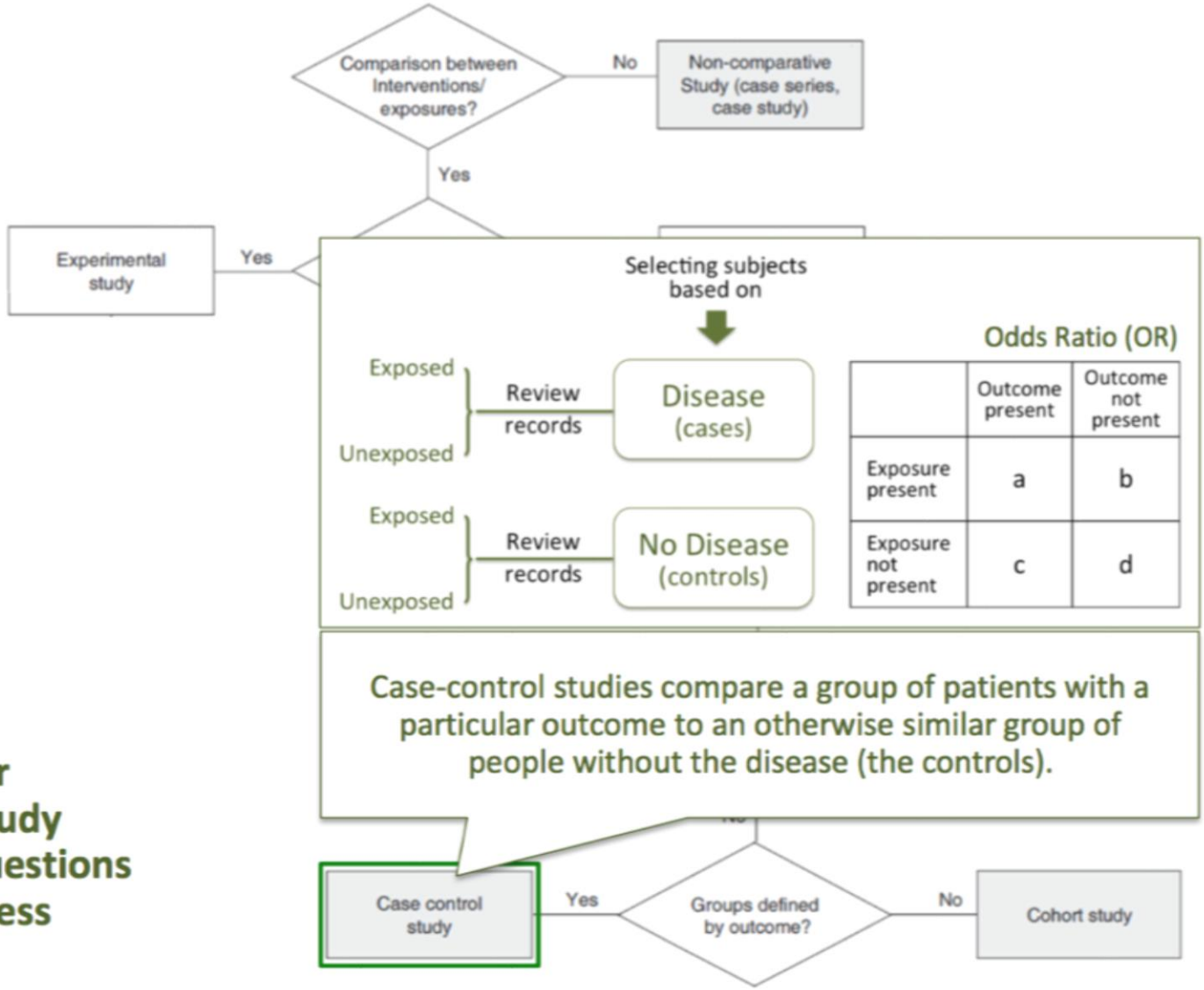
Explanatory Variable	Patients with Oropharyngeal Cancer (N=100)	Control Patients (N=200)	Unadjusted Odds Ratio (95% CI)†
	number (percent)		
Demographic characteristics			
Sex			
Female	14 (14)	28 (14)	1.0
Male	86 (86)	172 (86)	1.0 (0.5–2.0)
Age			
<50 yr	34 (34)	68 (34)	1.0
50–64 yr	51 (51)	102 (51)	1.0 (0.6–1.7)
≥65 yr	15 (15)	30 (15)	1.0 (0.5–2.0)
Highest educational level			
Some high school	11 (11)	15 (8)	1.0
High-school graduate or some college	41 (41)	71 (36)	0.8 (0.3–1.9)
College graduate	48 (48)	114 (57)	0.6 (0.3–1.4)‡
Race or ethnic group§			
White, non-Hispanic	87 (87)	171 (86)	1.0
Black, non-Hispanic	9 (9)	17 (8)	1.0 (0.5–2.4)
Other	4 (4)	12 (6)	0.7 (0.2–2.1)
Home state			
Maryland	50 (50)	138 (69)	1.0
Other	50 (50)	62 (31)	2.2 (1.3–3.6)
Oral hygiene			
Tooth loss			
None	62 (62)	163 (82)	1.0
Some	16 (16)	20 (10)	2.1 (1.0–4.4)
Complete	22 (22)	17 (8)	3.4 (1.7–6.8)¶
Mouthwash use during past yr			
<1 time/day	55 (55)	126 (63)	1.0
1–2 times/day	40 (40)	71 (36)	1.3 (0.8–2.1)
3–4 times/day	5 (5)	3 (2)	3.8 (0.9–16.5)‖


Cohort Type Studies
Exposed
Non-Exposed
Compare Incidence
Case-Control Studies
Diseased
Non-Diseased
Compare Prior Exposures

Algorithm for classifying study design for questions of effectiveness



Algorithm for classifying study design for questions of effectiveness



SIGN
Scottish Intercollegiate Guidelines Network

Table 3. Association of Oropharyngeal Cancer with Exposure to HPV and with Biomarkers of Cancer Associated with HPV-16.

Measure of HPV Exposure or Disease	Prevalence		Odds Ratio (95% CI)	
	Case Patients (N=100)	Control Patients (N=200)	Unadjusted	Adjusted*
	number (percent)			
HPV-16 L1 serologic status				
Seronegative	43 (43)	186 (93)	1.00	1.00
Seropositive	57 (57)	14 (7)	17.6 (8.8–34.5)	32.2 (14.6–71.3)
Oral HPV-16 infection†				
Negative	68 (68)	192 (96)	1.00	1.00
Positive	32 (32)	8 (4)	11.3 (5.0–25.7)	14.6 (6.3–36.6)
Any oral HPV infection‡				
Negative	63 (63)	189 (94)	1.00	1.00
Positive	37 (37)	11 (6)	10.0 (4.8–20.7)	12.3 (5.4–26.4)
HPV-16 E6 or E7 serologic status				
Seronegative for E6 and E7	36 (36)	192 (96)	1.00	1.00
Seropositive for E6 or E7	64 (64)	8 (4)	33.3 (16.2–68.6)	58.4 (24.2–138.3)
HPV-16 DNA in tumor				
Absent	28 (28)	—	—	—
Present	72 (72)	—	—	—

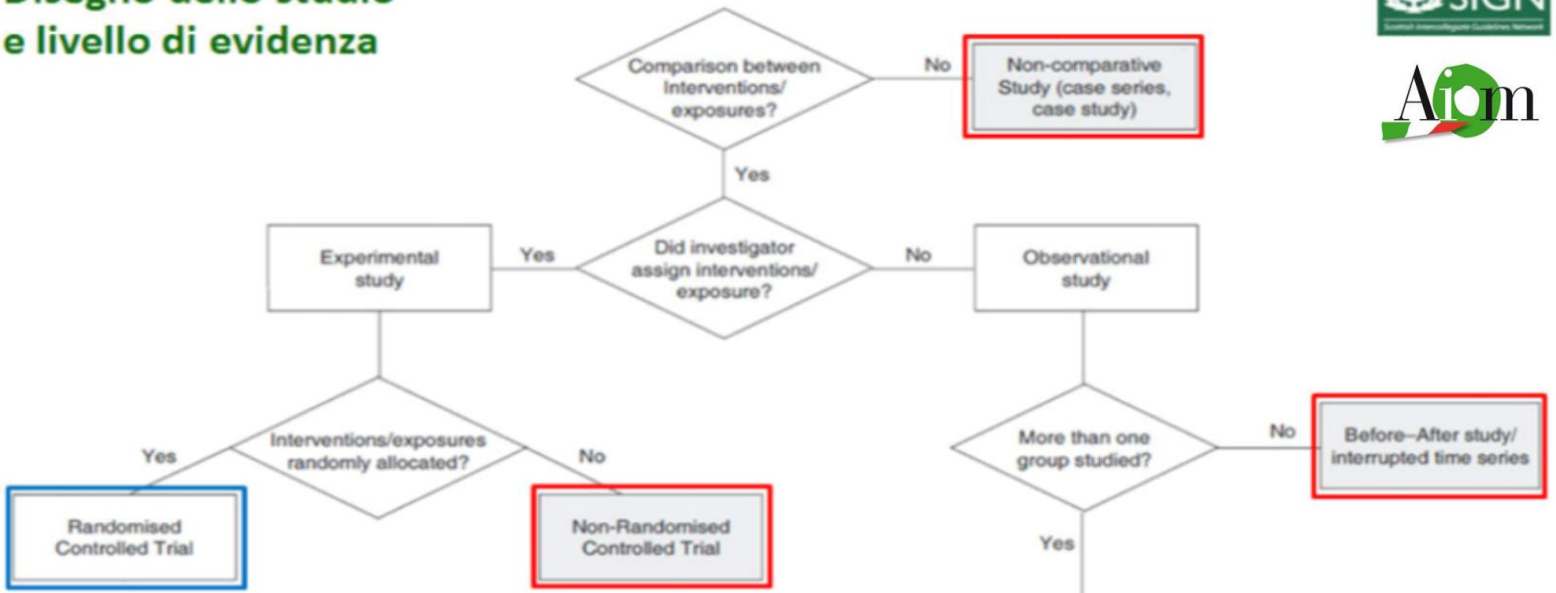
Table 2. Associations of Oropharyngeal Cancer with Sexual Behaviors.*

Sexual Behavior	Patients with Oropharyngeal Cancer (N=100)	Control Patients (N=200)	Adjusted Odds Ratio (95% CI)†	
			All Patients	HPV-16+ Patients‡
	number (percent)			
Lifetime no. of vaginal-sex partners				
0–5	31 (31)	108 (54)	1.0	1.0
6–25	41 (41)	63 (32)	2.2 (1.2–4.0)	2.7 (1.4–5.5)
≥26	28 (28)	29 (14)	3.1 (1.5–6.5)§	4.2 (1.8–9.4)¶
Lifetime no. of oral-sex partners				
0	12 (12)	38 (19)	1.0	1.0
1–5	46 (46)	110 (55)	1.9 (0.8–4.5)	3.8 (1.0–14.0)
≥6	42 (42)	52 (26)	3.4 (1.3–8.8)‖	8.6 (2.2–34.0)**
Anal sex				
No	55 (55)	129 (64)	1.0	1.0
Yes	45 (45)	71 (36)	1.3 (0.8–2.2)	1.6 (0.9–2.8)
Casual-sex partner††				
No	42 (42)	120 (60)	1.0	1.0
Yes	58 (58)	80 (40)	1.7 (1.0–3.0)	2.4 (1.2–4.7)
Age at first intercourse				
18 yr or older	30 (30)	87 (44)	1.0	1.0
17 yr or younger	70 (70)	113 (56)	1.3 (0.7–2.3)	2.1 (1.1–3.6)
Condom use				
Usually or always	28 (28)	90 (45)	1.0	1.0
Never or rarely	72 (72)	110 (55)	2.2 (1.2–3.8)	2.1 (1.1–4.0)

STUDI OSSERVAZIONALI

EPIDEMIOLOGICI	**Before-After**	**valutazione del problema prima e dopo un intervento**
	Cross-sectional	**valutazione del problema in una finestra temporale singola e definita**
	Case-control	**indentificazione dei predittori di un determinato outcome**
	Cohort	**identificazione dell'incidenza di un particolare problema nel tempo**
TERAPEUTICI	**Non comparativi**	**valutazione degli outcome dopo/con un determinato trattamento**
	Comparativi	**confronto degli outcome tra gruppi che hanno ricevuto diverso trattamento**

Disegno dello studio e livello di evidenza



1 = studi randomizzati

2 = studi di caso-controllo e studi di coorte

3 = serie di casi; studi osservazionali di altro tipo

4 = opinione di esperti

*adattata da SIGN (Algorithm for classifyingstudy design for questions of effectiveness)

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*.

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**

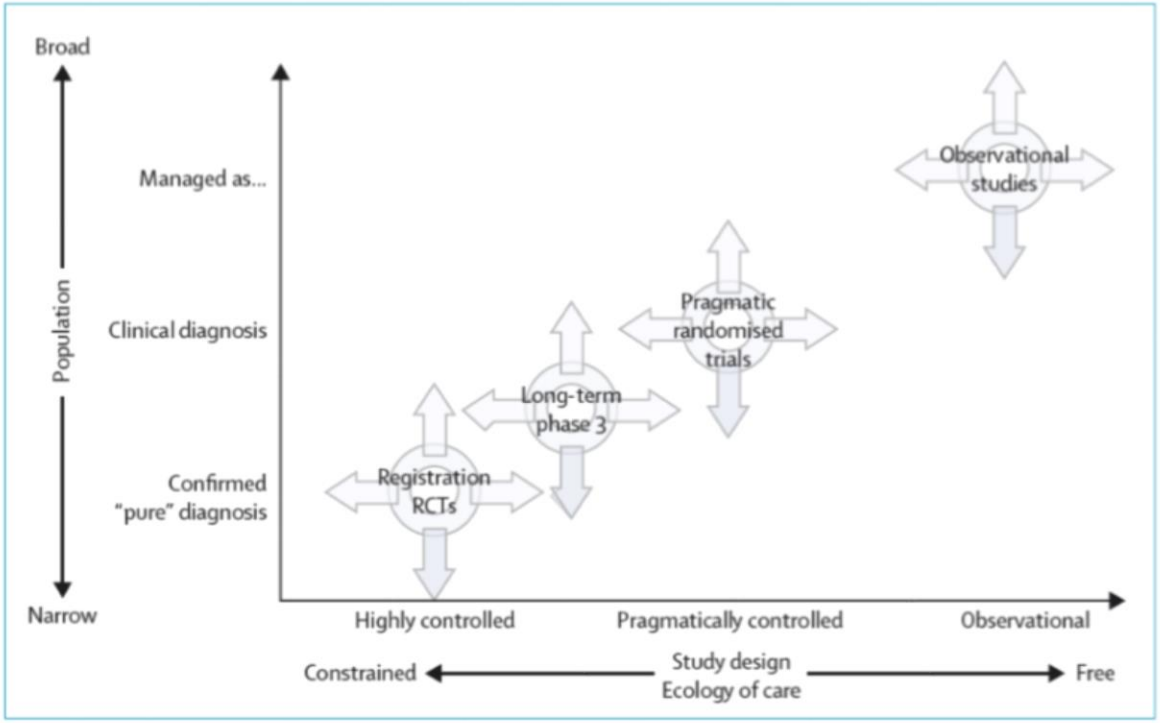


Figure 1: A conceptual framework for therapeutic research

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?

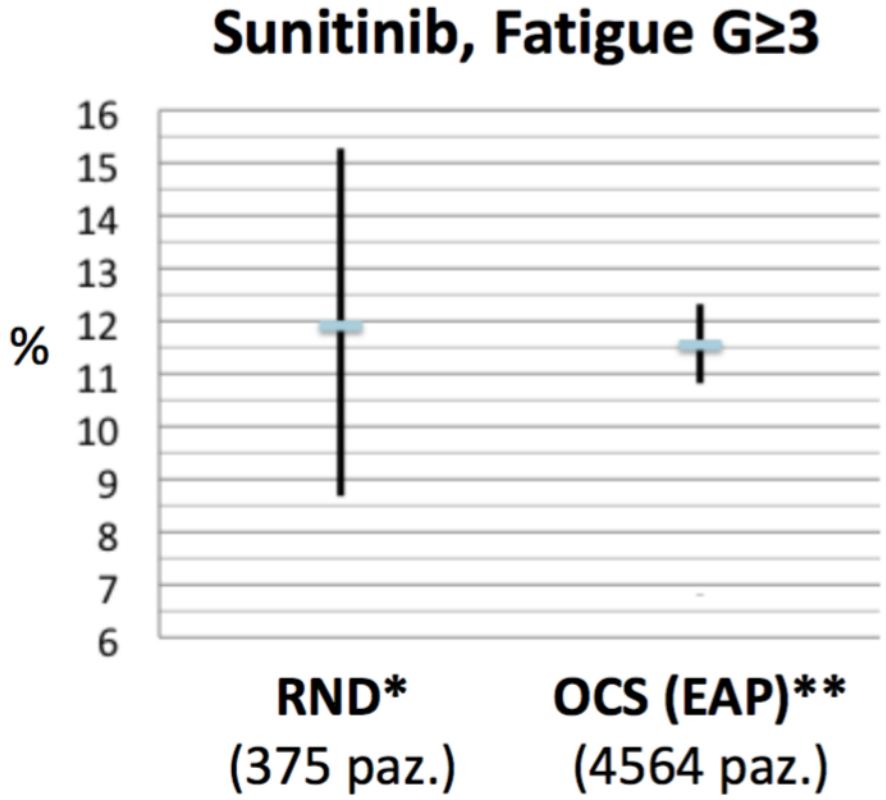
An OCS is an analysis of a group of individuals who have specific features in common and who are followed over a defined period of time.

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.

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

From Randomized Controlled Trials to Observational Studies

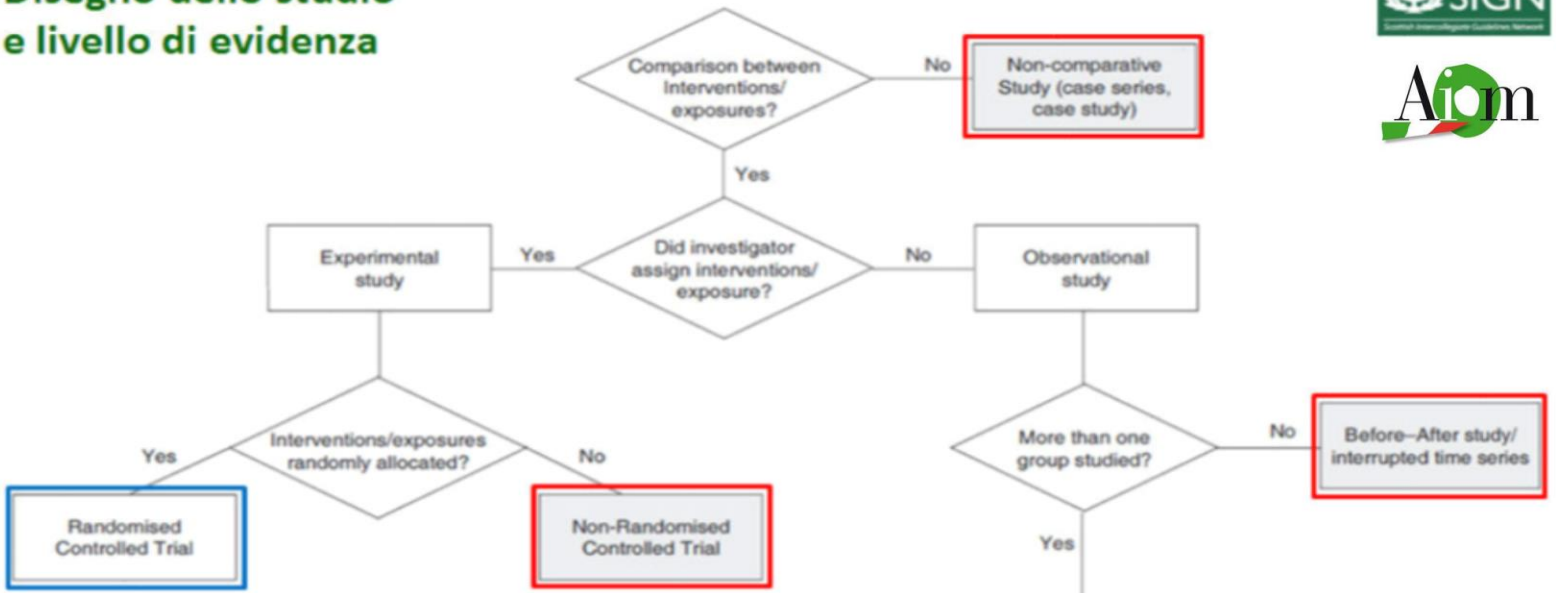
Stuart L. Silverman, MD

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

Table 1 Randomized Controlled Trial Methodology

Strengths	Limitations
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	

Disegno dello studio e livello di evidenza



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4 = opinione di esperti

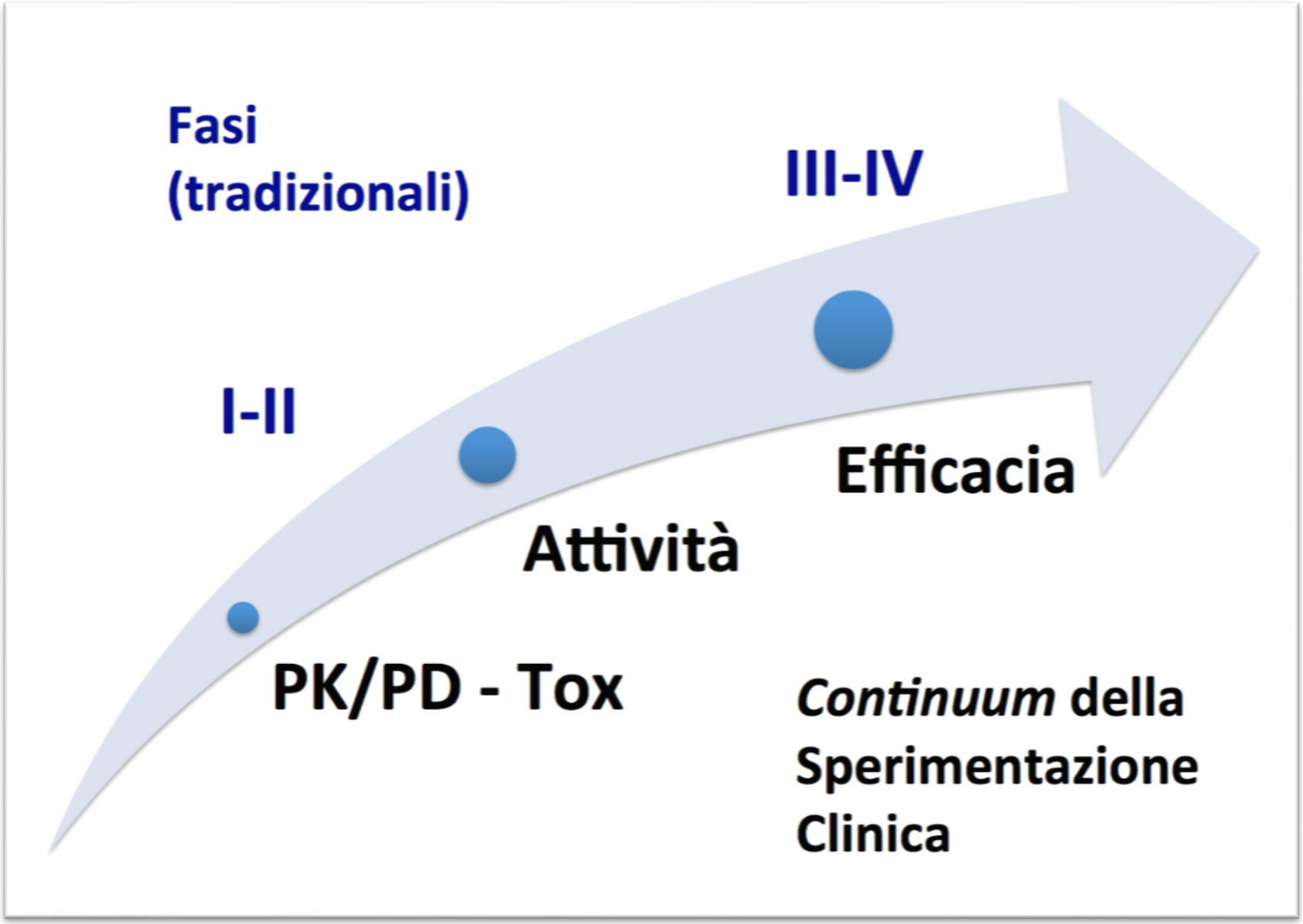
*adattata da SIGN (Algorithm for classifyingstudy design for questions of effectiveness)

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.

STUDI SPERIMENTALI

SPERIMENTALI	**Non comparativi**	**valutazione degli outcome dopo/con un determinato trattamento**
	Comparativi	**confronto degli outcome tra gruppi che hanno ricevuto diverso trattamento**


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

VOLUME 30 · NUMBER 6 · FEBRUARY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

STATISTICS IN ONCOLOGY

Design Issues in Randomized Phase II/III Trials

Edward L. Korn, Boris Freidlin, Jeffrey S. Abrams, and Susan Halabi

Edward L. Korn, Boris Freidlin, and Jeffrey S. Abrams, National Cancer Institute, Bethesda, MD; and Susan Halabi, Duke University Medical Center, Durham, NC.

Submitted July 29, 2011; accepted November 22, 2011; published online ahead of print at www.jco.org on January 23, 2012.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Edward L. Korn, PhD, Biometric Research Branch, EPN-8129, National Cancer Institute,

A B S T R A C T

Phase II trials are used to show sufficient preliminary activity of a new treatment (in single-arm designs or randomized screening designs) or to select among treatments with demonstrated activity (in randomized selection designs). The treatments prioritized in a phase II trial are then tested definitively against a control treatment in a randomized phase III trial. Randomized phase II/III trials use an adaptive trial design that combines these two types of trials in one, with potential gains in time and reduced numbers of patients required to be treated. Two key considerations in designing a phase II/III trial are whether to suspend accrual while the phase II data mature and the choice of phase II target treatment effect. We discuss these phase II/III design parameters, give examples of phase II/III trials, and provide recommendations concerning efficient phase II/III trial designs.

J Clin Oncol 30:667-671. *© 2012 by American Society of Clinical Oncology*

Table 1. Examples of Typical Trial Design Parameters for Stand-Alone Phase II and III Trials

Trial Type	Primary End Point	One-Sided Type I Error (%)	Power (%)	Target Alternative Hypothesis	Sample Size	No. of Events
Phase III design	OS	2.5	90	9- *v* 12-month median OS; HR, 0.75	600	509
Single-arm phase II design	RR	10	90	5% *v* 20% RR	40	NA
Randomized phase II screening design	PFS	10	90	4- *v* 7-month median PFS; HR, 0.57	100	84
Randomized phase II selection design	PFS	50	90	4- *v* 5.5-month median PFS; HR, 0.73	76	65

Abbreviations: HR, hazard ratio; NA, not applicable; OS, overall survival; PFS, progression-free survival; RR, response rate.

DISEGNI DI STUDI DI FASE II

- **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 $1\text{-}\beta = 90\%$. 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.

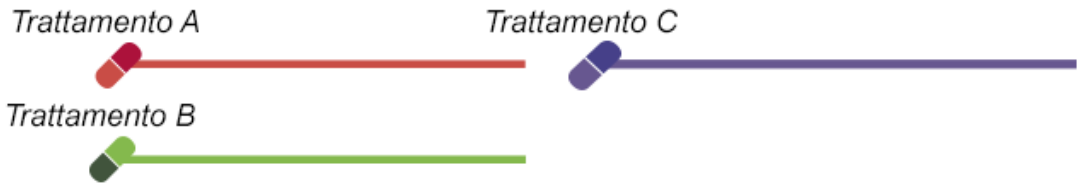
RANDOMIZED PHASE II SELECTION DESIGN

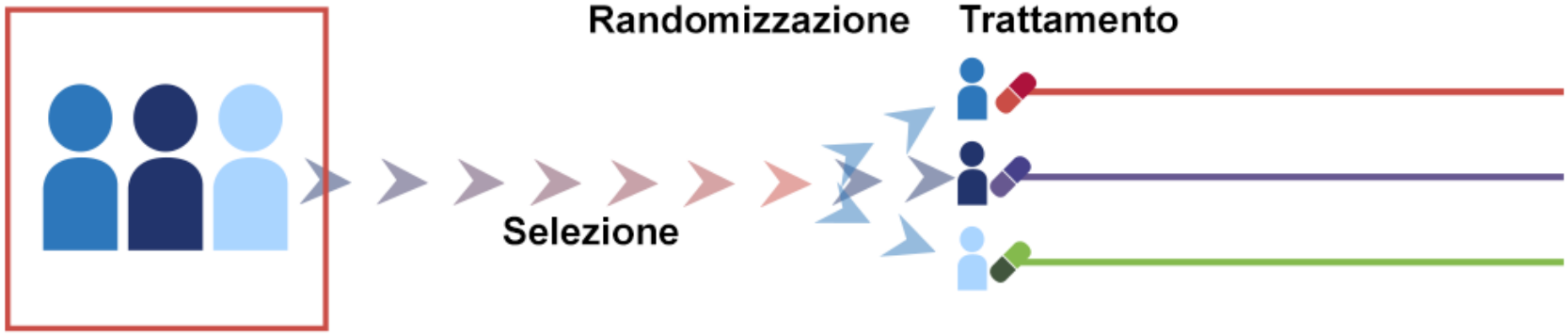
- *K* bracci sperimentali, ***no control arm***
- Selezione del braccio con miglior risposta o controllo di malattia

Simon et al. 1985

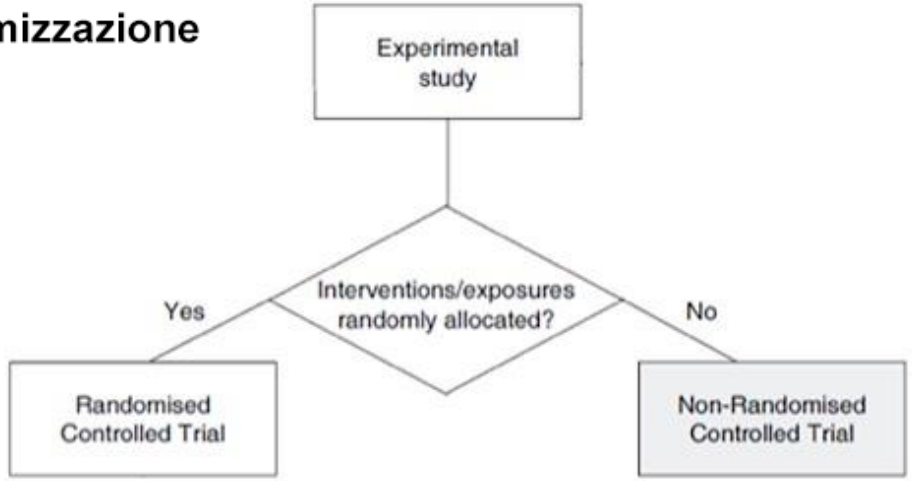
Studio a gruppi paralleli

EUPATI
European Patients' Academy
on Therapeutic Innovation
www.eupati.eu




Randomizzazione
Trattamento
Selezione

Randomizzazione



Minimizzare ***l'allocation bias***, bilanciando i gruppi per fattori prognostici conosciuti e sconosciuti

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

RANDOMIZATION COMPONENTS

Item	Descriptor
Sequence generation	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification)
Allocation concealment	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned
Implementation	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups

Documentazione dell'assegnazione

456 Tabella A6 – *Numeri casuali*

I

PETER ARMITAGE

STATISTICA MEDICA

METODI STATISTICI PER LA RICERCA IN MEDICINA

FELTRINELLI

03	47	43	73	86	36	96	47	36	61	46	98	63	71	62	33	26	16	80	45	60	11	14	10	95
97	74	24	67	62	42	81	14	57	20	42	53	32	37	32	27	07	36	07	51	24	51	79	89	73
16	76	62	27	66	56	50	26	71	07	32	90	79	78	53	13	55	38	58	59	88	97	54	14	10
12	56	85	99	26	96	96	68	27	31	05	03	72	93	15	57	12	10	14	21	88	26	49	81	76
55	59	56	35	64	38	54	82	46	22	31	62	43	09	90	06	18	44	32	53	23	83	01	30	30
16	22	77	94	39	49	54	43	54	82	17	37	93	23	78	87	35	20	96	43	84	26	34	91	64
84	42	17	53	31	57	24	55	06	88	77	04	74	47	67	21	76	33	50	25	83	92	12	06	76
63	01	63	78	59	16	95	55	67	19	98	10	50	71	75	12	86	73	58	07	44	39	52	38	79
33	21	12	34	29	78	64	56	07	82	52	42	07	44	38	15	51	00	13	42	99	66	02	79	54
57	60	86	32	44	09	47	27	96	54	49	17	46	09	62	90	52	84	77	27	08	02	73	43	28
18	18	07	92	46	44	17	16	58	09	79	83	86	19	62	06	76	50	03	10	55	23	64	05	05
26	62	38	97	75	84	16	07	44	99	83	11	46	32	24	20	14	85	88	45	10	93	72	88	71
23	42	40	64	74	82	97	77	77	81	07	45	32	14	08	32	98	94	07	72	93	85	79	10	75
52	36	28	19	95	50	92	26	11	97	00	56	76	31	38	80	22	02	53	53	86	60	42	04	53
37	85	94	35	12	83	39	50	08	30	42	34	07	96	88	54	42	06	87	98	35	85	29	48	39
70	29	17	12	13	40	33	20	38	26	13	89	51	03	74	17	76	37	13	04	07	74	21	19	30
56	62	18	37	35	96	83	50	87	75	97	12	25	93	47	70	33	24	03	54	97	77	46	44	80
99	49	57	22	77	88	42	95	45	72	16	64	36	16	00	04	43	18	66	79	94	77	24	21	90
16	08	15	04	72	33	27	14	34	09	45	59	34	68	49	12	72	07	34	45	99	27	72	95	14
31	16	93	32	43	50	27	89	87	19	20	15	37	00	49	52	85	66	60	44	38	68	88	11	80
68	34	30	13	70	55	74	30	77	40	44	22	78	84	26	04	33	46	09	52	68	07	97	06	67
74	57	25	65	76	59	29	97	68	60	71	91	38	67	54	13	58	18	24	76	15	54	55	95	52
27	42	37	86	53	48	55	90	65	72	96	57	69	36	10	96	46	92	42	45	97	60	49	04	91

Statistica medica

- ***A partire dalla prima riga, proseguire verso destra e quindi alle righe successive***
- ***Numeri dispari: braccio A; numeri pari: braccio B.***

Generatore di numeri casuali compresi fra 0 e un numero n a scelta

	A	B	C	D	E	F	G	H	I	J	K
1	**Generazione di numeri casuali compresi fra 1 e n**										
2											
3	Numero complessivo di elementi nella popolazione:					200					
4	(premi F9 per ottenere una nuova serie di numeri casuali)										
5											
6	18	14	19	14	13	18	7	13	7	1	
7	7	1	16	13	12	16	14	10	5	17	
8	1	13	13	6	14	8	3	6	19	15	
9	10	20	2	11	10	7	9	18	16	15	
10	12	13	16	5	12	6	14	11	2	2	
11	17	4	7	3	16	1	7	13	8	2	
12	18	18	5	14	3	5	9	6	3	12	
13	8	14	11	17	4	4	19	18	10	8	
14	15	18	13	4	5	17	8	10	4	13	
15	7	16	16	14	4	15	15	16	3	15	
16	19	18	3	12	20	11	19	13	16	5	
17	15	1	15	11	6	17	11	15	10	9	
18	7	17	7	16	17	7	15	17	5	10	
19	11	12	2	16	7	18	16	19	10	19	
20	11	8	15	10	1	19	16	8	11	20	
21	5	1	15	1	17	10	20	14	14	5	
22	5	14	3	15	14	8	1	20	16	19	
23	1	13	16	16	17	4	19	5	6	5	
24	7	8	10	2	2	14	9	14	19	7	
25	18	6	7	1	2	14	20	18	12	19	

questo numero può essere modificato a piacere

ATTENZIONE: MANIPOLABILE E NON VERIFICABILE!

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

DISEGNO

Randomizzazione usando la stratificazione

- Gli studi possono essere **stratificati** per più di un fattore, ad esempio, età e sesso.
- Fattori **di stratificazione comuni** comprendono sito, gruppi d'età, esposizione precedente, sesso, e fattori di stile di vita.

DISEGNO

Randomizzazione usando la stratificazione

- **La stratificazione assicura un'assegnazione bilanciata all'interno di ogni combinazione**
- Misura atta ad evitare sbilanciamenti fra i trattamenti a confronto per specifici fattori prognostici
- Possibili vantaggi di tipo organizzativo tra i centri

DISEGNO

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

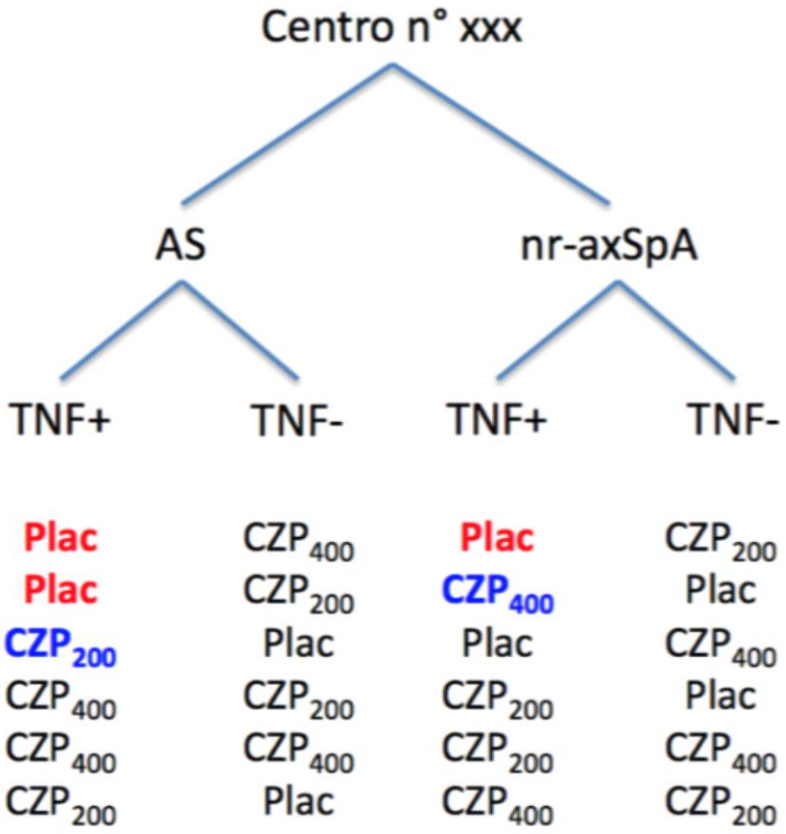
184 Liste di Randomizzazione

(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

LE VIRTU' del PLACEBO- Parte 1

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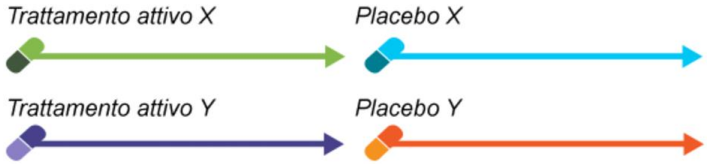
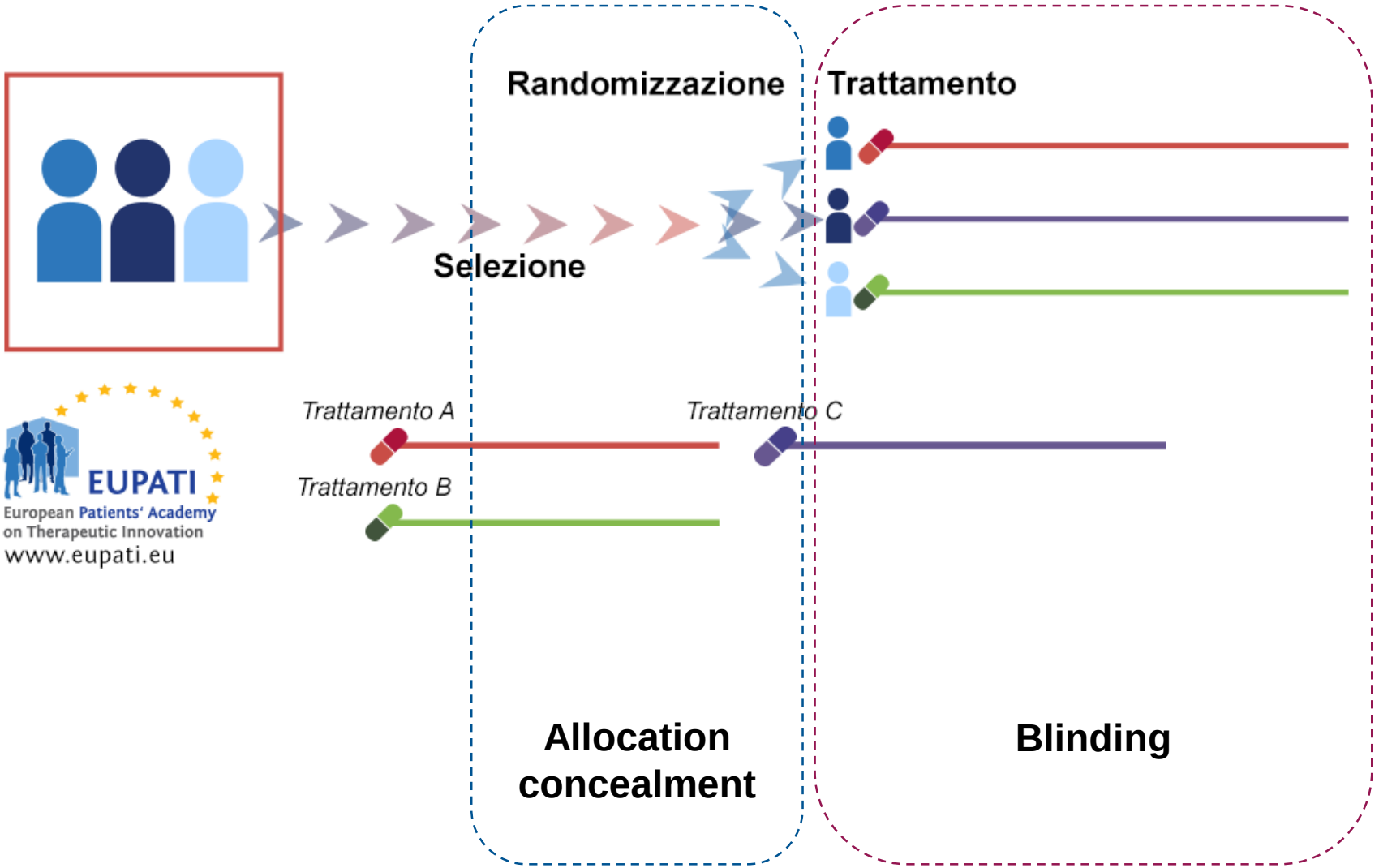


OPPORTUNITA' DEL MASCHERAMENTO

	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

RANDOMIZZAZIONE e MASCHERAMENTO



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.

FORZA DEL DISEGNO

Disegno fattoriale 2x2

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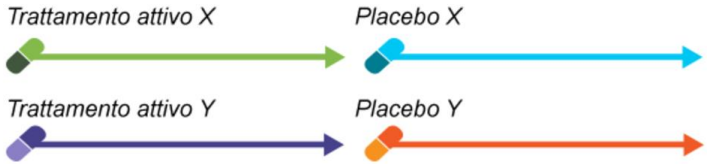
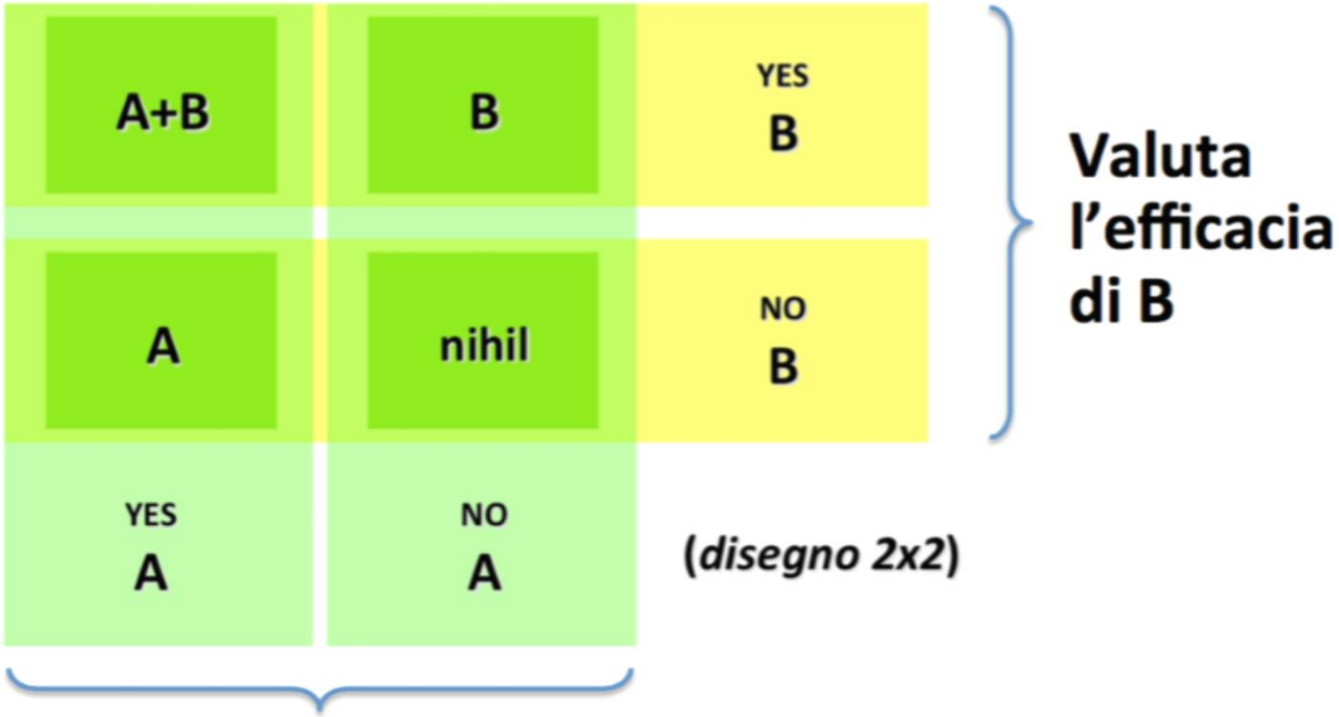


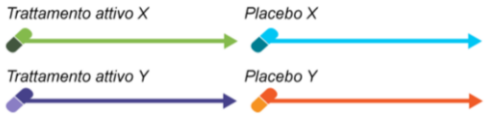
DISEGNO FATTORIALE



(*disegno 2x2*)

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

Disegno fattoriale 2x2



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

A+B	B	YES B
A	nihil	NO B
YES A	NO A	

Valuta l'efficacia di B

(*disegno 2x2*)

Valuta l'efficacia di A

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	

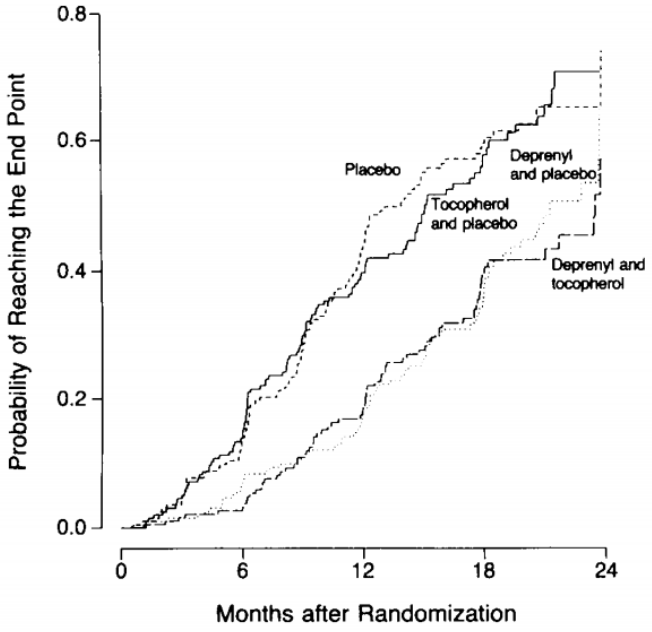
EFFECTS OF TOCOPHEROL AND DEPRENYL ON THE PROGRESSION OF DISABILITY IN EARLY PARKINSON'S DISEASE

THE PARKINSON STUDY GROUP*

Abstract *Background and Methods.* In 1987 we began a multicenter controlled clinical trial of deprenyl (a monoamine oxidase inhibitor) and tocopherol (a component of vitamin E that traps free radicals) in the treatment of early Parkinson's disease. We randomly assigned 800 patients to one of four treatments: placebo, active tocopherol and deprenyl placebo, active deprenyl and tocopherol placebo, or both active drugs. The primary end point was the onset of disability prompting the clinical decision to begin administering levodopa. An interim analysis showed that deprenyl was beneficial (N Engl J Med 1989;321:1364-71). We report the results of tocopherol treatment after a mean (±SD) follow-up of 14±6 months, as well as the follow-up results for deprenyl.

Results. There was no beneficial effect of tocopherol or any interaction between tocopherol and deprenyl. The beneficial effects of deprenyl, which occurred largely during the first 12 months of treatment, remained strong and significantly delayed the onset of disability requiring levodopa therapy (hazard ratio, 0.50; 95 percent confidence interval, 0.41 to 0.62; $P<0.001$). The difference in the estimated median time to the end point was about nine months. The ratings for Parkinson's disease improved during the first three months of deprenyl treatment; the motor performance of deprenyl-treated patients worsened after the treatments were withdrawn.

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. The action of deprenyl that accounts for its beneficial effects remains unclear. (N Engl J Med 1993;328:176-83.)



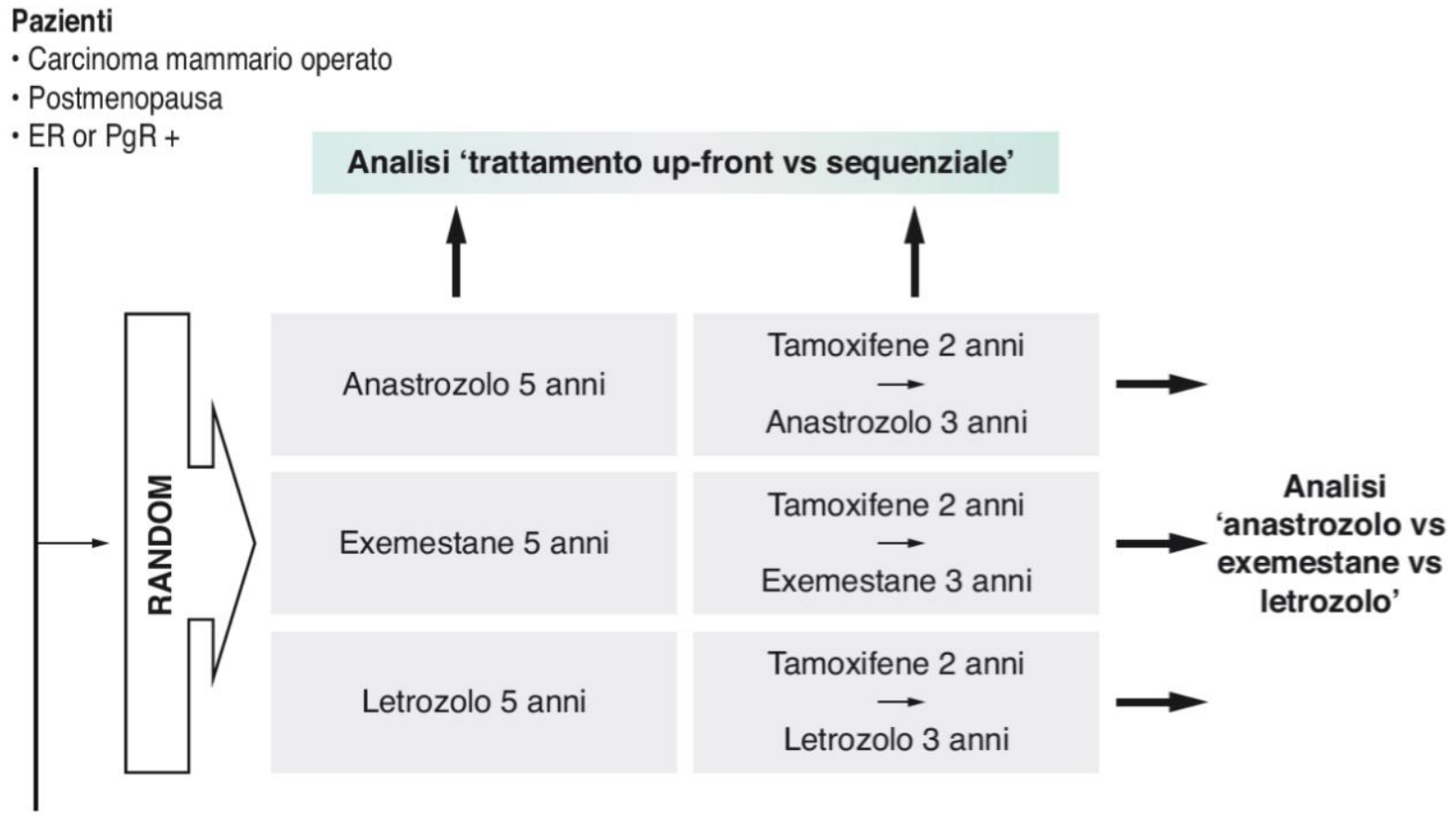
Placebo	199	164	102	50	3
Tocopherol and placebo	202	165	109	48	0
Deprenyl and placebo	202	181	153	81	3
Deprenyl and tocopherol	197	184	143	72	8

Therapeutic Recommendations

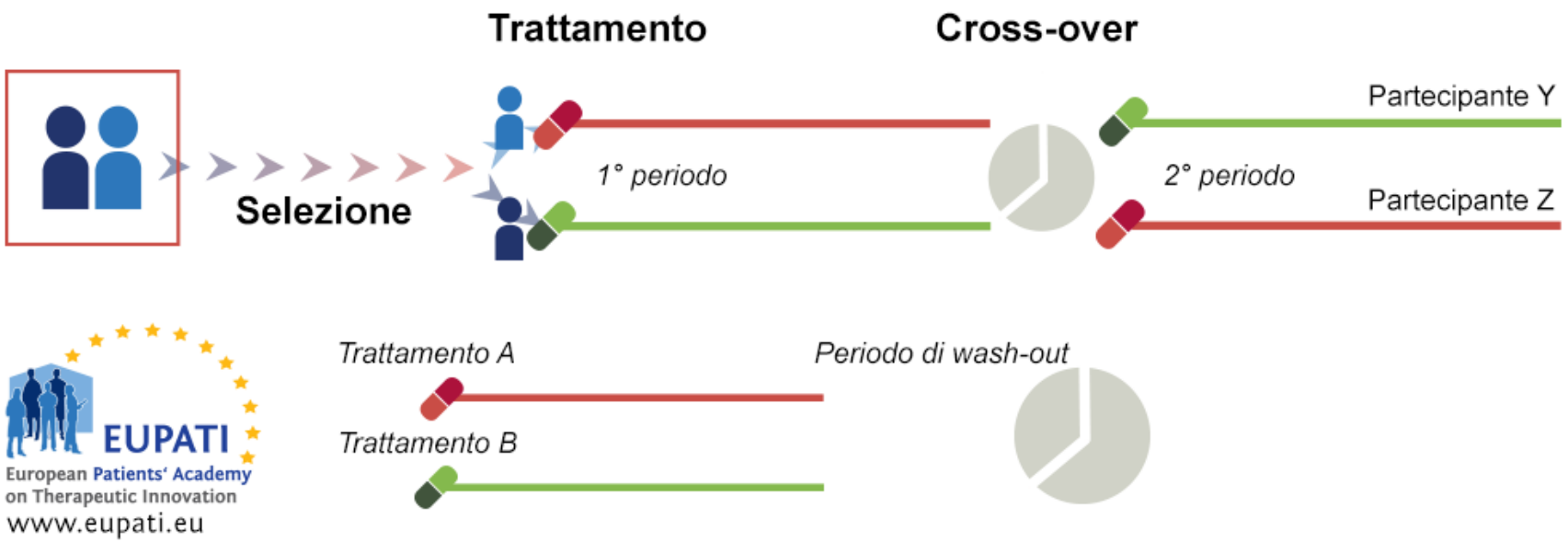
In contrast to the findings from an uncontrolled pilot study,[24] our larger controlled study does not support the use of tocopherol at a dosage of 2000 IU per day in patients who have early Parkinson's disease. The use of deprenyl in a dose of 10 mg per day as monotherapy for early Parkinson's disease delays the development of disability requiring levodopa therapy. Therefore, deprenyl should be considered among the available therapeutic options for the initial treatment of early Parkinson's disease.

Gruppo Italiano Mammella (GIM) Studies

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



Studio clinico cross-over



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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.

DISEGNO

Studio clinico cross-over

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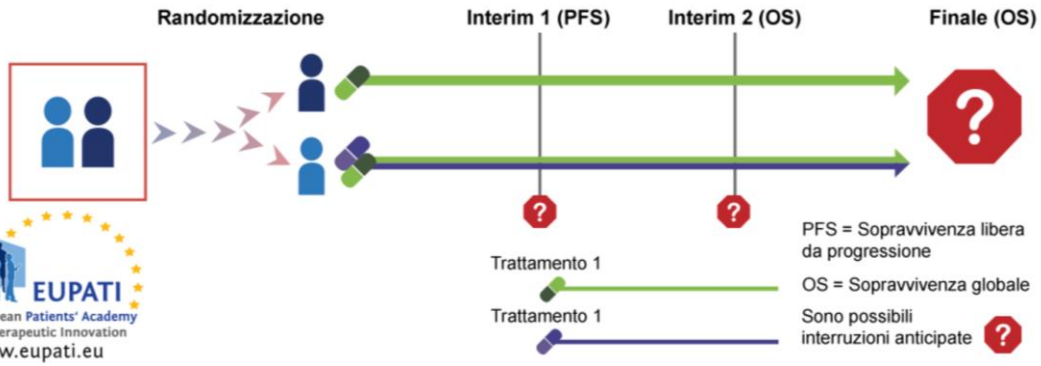
Disegno sequenziale a gruppi

Un esempio di studio che usa un disegno sequenziale a gruppi



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DISEGNO


ATTENZIONE A NON CONFONDERE
UN DISEGNO CROSSOVER…
RND
trattamento A
trattamento B
trattamento B
trattamento A
rilevazione esito
rilevazione esito
…CON UN DISEGNO A BRACCI PARALLELI DI
TIPO SEQUENZIALE
RND
trattamento A
trattamento B
trattamento B
trattamento A
rilevazione esito

VOLUME 32 · NUMBER 14 · MAY 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized, Controlled, Double-Blind, Cross-Over Trial Assessing Treatment Preference for Pazopanib Versus Sunitinib in Patients With Metastatic Renal Cell Carcinoma: PISCES Study

Bernard Escudier, Camillo Porta, Petri Bono, Thomas Powles, Tim Eisen, Cora N. Sternberg, Jürgen E. Gschwend, Ugo De Giorgi, Omi Parikh, Robert Hawkins, Emmanuel Sevin, Sylvie Négrier, Sadya Khan, Jose Diaz, Suman Redhu, Faisal Mehmud, and David Cella

See accompanying editorial on page 1392

Bernard Escudier, Institut Gustave Roussy, Villejuif; Emmanuel Sevin, Centre François Baclesse, Caen; Sylvie Négrier, Leon Berard Cancer Center, Lyon, France; Camillo Porta, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico S. Matteo, Pavia; Cora N. Sternberg, San Camillo Forlanini Hospital, Rome; Ugo De Giorgi, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Italy; Petri Bono, Helsinki University Central Hospital, Helsinki, Finland; Thomas Powles, Barts Experimental Cancer Medicine Centre, Barts Cancer Institute, Queen Mary University of London, London; Tim Eisen, Cambridge University Health Partners, Cambridge; Omi Parikh, Royal Preston Hospital, Lancashire; Robert Hawkins, Christie Cancer Research UK, Manchester; Sadya Khan, Jose Diaz, and Faisal Mehmud, GlaxoSmithKline, Uxbridge, United Kingdom; Jürgen E. Gschwend, Klinikum Rechts der Isar der Technischen Universität München, Munich, Germany; Suman Redhu, GlaxoSmithKline, Collegeville, PA; and David Cella, Northwestern University Feinberg School of Medicine, Chicago, IL.

Published online ahead of print at www.jco.org on March 31, 2014.

Supported by GlaxoSmithKline Pharmaceuticals, Philadelphia, PA.

Presented in part at the 48th Annual Meeting of the American Society of Clinical Oncology, June 1-5, 2012.

ABSTRACT

Purpose

Patient-reported outcomes may help inform treatment choice in advanced/metastatic renal cell carcinoma (RCC), particularly between approved targeted therapies with similar efficacy. This double-blind cross-over study evaluated patient preference for pazopanib or sunitinib and the influence of health-related quality of life (HRQoL) and safety factors on their stated preference.

Patients and Methods

Patients with metastatic RCC were randomly assigned to pazopanib 800 mg per day for 10 weeks, a 2-week washout, and then sunitinib 50 mg per day (4 weeks on, 2 weeks off, 4 weeks on) for 10 weeks, or the reverse sequence. The primary end point, patient preference for a specific treatment, was assessed by questionnaire at the end of the two treatment periods. Other end points and analyses included reasons for preference, physician preference, safety, and HRQoL.

Results

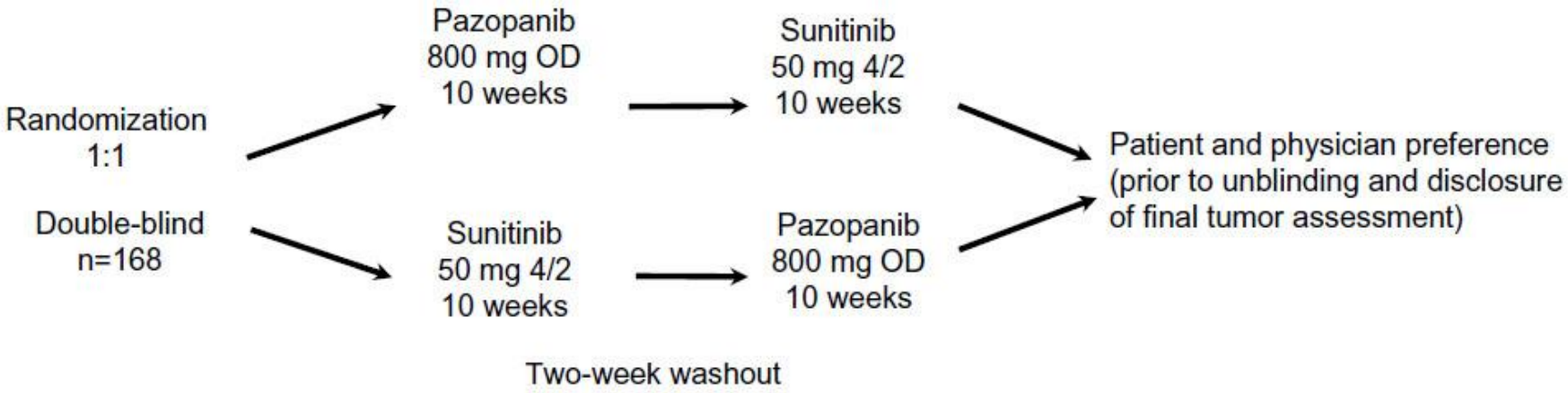
Of 169 randomly assigned patients, 114 met the following prespecified modified intent-to-treat criteria for the primary analysis: exposure to both treatments, no disease progression before cross over, and completion of the preference questionnaire. Significantly more patients preferred pazopanib (70%) over sunitinib (22%); 8% expressed no preference ($P < .001$). All preplanned sensitivity analyses, including the intent-to-treat population, statistically favored pazopanib. Less fatigue and better overall quality of life were the main reasons for preferring pazopanib, with less diarrhea being the most cited reason for preferring sunitinib. Physicians also preferred pazopanib (61%) over sunitinib (22%); 17% expressed no preference. Adverse events were consistent with each drug's known profile. Pazopanib was superior to sunitinib in HRQoL measures evaluating fatigue, hand/foot soreness, and mouth/throat soreness.

Conclusion

This innovative cross-over trial demonstrated a significant patient preference for pazopanib over sunitinib, with HRQoL and safety as key influencing factors.

J Clin Oncol 32:1412-1418. *© 2014 by American Society of Clinical Oncology*

Cross-over trial



Week	0	4	6	8	10	12	14	16	18	20	22
CT assessment	✓					✓					✓
Patient preference											✓
FACIT-Fatigue	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SQLQ	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

DISEGNO

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	studio di non inferiorità
A > B di una quantità Δ di interesse clinico	A < B non oltre una quantità M di rilevanza clinica

DISEGNO

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

STUDI DI EFFICACIA E SCELTA DEL BRACCIO DI CONTROLLO

STUDIO DI SUPERIORITA'

QUESITO: L'uso del nuovo farmaco comporta beneficio clinico per i pazienti?

CONTROLLO: placebo o nulla

QUESITO: Il nuovo farmaco è più efficiente di un altro farmaco?

CONTROLLO: il miglior trattamento disponibile

STUDIO DI NON INFERIORITA'

QUESITO: cosa siamo disposti a perdere in cambio di un minor costo (es. in effetti collaterali/disagio) per il paziente?

CONTROLLO: il miglior trattamento disponibile

Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial

Gérard Zalcman, Julien Mazieres, Jacques Margery, Laurent Greillier, Clarisse Audigier-Valette, Denis Moro-Sibilot, Olivier Molinier, Romain Corre, Isabelle Monnet, Valérie Gounant, Frédéric Rivière, Henri Janicot, Radj Gervais, Chrystèle Locher, Bernard Milleron, Quan Tran, Marie-Paule Lebitasy, Franck Morin, Christian Creveuil, Jean-Jacques Parienti, Arnaud Scherpereel, on behalf of the French Cooperative Thoracic Intergroup (IFCT)

Summary

Background Malignant pleural mesothelioma is an aggressive cancer with poor prognosis, linked to occupational asbestos exposure. Vascular endothelial growth factor is a key mitogen for malignant pleural mesothelioma cells, therefore targeting of vascular endothelial growth factor might prove effective. We aimed to assess the effect on survival of bevacizumab when added to the present standard of care, cisplatin plus pemetrexed, as first-line treatment of advanced malignant pleural mesothelioma.

Methods In this randomised, controlled, open-label, phase 3 trial, we recruited patients aged 18–75 years with unresectable malignant pleural mesothelioma who had not received previous chemotherapy, had an Eastern Cooperative Oncology Group performance status of 0–2, had no substantial cardiovascular comorbidity, were not amenable to curative surgery, had at least one evaluable (pleural effusion) or measurable (pleural tumour solid thickening) lesion with CT, and a life expectancy of >12 weeks from 73 hospitals in France. Exclusion criteria were presence of central nervous system metastases, use of antiaggregant treatments (aspirin ≥325 mg per day, clopidogrel, ticlopidine, or dipyridamole), anti-vitamin K drugs at a curative dose, treatment with low-molecular-weight heparin at a curative dose, and treatment with non-steroidal anti-inflammatory drugs. We randomly allocated patients (1:1; minimisation method used [random factor of 0·8]; patients stratified by histology [epithelioid *vs* sarcomatoid or mixed histology subtypes], performance status score [0–1 *vs* 2], study centre, or smoking status [never smokers *vs* smokers]) to receive intravenously 500 mg/m² pemetrexed plus 75 mg/m² cisplatin with (PCB) or without (PC) 15 mg/kg bevacizumab in 21 day cycles for up to six cycles, until progression or toxic effects. The primary outcome was overall survival (OS) in the intention-to treat population. Treatment was open label. This IFCT-GFPC-0701 trial is registered with ClinicalTrials.gov, number NCT00651456.

Findings From Feb 13, 2008, to Jan 5, 2014, we randomly assigned 448 patients to treatment (223 [50%] to PCB and 225 [50%] to PC). OS was significantly longer with PCB (median 18·8 months [95% CI 15·9–22·6]) than with PC (16·1 months [14·0–17·9]; hazard ratio 0·77 [0·62–0·95]; p=0·0167). Overall, 158 (71%) of 222 patients given PCB and 139 (62%) of 224 patients given PC had grade 3–4 adverse events. We noted more grade 3 or higher hypertension (51 [23%] of 222 *vs* 0) and thrombotic events (13 [6%] of 222 *vs* 2 [1%] of 224) with PCB than with PC.

Interpretation Addition of bevacizumab to pemetrexed plus cisplatin significantly improved OS in malignant pleural mesothelioma at the cost of expected manageable toxic effects, therefore it should be considered as a suitable treatment for the disease.

Funding Intergroupe Francophone de Cancérologie Thoracique (IFCT).

Lancet 2016; 387: 1405–14

Published Online December 21, 2015 http://dx.doi.org/10.1016/S0140-6736(15)01238-6

This online publication has been corrected. The corrected version first appeared at thelancet.com on Jan 6, 2016

See Comment page 1352

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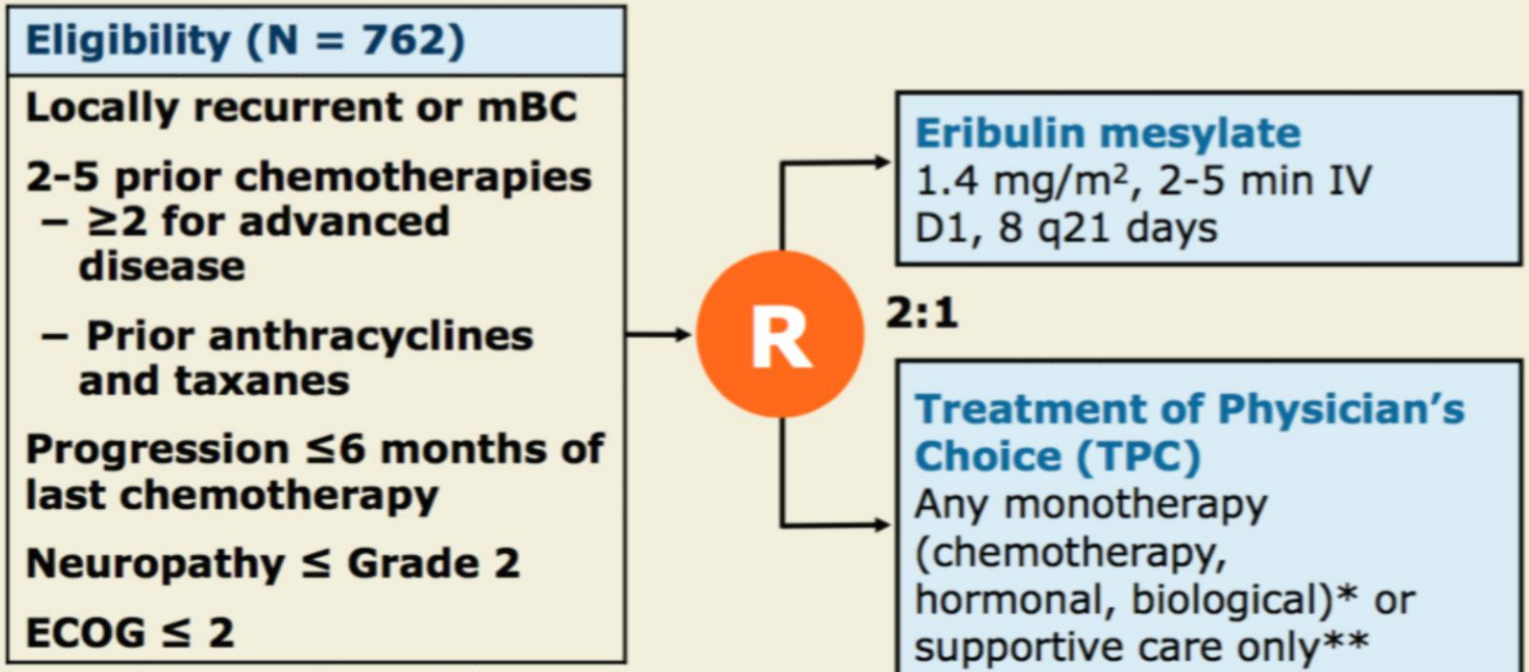
EMBRACE Study Design



* Approved for cancer treatment

** Or palliative treatment or radiotherapy according to local practice

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

LE VIRTU' del PLACEBO- Parte 2

Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-[illegible]ontaining Regimen in Patients With Advanced Transi[illegible] Cell Carcinoma of the Urothelial Tract

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

[illegible]4-4461. © 2009 by American Society of Clinical Oncology

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)
[illegible]1 to 0.99)
[illegible]03

Overall S
0.2
0
Popolazio

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.

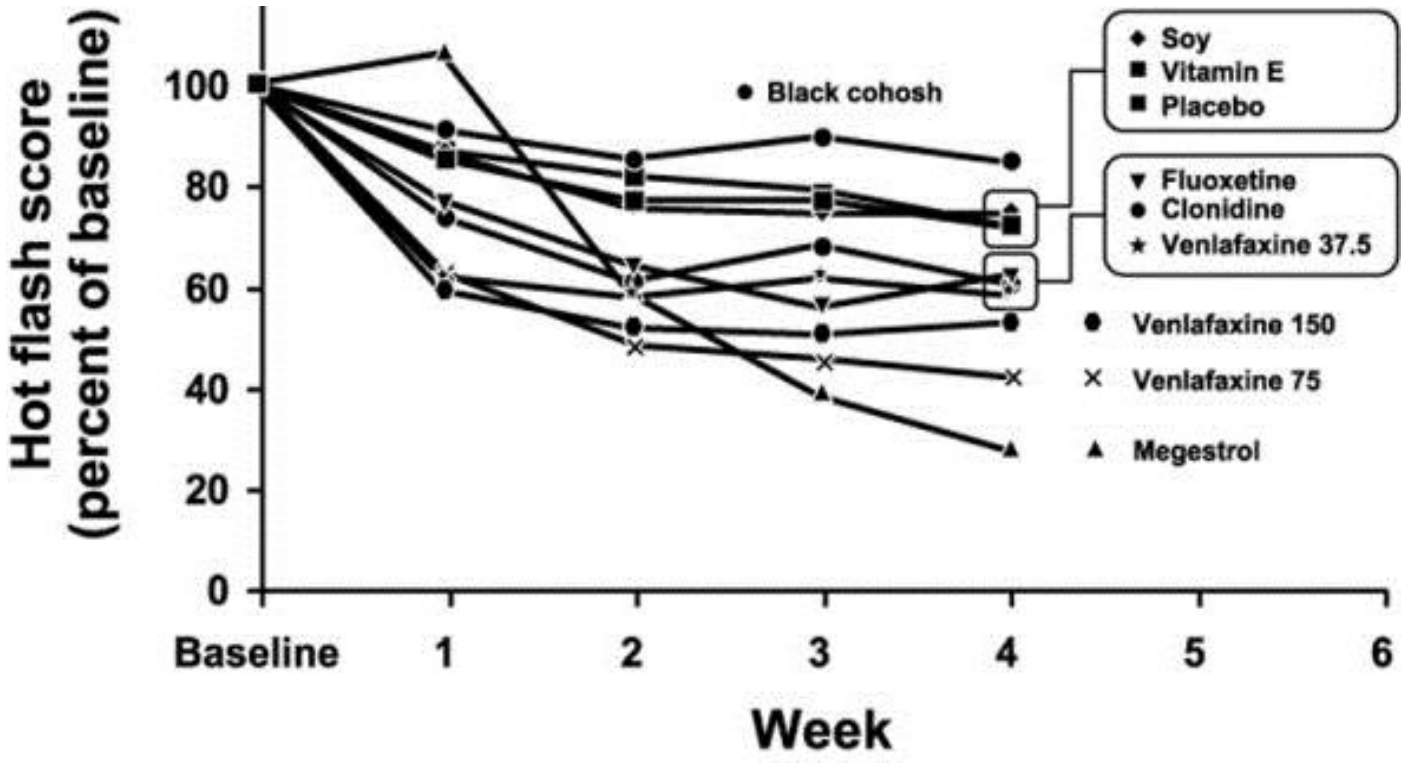
Placebo/No Tx Arms In Absence Of Effective Therapy

- 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

Hot flash score changes from baseline

for a series of 8 randomized, placebo-controlled, double-blind clinical trials in women

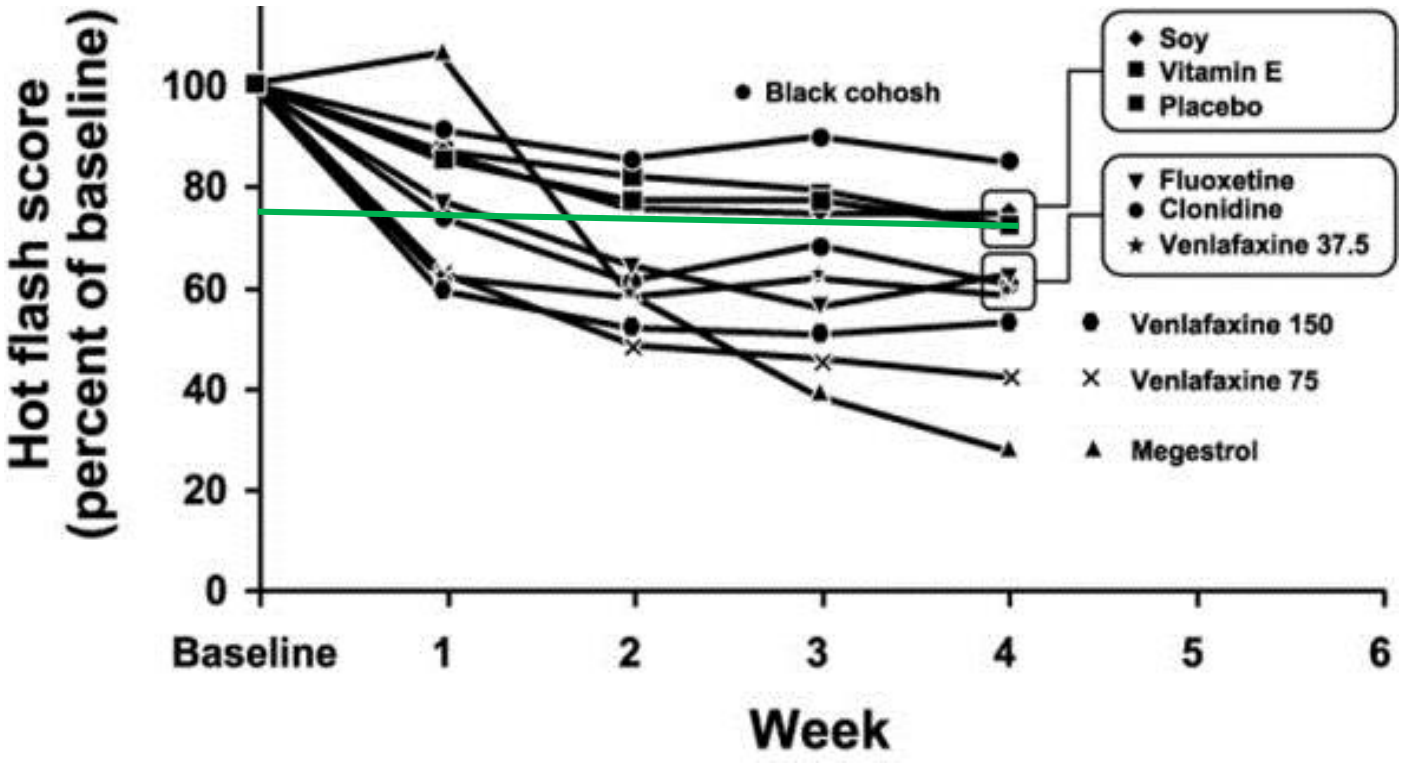


Loprinzi, Mayo Clinic and North Central Cancer Treatment Group hot flash studies: a 20-year experience. Menopause. 2008

Hot flash score changes from baseline

for a series of 8 randomized, placebo-controlled, double-blind clinical trials in women

EFFETTO PLACEBO



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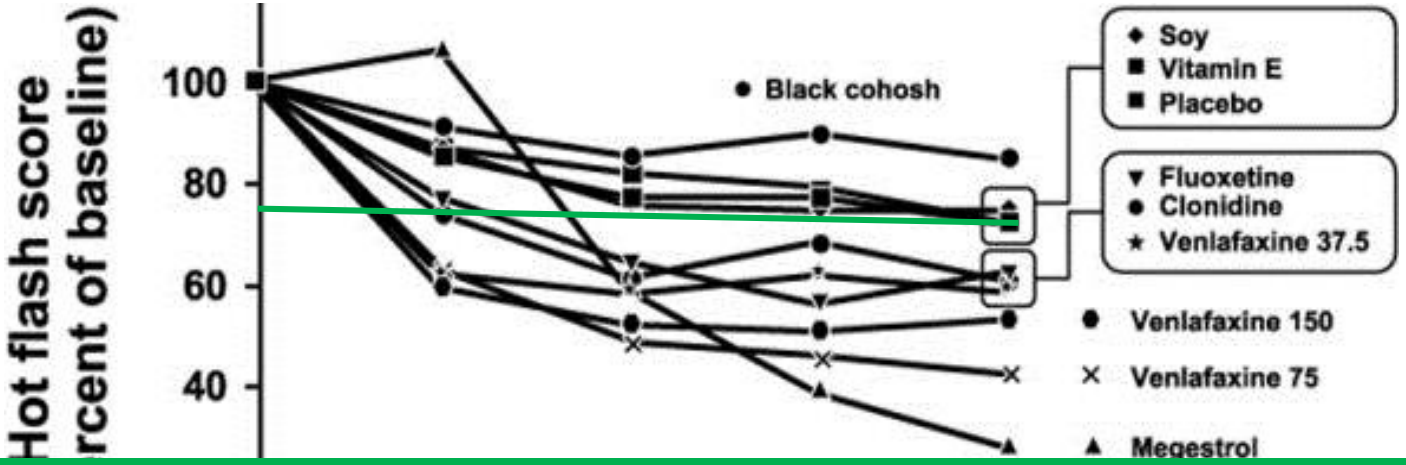

Nei casi in cui l'effetto placebo molto verosimilmente ci sarà, il controllo placebo è IRRINUNCIABILE

Loprinzi, Mayo Clinic and North Central Cancer Treatment Group hot flash studies: a 20-year experience. Menopause. 2008