I diversi tipi di disegno sperimentale

Eva Pagano

SID Academy: Metodologia degli studi clinici in diabetologia

Roma, 29-30 marzo 2017

Types of RCT's - classification schemes

RCTs can be classified according to:

- The object of randomization
- The aspect of interventions being evaluated
- How participants are exposed to interventions
- The number of participants
- Whether investigators and/or participants know which intervention is being studied

From: Alejandro Jadad

Which is the randomisation object?

- Individually randomized trials
  - Eligible individuals are randomized (conventional medical RCTs and many behavioral RCTs)
  - Self-selection of persons volunteering for enrollment

- Cluster randomized trials
  - Clusters (e.g., communities, hospitals) or other aggregates of people (e.g., workplace) are randomized, and all (consenting) persons enrolled

Cluster trial: PROs

- Reduce the threat of “contamination”
- Randomization by group may be the only feasible method of conducting a trial (intervention naturally applied at a cluster level)
- Enhance subject compliance
- Increase administrative efficiency

Cluster RCT may have different design (parallel, factorial, ecc.)

Cluster trial: CONs

- Commonly, prior consent to randomization by individual cluster partecipant is not feasible
- Blinding of a cluster RCT is difficult
- The conclusion may relate to clusters, to individual partecipant or both
- Difficulties associated with prevention trials (ie. low event rate, low compliance)
- Reduced statistical efficiency

Original Article

Integrated Personalized Diabetes Management (PDM): Design of the ProValue Studies: Prospective, Cluster-Randomized, Controlled, Intervention Trials for Evaluation of the Effectiveness and Benefit of PDM in Patients With Insulin-Treated Type 2 Diabetes

Journal of Diabetes Science and Technology
2016, Vol. 10(3) 772–781

DOI: 10.1177/1932296815617487
dst.sagepub.com
SAGE

Bernhard Kulzer, PhD[1], Wilfried Daenschel, MD[2], Ingrid Daenschel, MD[3], Erhard G. Siegel, MD[4], Wendelin Schramm, MD[5], Christopher G. Parkin, MS[6], Diethelm Messinger, MSc[7], Joerg Weissmann, MD[8], Zdenka Djuric, MD[8], Angelika Mueller, PhD[8], Iris Vesper, MS[8], and Lutz Heinemann, PhD[9]

- To determine if use of integrated PDM in daily life improve glycemic control in insulin-treated type 2 diabetes patients:

PDM versus usual care

- 12-months, cluster-randomized, multicentre clinical trials at two different levels of ambulatory care:
  1. General practitioners (PDM-ProValue GP study)
  2. Diabetes specialists (PDM-PRoValue DSP study)
- Study outcome: change in HbA1c from baseline to 12 months

"Although randomization of patients within a clinic or practice site is the most commonly used study design, this "within site" approach has the potential to impact investigator behaviors as they become knowledgeable and experienced in both the experimental and the control treatment protocols. This creates a strong potential for "cross-contamination" of study participants (patients and clinicians), which may reduce any potential differences seen between the study groups"

Which aspect of the interventions is being evaluated?

- Efficacy vs effectiveness trials
- Superiority vs equivalence trials/ non inferiority
- Phase I, II, III trials

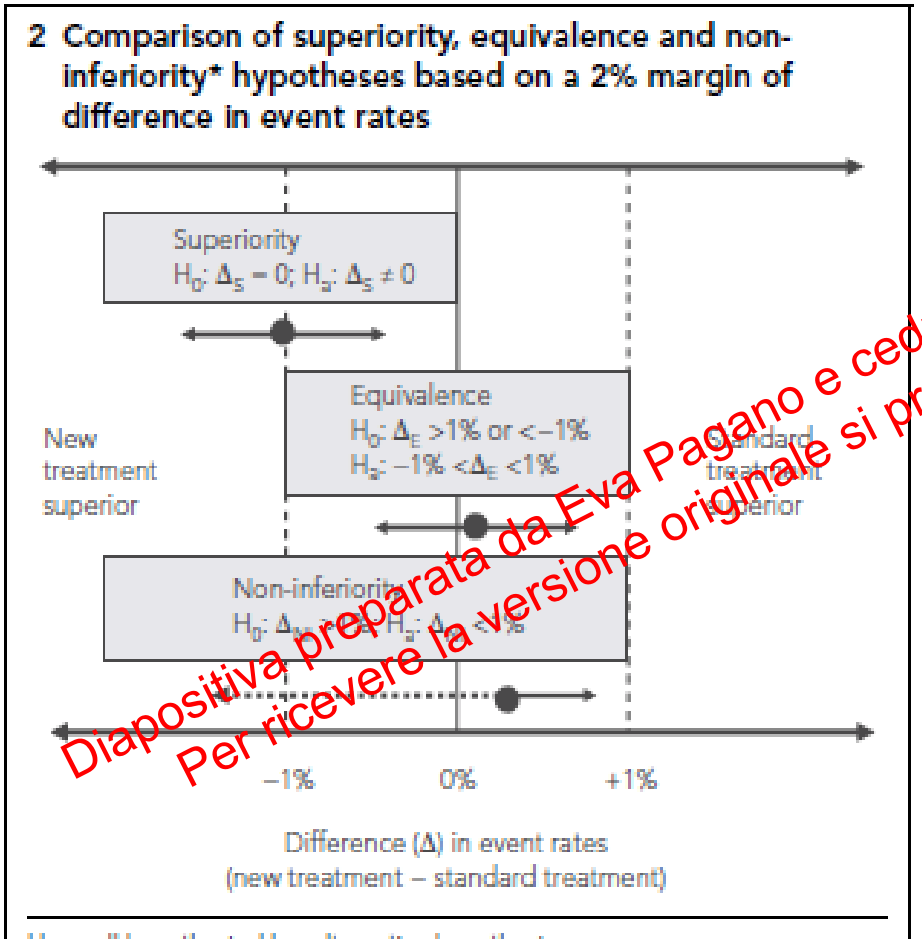
Efficacy vs. effectiveness

- Efficacy: does the intervention work in the people who actually receive it?
  - These trials tend to be explanatory
  - Goal here is high compliance
- Effectiveness: how does the intervention work in people to whom it has been offered
  - Tend to be pragmatic
  - For intervention with proven efficacy offered to hetrogeneous group of patient

Superiority vs. equivalence/ non inferiority trials

- Superiority trials:
  - Intended to determine if new treatment is different from (better than) placebo or existing treatment (active control)
- Equivalence trials:
  - Intended to determine if a new treatment is therapeutically similar to a reference treatment (margin of equivalence)
- Non-inferiority trials:
  - Intended to determine that new treatment is not worse then a reference treatment by more then an acceptable amount (margin of non-inferiority)

Reasons for equivalence / non inferiority trials



- Existing effective treatment
- Placebo-controlled trial unethical
  - Life-threatening illness
- New treatment not substantially better than existing treatment
  - May have fewer side effects, greater convenience, lower cost, higher quality of life, or provide an alternative or second line therapy

Noniferiority and equivalence: CONs

- A well executed trial cannot be distinguished, on the basis of data alone, from a poorly executed trial that fails to find a true difference (ie. poor compliance, poor diagnostic criteria, bias endpoint assessment)
- Difficult to specify an appropriate noninferiority margin
- Large sample size required compared to superiority trials

The NEW ENGLAND

ORIGIN

Alogliptin after Acu
in Patients witl

William B. White, M.D., Chris
Steven E. Nissen, M.D., Richa
Alfonso T. Perez, M.D., P

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

Jennifer B. Green, M.D., M. Angelyn Bethel, M.D., Paul W. Armstrong, M.D.,
John R. Buse, M.D., Ph.D., Samuel S. Engel, M.D., Jyotsna Garg, M.S.,
Robert Josse, M.B., B.S., Keith D. Kaufman, M.D., Joerg Koglin, M.D.,
Scott Korn, M.D., John M. Lachin, Sc.D., Darren K. McGuire, M.D., M.H.Sc.,
Michael J. Pencina, Ph.D., Eberhard Standl, M.D., Ph.D., Peter P. Stein, M.D.,
Shailaja Suryawanshi, Ph.D., Frans Van de Werf, M.D., Ph.D.,
Eric D. Peterson, M.D., M.P.H., and Rury R. Holman, M.B., Ch.B.,
for the TECOS Study Group*

Tanaka *et al. Cardiovasc Diabetol (2016) 15:57*
DOI 10.1186/s12933-016-0381-x

Cardiovascular Diabetology

STUDY PROTOCOL

Open Access

Rationale and design of a randomized trial to test the safety and non-inferiority of canagliflozin in patients with diabetes with chronic heart failure: the CANDLE trial

hi Oyama[4], Masataka Sata[5], Isao Taguchi[6],
, Junya Ako[10], Yasushi Sakata[11], Toshihisa Anzai[12],
ira Yamashina[9], Yoshihiko Saito[16], Yasunori Sato[17],

etes Mellitus

natt, M.D., M.P.H.,
ime Davidson, M.D.,
Frederich, M.D., Ph.D.,
nan, Ph.D.,
dell, M.D., M.P.H.,
Darren K. McGuire, M.D.,
d Itamar Raz, M.D.,
id Investigators*

Phase I, II, III, IV trials

Phase I	Phase II	Phase III	Phase IV
• Initial safety and tolerability • Determine safe dosage range • Identify side effects	• Efficacy • Dose response • Further evaluation of safety	• Effectiveness • Compare to commonly usde therapies • Monitor side effects	• Post-marketing studies • Effectiveness in the general population • Optimze drug usage
20-50	50-150	300-1000	Patient popultion sample

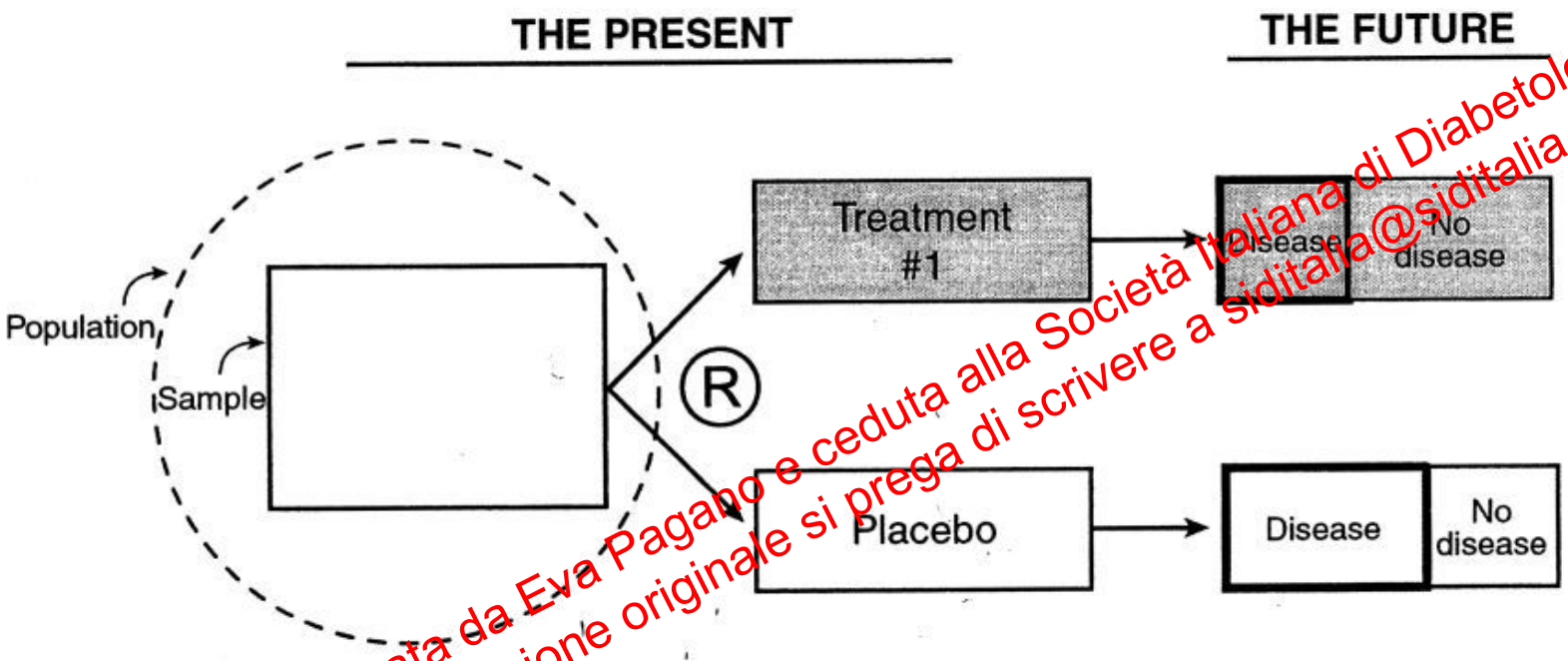
How the participants are exposed to the intervention?

- Parallel trials
- Crossover trials
- Factorial design

Parallel design

- Subjects are randomised to one of two or more arms
- Each arm being allocated to different treatment
- Most commonly used design

Parallel design



■ **FIGURE 10.1**

In a randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions (one should be a blinded placebo, if possible), (e) follows up the cohort, (f) measures outcome variables (blindly, if possible) and analyzes the results.

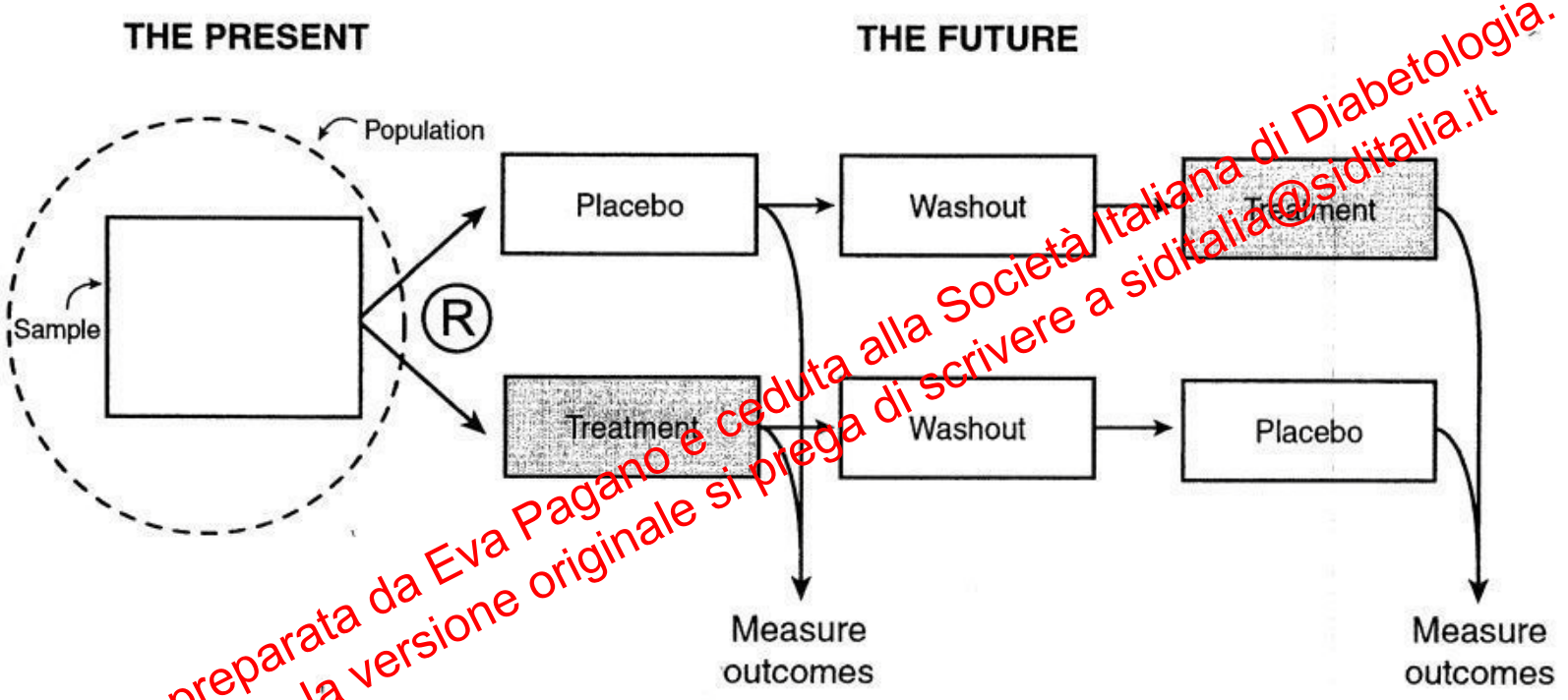
Crossover trial: design

- Each patient is given more than one treatment, each at different times in the study, with the intent of estimating differences between them

- The simplest trial is the two-treatment (A and B), two-period design. Patients are randomized to receive either A followed by B or B followed by A

- Washout period between treatment periods

Crossover design



■ **FIGURE 11.4**
In the cross-over randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions, (e) measures outcome variables, (f) allows washout period to reduce carryover effect, (g) applies intervention to former placebo group, (h) measures outcome variables again.

Crossover trial: when to use it

- In chronic, incurable disease (to keep same patients in all the study periods)
- The condition must be stable (to avoide “period effects”)
- The effects of interventions should have rapid onset and short duration (to avoide “carry-over effect”)

Crossover trial: PROs

- In respect to prognostic factors, the treatment groups are identical, simply because the same individuals receive both treatments
- Increased compliance and recruitment
- Increased efficiency then parallel designs
  - Lower variability (within-subject)
  - Lower sample size

Crossover trial: CONs

- Possibility of «carryover» effect
- Increased likelihood of dropouts (longer time and possible side effects)
- The underlying disease must have a constant intensity during all treatments periods

JAMA | Original Investigation

Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections

The GOLD Randomized Clinical Trial

Marcus Lind, MD, PhD; William Polonsky, PhD; Irl B. Hirsch, MD; Tim Heise, MD; Jan Bolinder, MD, PhD; Sofia Dahlqvist; Erik Schwarz, MD, PhD; Arndís Finna Ólafsdóttir, RN; Anders Frid, MD, PhD; Hans Wedel, PhD; Elsa Ahlén, MD; Thomas Nyström, MD, PhD; Jarl Hellman, MD

IMPORTANCE The majority of individuals with type 1 diabetes do not meet recommended glycemic targets.

OBJECTIVE To evaluate the effects of continuous glucose monitoring in adults with type 1 diabetes treated with multiple daily insulin injections.

DESIGN, SETTING, AND PARTICIPANTS Open-label crossover randomized clinical trial conducted in 15 diabetes outpatient clinics in Sweden between February 24, 2014, and June 1, 2016 that included 161 individuals with type 1 diabetes and hemoglobin A_{1c} (HbA_{1c}) of at least 7.5% (58 mmol/mol) treated with multiple daily insulin injections.

INTERVENTIONS Participants were randomized to receive treatment using a continuous glucose monitoring system or conventional treatment for 26 weeks, separated by a washout period of 17 weeks.

Editorial page 363
Related article page 371
Supplemental content

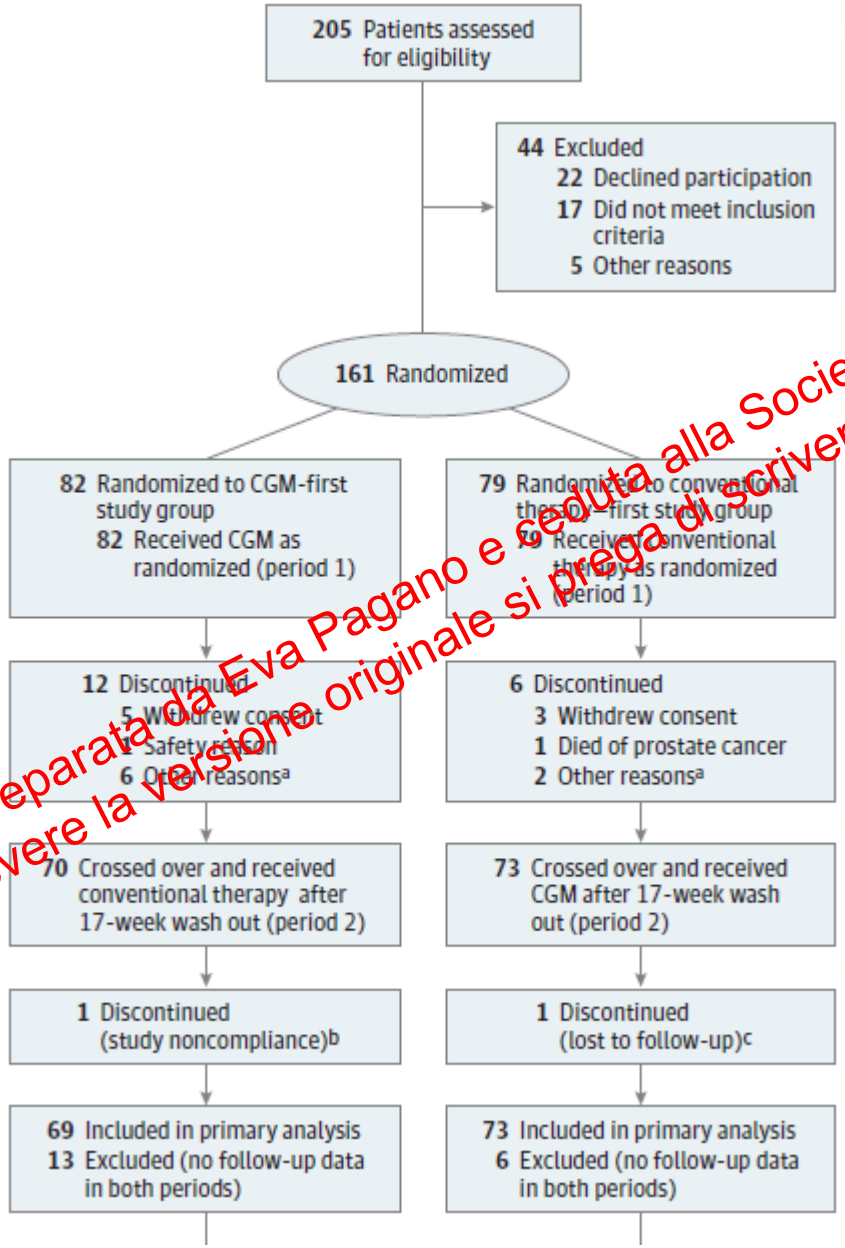
- To evaluate the effects of continuous glucose monitoring in adults with type 1 diabetes treated with multiple daily injections:

  CGM versus conventional therapy using only self-monitoring of blood glucose

- Open-label crossover randomized clinical trial in Sweden (15 diabetes outpatient clinics)

- Outcome measures: difference in HbA1c between weeks 26 and 69 for the two treatments, hypoglycaemia, well-being, and glycemic variability

Figure 1. Screening, Randomization, and Analysis for Continuous Glucose Monitoring and Conventional Treatment Groups



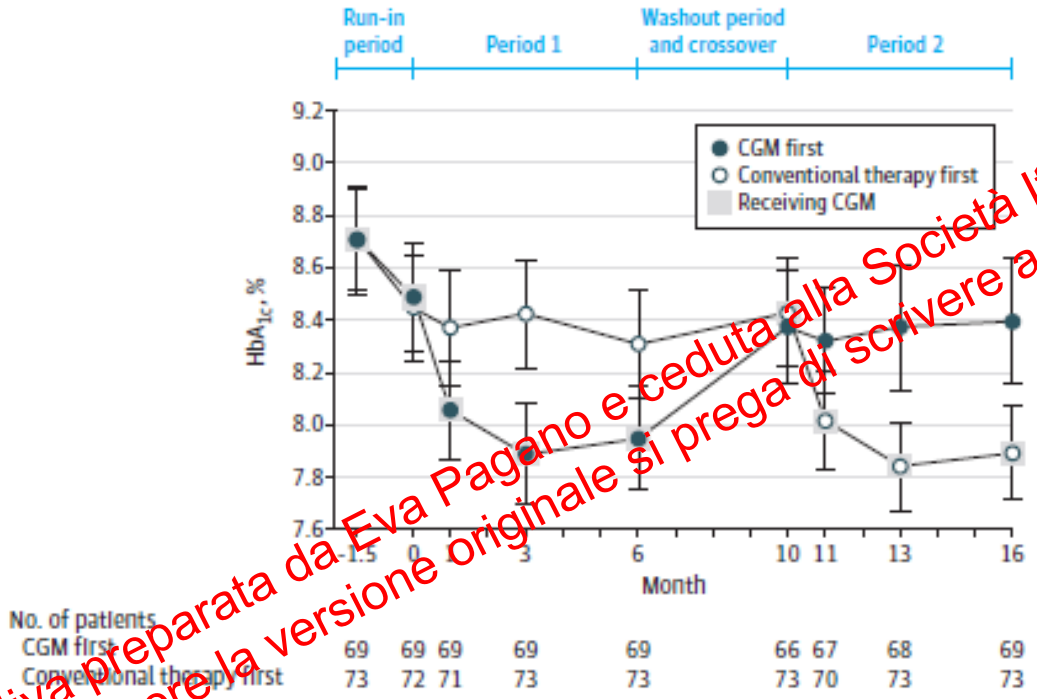
Run-in-period
6-weeks

Treatment
period 1
1-26-weeks

Wash out
17-weeks

Treatment
period 2
43-69 weeks

Figure 2. HbA_{1c} Values at Inclusion, Randomization, and During the 2 Different Periods of Treatment

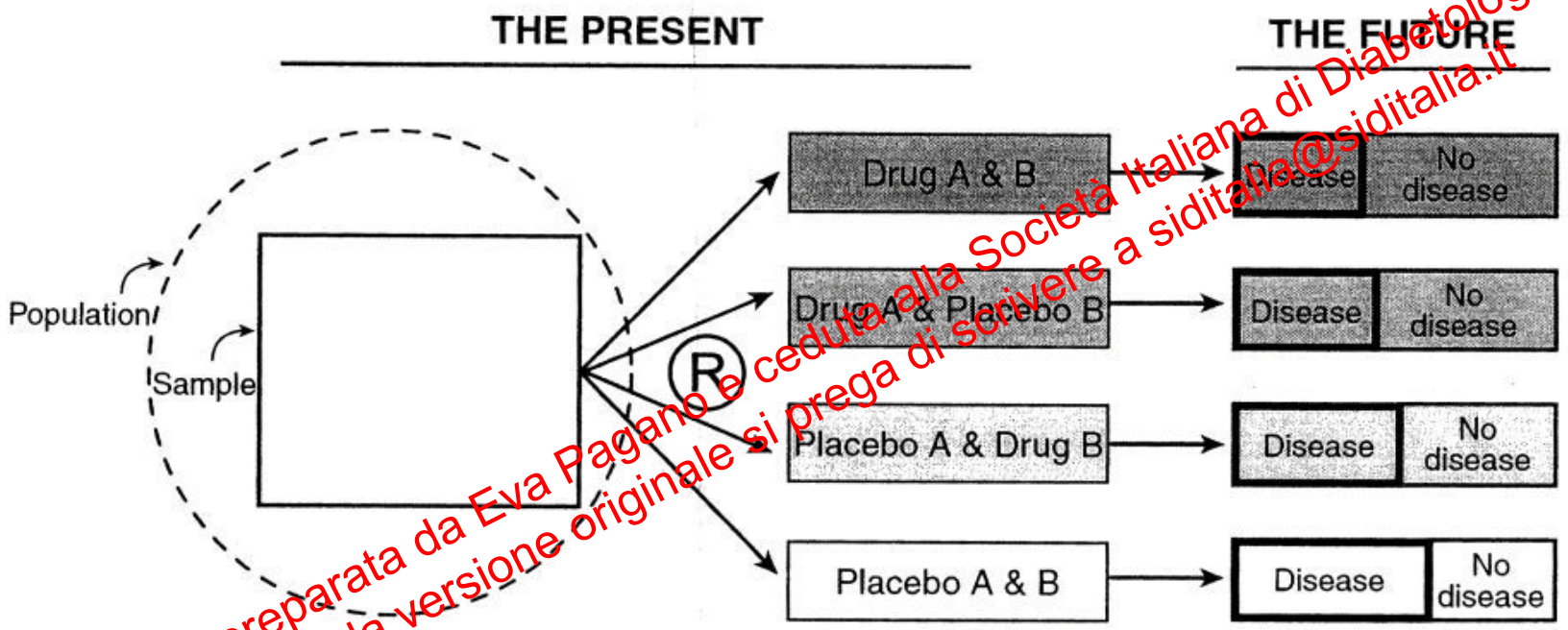


Hemoglobin A1c (HbA_{1c}) was measured according to the National Glycohemoglobin Standardization Program (NGSP). Data markers and error bars indicate mean (95% CIs). Data were plotted using the last-observation-carried-forward approach.

Factorial design: definition

- Two or more treatments are evaluated not only separately, but also in combination and against a control
- Each explanatory variable (factor) consists of two or more categories (levels)
- Data collected for all possible combination of the X levels of the N factors of interest
- The simplest case is a 2×2 design, a study involving two treatment factors, each with two levels

Factorial design



■ **FIGURE 11.2**

In a factorial randomized trial, the investigator (a) selects a sample from the population; (b) measures baseline variables; (c) randomly assigns two active interventions and their controls to four groups, as shown; (d) applies interventions; (e) follows up the cohorts; (f) measures outcome variables.

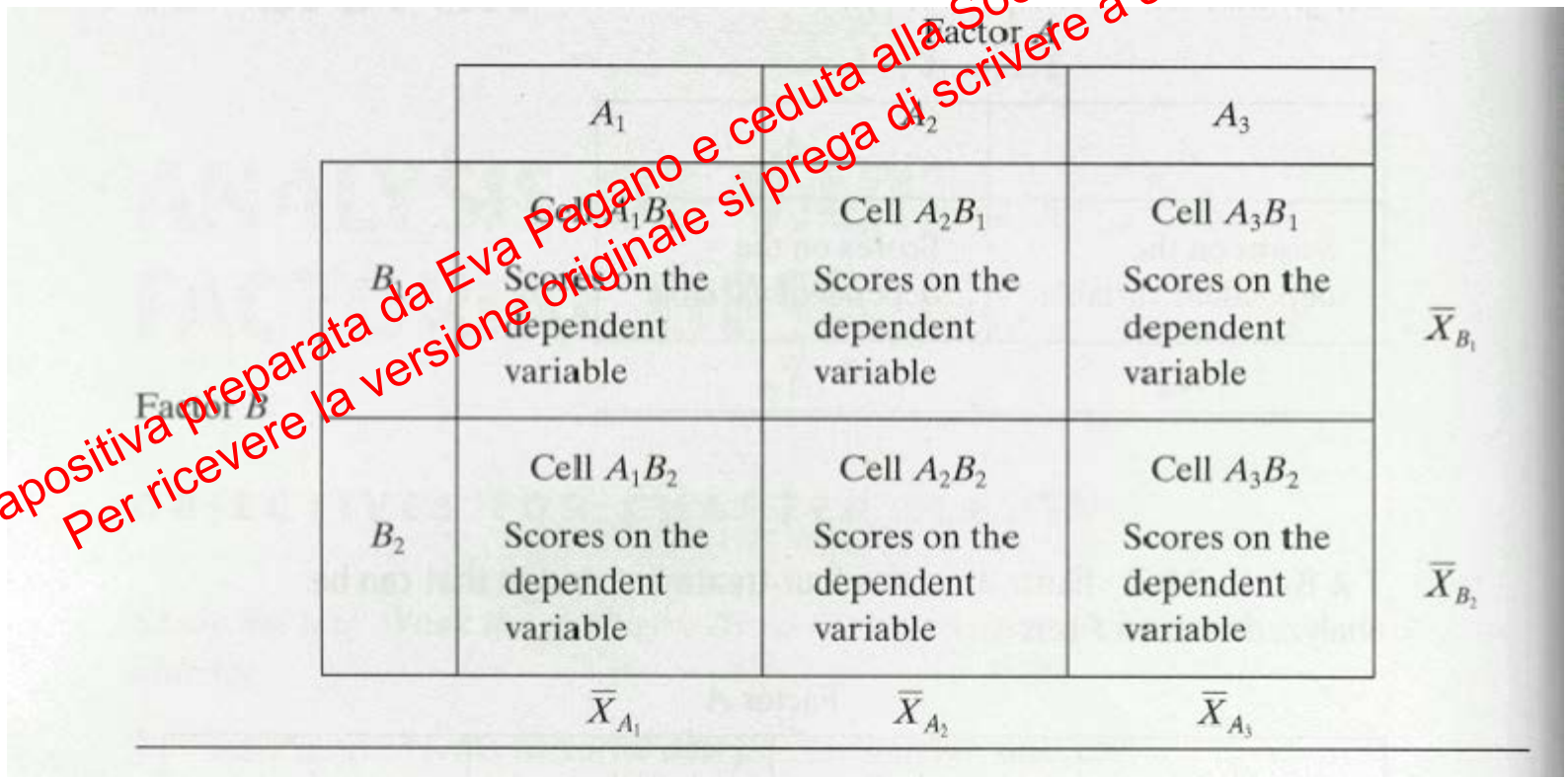
Factorial design: when to use it

- To examine the dose-response characteristics of the simultaneous use of treatments
- To be interested in learning about treatment combinations
  - Examing the interaction between treatments

Main effect

Average change in the response associated with a change in the level of the factor: marginal totals

(Design 3X2)



Interaction effect

- An interaction is between factors (not levels)
- When differences on one factor depend on the level you are on another factor (e.g. treatment or placebo)
- You know there's an interaction if when can't talk about effect on one factor without mentioning the other factor
- In the presence of interaction, the marginal estimates of the effects are biased

Factorial design: PROs

- In the absence of interaction, allows great efficiency in estimating main effects (same precision as two single-factor trials using twice the sample size)
- In the presence of interaction, is the only type of design that permits study of treatment interaction
- Treatments acting through different mechanism are more appropriate for factorial design

Factorial design: CONs

- Treatments must be administered without changing dosage in the presence of each other (ie cumulative side effect)
- There must be acceptable not to administer the individual treatments (no treatment or placebo group) or administer them at a lower dose
- Potential for adverse effects due to “poly-pharmacy”

Am J Clin Nutr 2014;99:463–71.

Diets naturally rich in polyphenols improve fasting and postprandial dyslipidemia and reduce oxidative stress: a randomized controlled trial[1–3]

Giovanni Annuzzi, Lutgarda Bozzetto, Giuseppina Costabile, Rosalba Giacco, Anna Mangione, Gaia Anniballi, Marilena Vitale, Claudia Vetrani, Paola Cipriano, Giuseppina Della Corte, Fabrizio Pesanisi, Gabriele Riccardi, and Angela A Rivellese

Diabetologia (2015) 58:1551–1560
DOI 10.1007/s00125-015-3592-1

ARTICLE

Polyphenol-rich diets improve glucose metabolism in people at high cardiometabolic risk: a controlled randomised intervention trial

Lutgarda Bozzetto[1] · Giovanni Annuzzi[1] · Giovanni Pacini[2] · Giuseppina Costabile[1] · Claudia Vetrani[1] · Marilena Vitale[1] · Ettore Griffo[1] · Angela Giacco[1] · Claudia De Natale[1] · Sara Cocozza[1] · Giuseppe Della Pepa[1] · Andrea Tura[2] · Gabriele Riccardi[1] · Angela A. Rivellese[1]

- To elucidate in individuals at high risk of type 2 diabetes and CVD, the medium-term effects of diets naturally rich in different sources of polyphenols and/or marine LCn3s
- Outcome measures: 8 weeks triglyceride concentrations and oxidative distress
- A 2X2 factorial design comparing:
  1. Control diet, low in LCn3 and polyphenols
  2. High LCn3 diet, rich in LCn3 and low in polyphenols;
  3. High polyphenol diet, low in LCn3 and rich in polyphenols;
  4. High LCn3 and high polyphenol diet, rich in LCn3 and polyphenols.

TABLE 4

Absolute changes after the intervention (8 wk minus baseline) in postprandial incremental AUCs of plasma and lipoprotein triglycerides, cholesterol, and apo B-48[1]

	Control (n = 20)	High LCn3s (n = 19)	High polyphenols (n = 20)	High polyphenols and high LCn3s (n = 19)	LCn3 effect	Polyphenol effect	Polyphenol-LCn3 interaction
Plasma triglyceride (mg/dL · 6 h)	52 ± 294	−69 ± 275	−47 ± 236	−40 ± 149	0.310	0.526	0.252
Plasma total cholesterol (mg/dL · 6 h)	−16 ± 42	−2 ± 72	14 ± 58	−10 ± 52	0.816	0.476	0.187
Chylomicron triglycerides (mg/dL · 6 h)	54 ± 173	−53 ± 229	3 ± 194	−17 ± 74	0.189	0.939	0.174
Chylomicron cholesterol (mg/dL · 6 h)	1.4 ± 6.8	−3.1 ± 7.5*	−1.8 ± 5.7	−0.4 ± 2.8	0.351	0.742	0.047
Large VLDL triglycerides (mg/dL · 6 h)	16 ± 136	−35.8 ± 100	9.8 ± 136	−42 ± 63	0.169	0.384	0.542
Large VLDL cholesterol (mg/dL · 6 h)	1.0 ± 13	−7.8 ± 21	0.1 ± 21	−5.8 ± 14	0.297	0.676	0.825
Large VLDL apo B-48 (μg/mL · 6 h)	4.53 ± 12	0.27 ± 9.83	0.29 ± 7.86	0.12 ± 4.80	0.741	0.750	0.802

[1] All values are means ± SDs. *Significantly different from the control group, $P < 0.05$ (ANOVA and least-significant-difference post hoc test). apo B-48, apolipoprotein B-48; LCn3, long-chain n−3 PUFA.

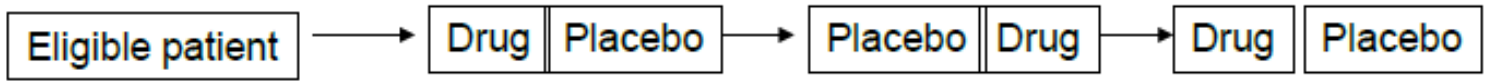
[2] Two-factor ANOVA of absolute values at 8 wk adjusted for baseline values as covariate. $P < 0.05$ indicates a significant difference.

How many participants are included?

- N-of-1 trials to mega-trials
- Fixed size
- Sequential trials

N-of-1 trial or individual patient trial

- These can be thought of as a form of crossover trial
- Each participant receives the experimental arm for a period of time and then the control/ comparison arm during a different period of time
- There can be many such periods of time in these studies
  - XCCCXXCCXX
- The participant does not know which intervention is occurring during each period



Rheumatology 2007;46:135–140
Advance Access publication 15 June 2006
doi:10.1093/rheumatology/kel195

Celecoxib compared with sustained-release paracetamol for osteoarthritis: a series of n-of-1 trials

M. J. Yelland[1], C. J. Nikles[2], N. McNairn[3], C. B. Del Mar[4], P. J. Schluter[5] and R. M. Brown[6]

- To assess the effectiveness for the short term choice of drugs for osteoarthritis
- Sustained release paracetamol versus colecoxib
- 2 weeks of each treatment, for 3 treatment cycles
- Outcome measures: pain, stiffness and functional limitation scores
- 41 patients completing the n-of-1 trial
- Patient receives each treatment, with treatment order decided at random
- A crossover trial in a single patient; enable decision on the single patient

Mega trials

- These studies are meant to be HUGE but to collect only a limited amount of data (to make them affordable and practical)
- Are usually multi-center, from different countries
- Have the aim to obtain ‘increased statistical power’ and to achieve wider generalizability and can pick up small effects

Aung *et al. Trials* (2016) 17:286
DOI 10.1186/s13063-016-1354-9

Trials

METHODOLOGY Open Access

Cost-effective recruitment methods for a large randomised trial in people with diabetes: A Study of Cardiovascular Events iN Diabetes (ASCEND)

Theingi Aung[2], Richard Haynes[1], Jill Barton[1], Jolyon Cox[1], Aleksandra Murawska[1], Kevin Murphy[1], Michael Lay[1], Jane Armitage[1], Louise Bowman[1*] and ASCEND Study Collaborative Group

ASCEND (A Study of Cardiovascular Events iN Diabetes) is a 2 × 2 factorial design randomised study to assess whether aspirin 100 mg daily versus placebo and separately, omega-3 fatty acids 1 g daily versus placebo, reduce the risk of cardiovascular events in individuals with diabetes who do not already have diagnosed occlusive arterial disease, and whether any such benefits outweigh any hazards from bleeding. To minimise costs

- To identify people with diabetes:
  1. Centrally held diabetes registers
  2. General practice diabetes registeres

"Information on approximately 600,000 people listed on 58 centrally held diabetes registers was obtained, and 300,188 potentially eligible patients were invited to join the study. In addition, 785 GP practices mailed invitations to 120,875 patients. A further 2,340 potential study participants were identified via other routes. In total, 423,403 people with diabetes were invited to take part; 26,462 entered the 2-month, pre-randomisation, run-in phase; and 15,480 were randomised."

Fixed size trial

- The investigator establish deductively the number of partecipants (sample size) that they will include

- Statistical methods used to calculate sample size maximize the chance of detecting a statistically and clinically significant difference between the interventions when a difference really exist

Sequential trial

- Contrast is with the more traditional fixed size trial in which the number of participants is determined based on a priori sample size calculations
- Has a parallel design
- Number of participants is NOT specified before the trial begins
- Participants are recruited until the question is answered (or it becomes clear that there is no possibility to detect a difference between the arms)

Interim analysis

- Analysis comparing intervention groups at any time before the formal completion of the trial, usually before recruitment is complete.
- Often used with "stopping rules" so that a trial can be stopped if participants are being put at risk unnecessarily.
- Timing and frequency of interim analyses should be specified in the protocol.

Sequential trial: PROs and CONs

- Stopping for efficacy:
  - Patients benefit sooner from the new treatment
  - Less information on secondary outcomes (including safety) and subgroups
- Stopping for futility:
  - Efficient with respect of costs, time, effort,
  - Reduces expected sample size
  - Helps protection of participants against unnecessary exposure to potentially harmful treatment
  - May not be able to determine if the treatment is merely ineffective or actually harmful

Who knows which intervention is being assessed?

- Open trials
- Single-blind trials
- Double-blind trials
- Triple and quadruple-blind trials

- Blinding: Relevant groups who may/may not have knowledge of treatment assignments
  - Participants, investigators/clinicians administering intervention, investigators assessing outcomes, data analyst(s)

- Open trials
  - All participants and investigators know who is getting which intervention
- Single-blind
  - The participants (usually) or the investigators assessing outcome (alternately) do not have knowledge of the treatment assignments
- Double-blind
  - Two groups do not know—usually it is the participants and the outcome assessors/investigators
- Triple or quadruple blinding
  - Three or four of the relevant groups (prior slide) are not aware of the treatment assignment

Innovative designs: Adaptive design

- Allows adaptations or modifications to trial design after its initiation without undermining validity and integrity of trial
- Requires the trial to be conducted in several stages with access to the accumulated data (real-time data)
- At any stage, the data may be analyzed and next stages redesigned taking into account all available data

Adaptive design: institutional definitions

- EMA: “An adaptive design clinical study is defined as a study design if statistical methodology allows the modification of a design element (e.g. sample size, randomisation ratio, number of treatment arms) at an interim analysis with full control of the type I error”

- FDA: “An adaptive design clinical study is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study

Adaptive design: PROs and CONs

- May improve trial efficiency for the sponsor and the participants in the trial

But

- Can pose operational challenges because of their complexity, and the process of adapting a trial can introduce bias

Typea of adaptive design trials

Adaptive randomization design

Group sequential design

Sample size re-estimation design

Drop-the-loser design

Adaptive dose-finding design

Biomarker-adaptive design

Adaptive treatment-switching design

Hypothesis-adaptive design

Adaptive seamless phase II/III design

A multiple-adaptive design

STATE OF THE ART

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 91 NUMBER 3 | MARCH 2012

Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval

H-G Eichler[1,2], K Oye[2,3,4], LG Baird[2], E Abadie[5], J Brown[6], CL Drum[2], J Ferguson[7], S Garner[8,9], P Honig[10], M Hukkelhoven[11], JCW Lim[12], R Lim[13], MM Lumpkin[14], G Neil[15], B O'Rourke[16], E Pezalla[17], D Shoda[18], V Seyfert-Margolis[14], EV Sigal[19], J Sobotka[20], D Tan[12], TF Unger[18] and G Hirsch[3]

Adaptive Licensing can be defined as a prospectively planned, adaptive approach to bringing drugs to market. Starting from an authorised indication (most likely a "niche" indication) for a given drug, through iterative phases of evidence gathering and progressive licensing adaptations concerning both the authorised indication and the potential further therapeutic uses of the drug concerned, AL seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to provide adequate evolving information on benefits and harms.

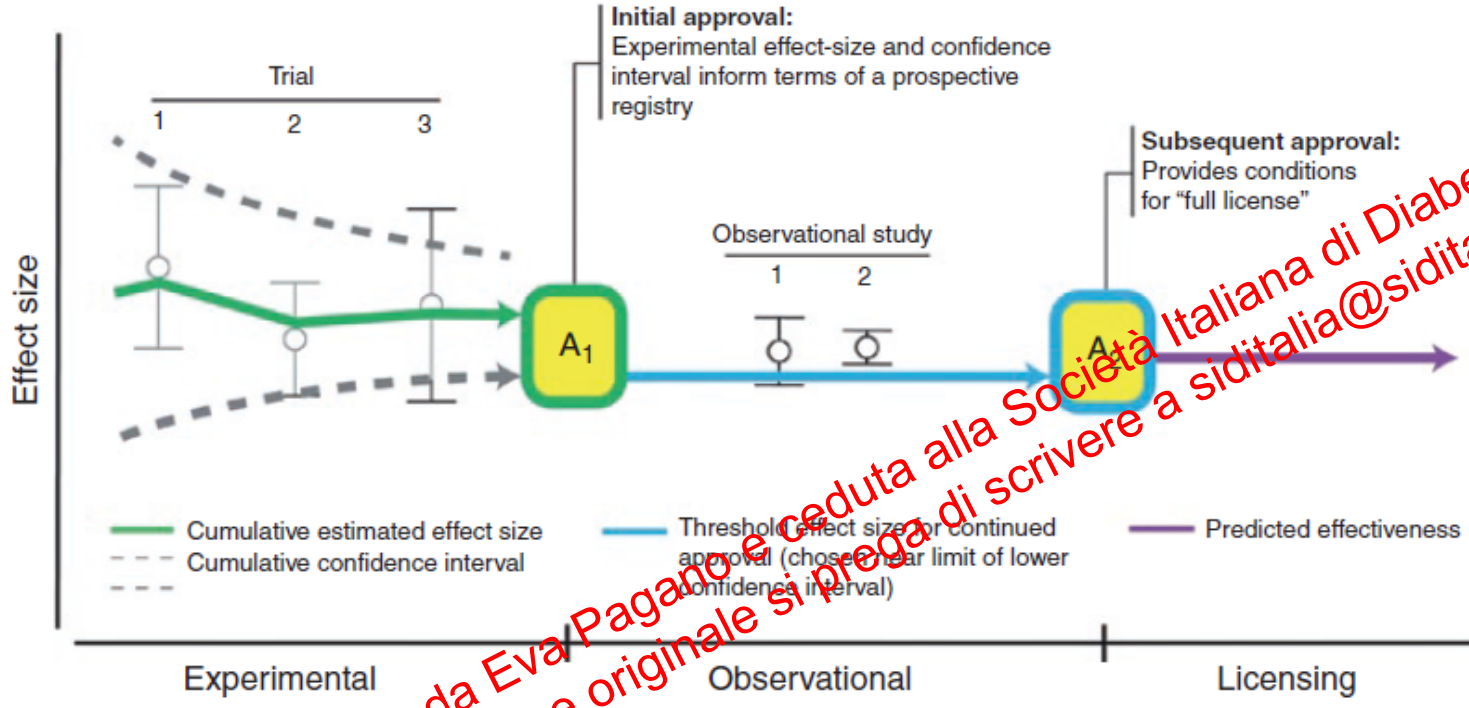


Figure 2 The threshold approach to evidence generation when randomized controlled trials (RCTs) are not practically or ethically feasible after an initial license. The threshold approach to adaptive licensing might lend itself to situations in which conventional, adequately powered RCTs are difficult to perform before licensing and clearly impossible after an (initial) license is granted; this may apply to orphan conditions for which no proven alternative treatment exists. Under this pathway, the sponsor would initially conduct one (or possibly more) small RCTs. If successful, an initial license may be granted on the basis of this limited information. Subsequent uncontrolled observational studies would aim to show that the treatment outcome under real-life conditions (e.g., mortality, time to event) remains above a pre-agreed threshold. The threshold value itself is based on the point estimate and confidence interval obtained from the initial RCTs, and prior knowledge of outcome with, for example, best supportive care. If efficacy were thus confirmed, the drug could transition to a "full" license. Note that the concept might also be applied to safety, e.g., to demonstrate that the drug does not produce an incidence of greater than *x* of a life-threatening adverse effect such as progressive multifocal leukoencephalopathy (not shown in graph).

Eva Pagano
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Grazie per l'attenzione!