LA COMPLESSITÀ DEGLI STUDI CLINICI

RIFLESSIONI SULLE ATTIVITÀ DEL TEAM DI RICERCA CLINICO

Responsabile scientifico:
Stefania Gori

Reggio Emilia
29 Novembre 2019
Centro Internazionale
Loris Malaguzzi

Gli studi adattativi: flessibilità e tempestività

G. Pappagallo (Mirano, VE)

G.L. Pappagallo: relazioni con l'Industria farmaceutica e potenziali conflitti di interesse (11.2019)

Azienda	Relazione	Patologia
Astellas	training, partecipazione advisory board	ca. prostata
AstraZeneca	partecipazione advisory board, valutazioni clinico-epidemiologiche	ca. polmone, ca. ovaio, ca. mammario, B-LLC
Clovis	partecipazione advisory board	ca. ovaio, ca. prostata
IPSEN	training, valutazioni clinico-epidemiologiche, partecipazione advisory board	ca. rene, epatocarcinoma
Janssen	partecipazione advisory board, valutazioni clinico-epidemiologiche	ca. prostata, depressione maggiore
MSD	valutazioni clinico-epidemiologiche	melanoma, ca. polmone, ca. vescica, VAP
Pierre Fabre	training, valutazioni clinico-epidemiologiche, partecipazione ad advisory board	ca. vescica, melanoma, ca. mammario
Pfizer	training, valutazioni clinico-epidemiologiche	ca. mammario, ca. rene, artrite reumatoide, m. cardiovascolari, amiloidosi
Roche	training, valutazioni clinico-epidemiologiche, partecipazione ad advisory board	ca. polmone, ca. mammella, ca. ovaio, sclerosi multipla, emofilia, linfomi, ACG
Servier	partecipazione advisory board, valutazioni clinico-epidemiologiche	ca. pancreas, ca. gastrico
Teva	training	emicrania

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L'incubo del data lock: il punto di vista dello Sponsor/CRO
L. Cottini (Milano)

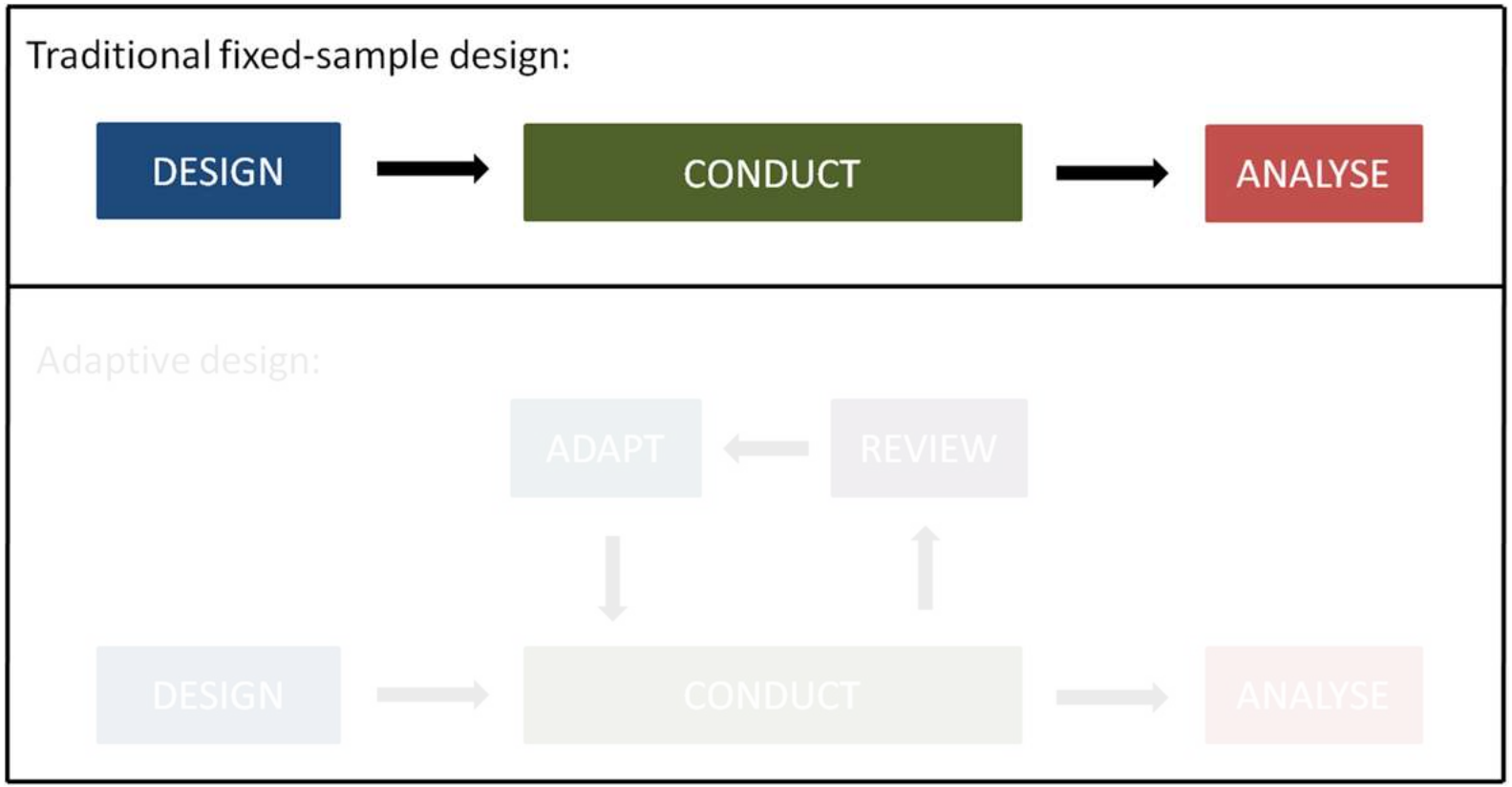
L'incubo del data lock: il punto di vista del CRC
G. Tabaro (Aviano, PN)

Trials con componenti adattative:

- Incubo metodologico-statistico
- Incubo regolatorio/documentale/etico
- Incubo organizzativo

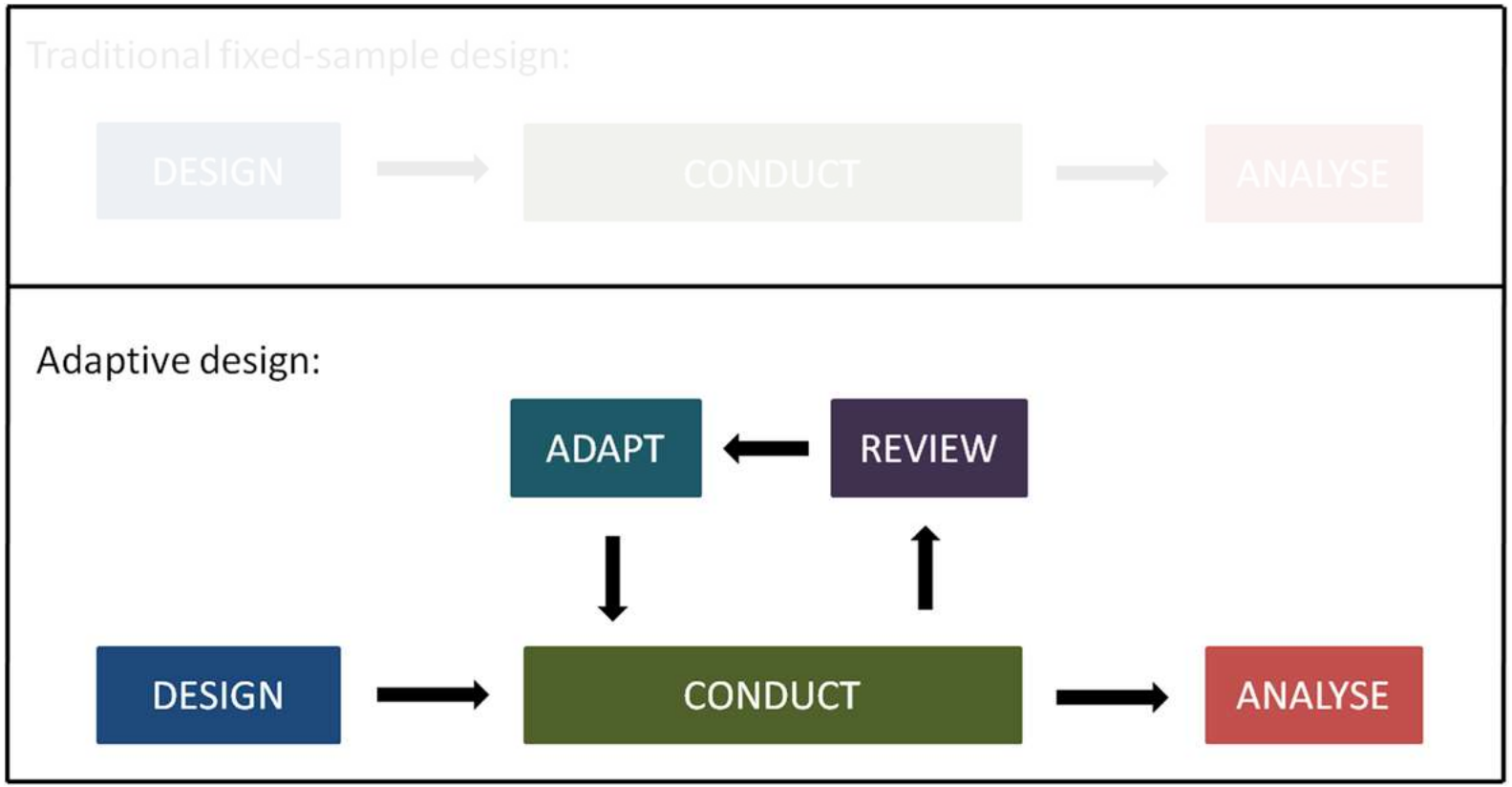
Paolo Bruzzi, 2015

Non possibilità di utilizzare le informazioni raccolte nel corso dello studio per modificarne gli aspetti critici (generazione Vs verifica di ipotesi; molteplicità)



Possibilità di modifiche nel corso dello studio al fine di velocizzare e ottimizzare il processo (punti temporali pre-pianificati, in cieco / in aperto, con / senza test di verifica ipotesi)

Non possibilità di utilizzare le informazioni raccolte nel corso dello studio per modificarne gli aspetti critici (generazione Vs verifica di ipotesi; molteplicità)



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Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

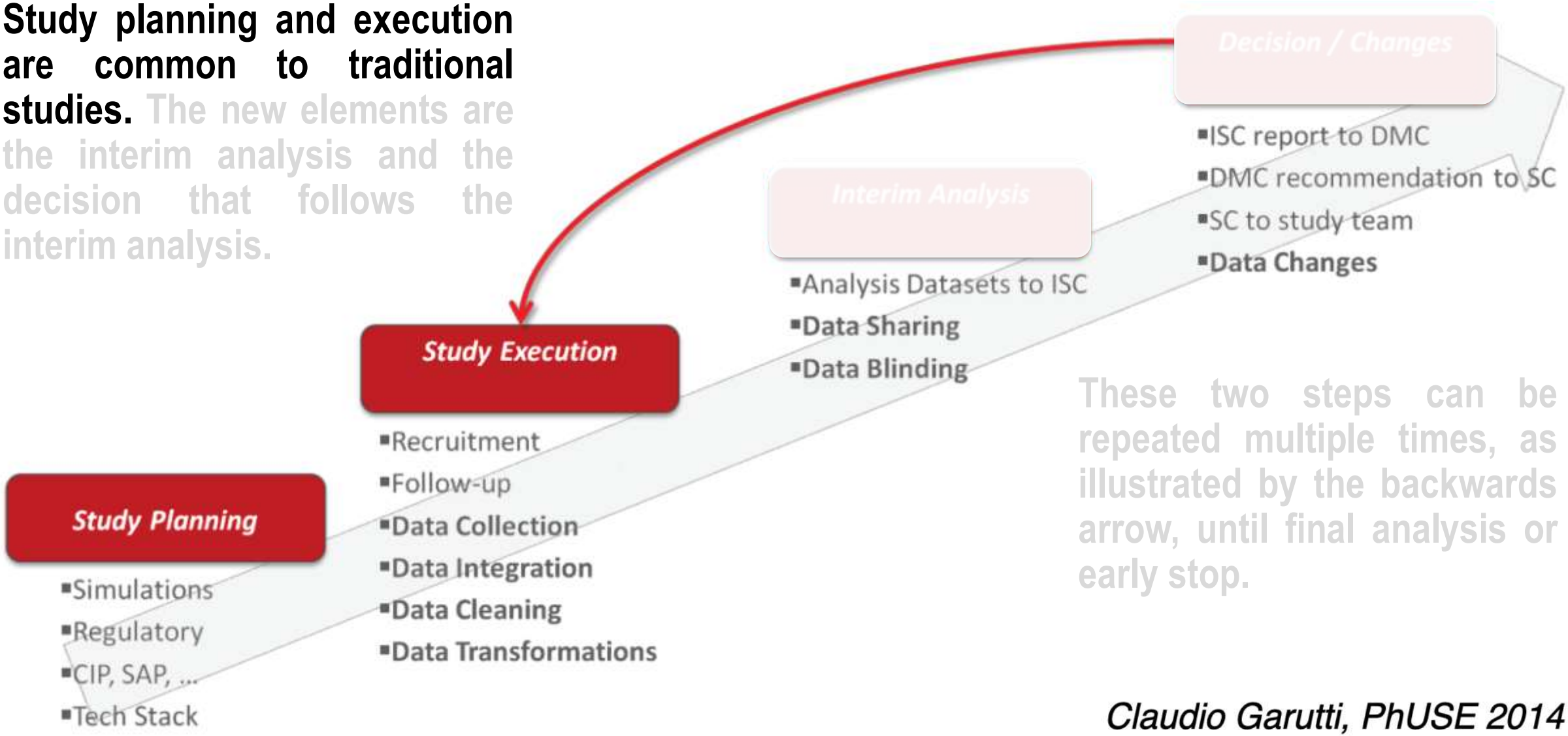
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2018
Clinical/Medical

For the purposes of this guidance, an *adaptive design* is defined as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.

Example of study flow in adaptive trials

Study planning and execution are common to traditional studies. The new elements are the interim analysis and the decision that follows the interim analysis.



These two steps can be repeated multiple times, as illustrated by the backwards arrow, until final analysis or early stop.

Claudio Garutti, PhUSE 2014

Example of study flow in adaptive trials

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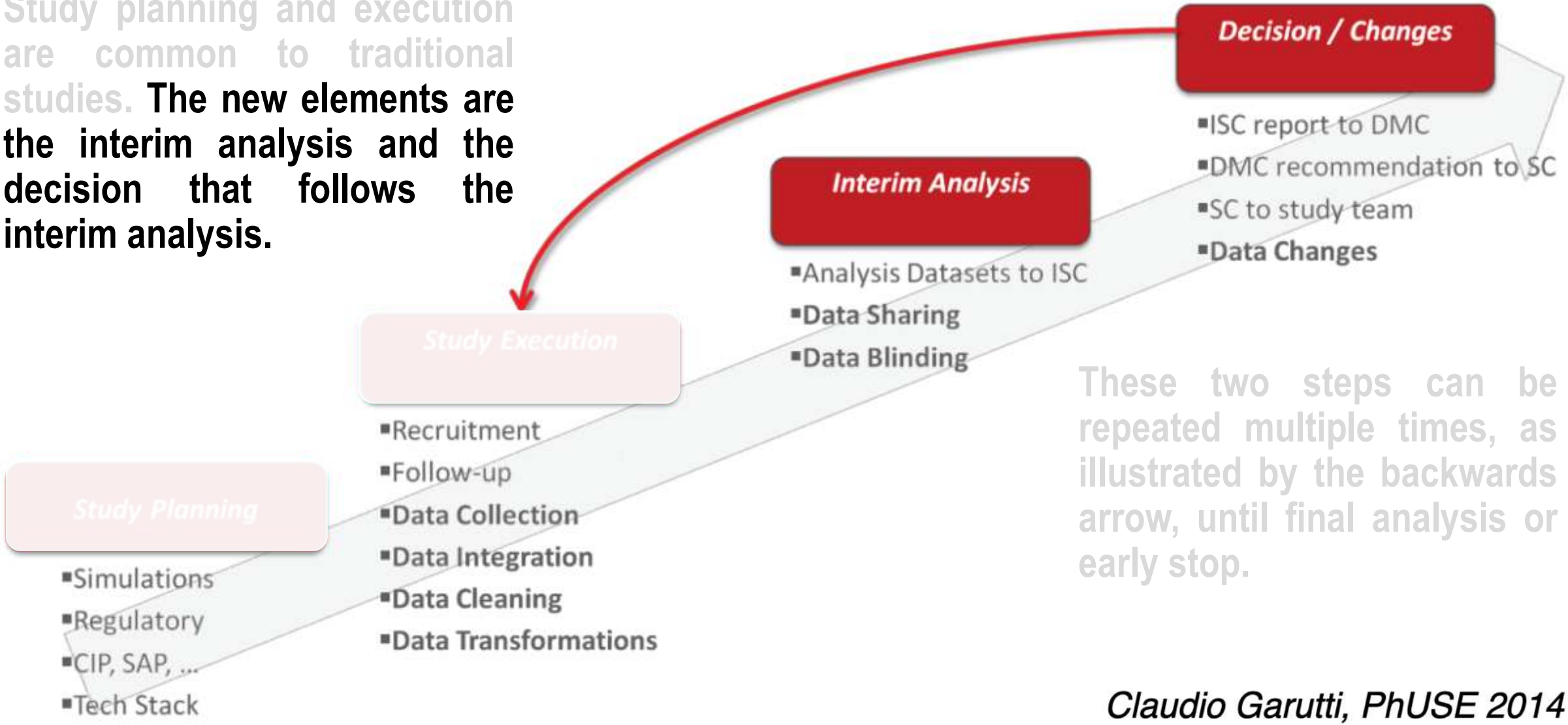

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Claudio Garutti, PhUSE 2014

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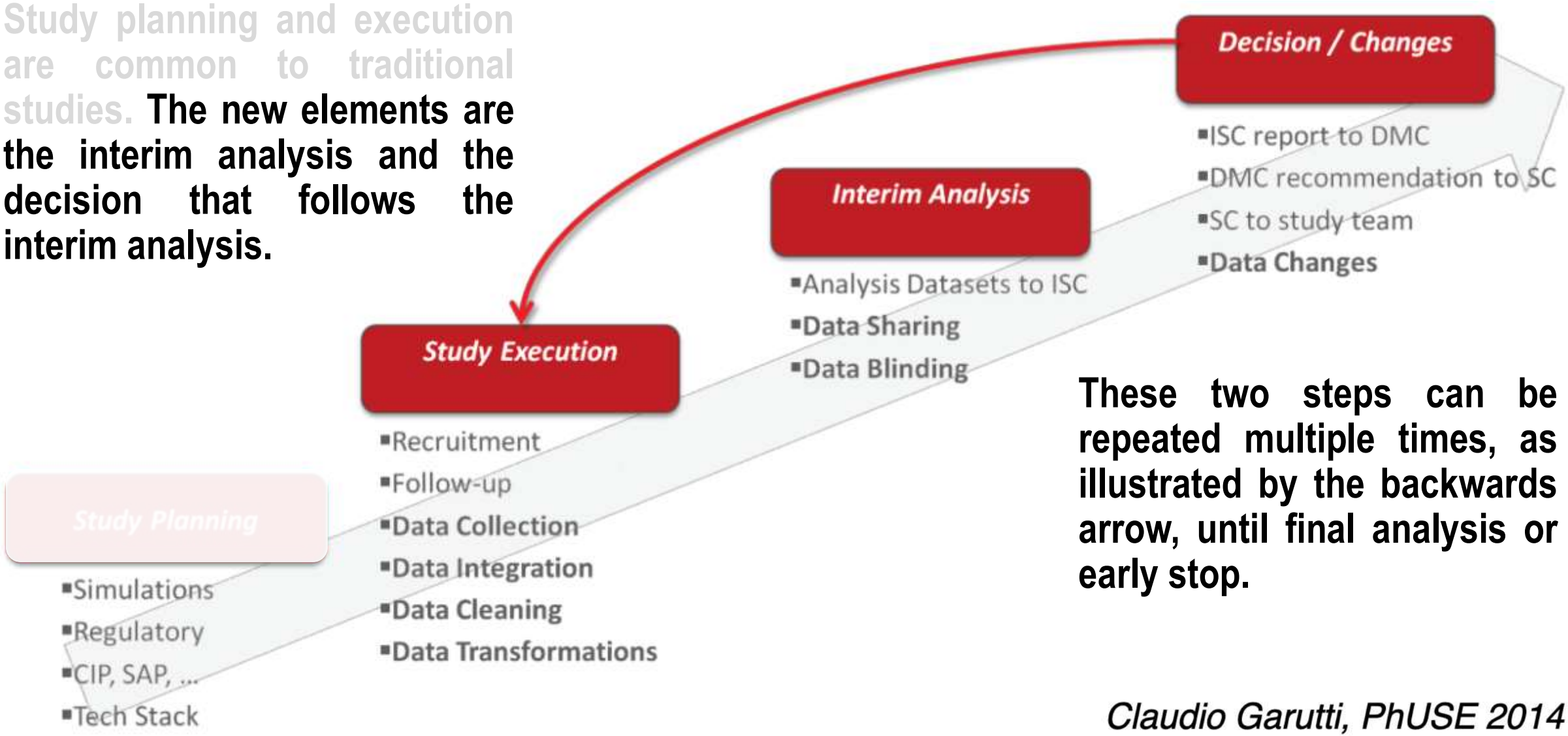

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Claudio Garutti, PhUSE 2014

Gli studi convenzionali hanno spesso una componente adattativa

- ***Stopping Rules*** **basate su analisi intermedie**
- Modificazioni dei criteri di selezione
- Modificazioni per conservare la potenza statistica dello studio

- **Eventi / Reazioni Avverse**
- **Evidenza di Efficacia**
- ***Futility***

modif. da Paolo Bruzzi, 2015

Gli studi convenzionali hanno spesso una componente adattativa

- *Stopping Rules* basate su analisi intermedie
- **Modificazioni dei criteri di selezione**
- Modificazioni per conservare la potenza statistica dello studio

- **Difficoltà di reclutamento**
- **Costi inaspettati**
- **Informazioni da altri studi**

modif. da Paolo Bruzzi, 2015

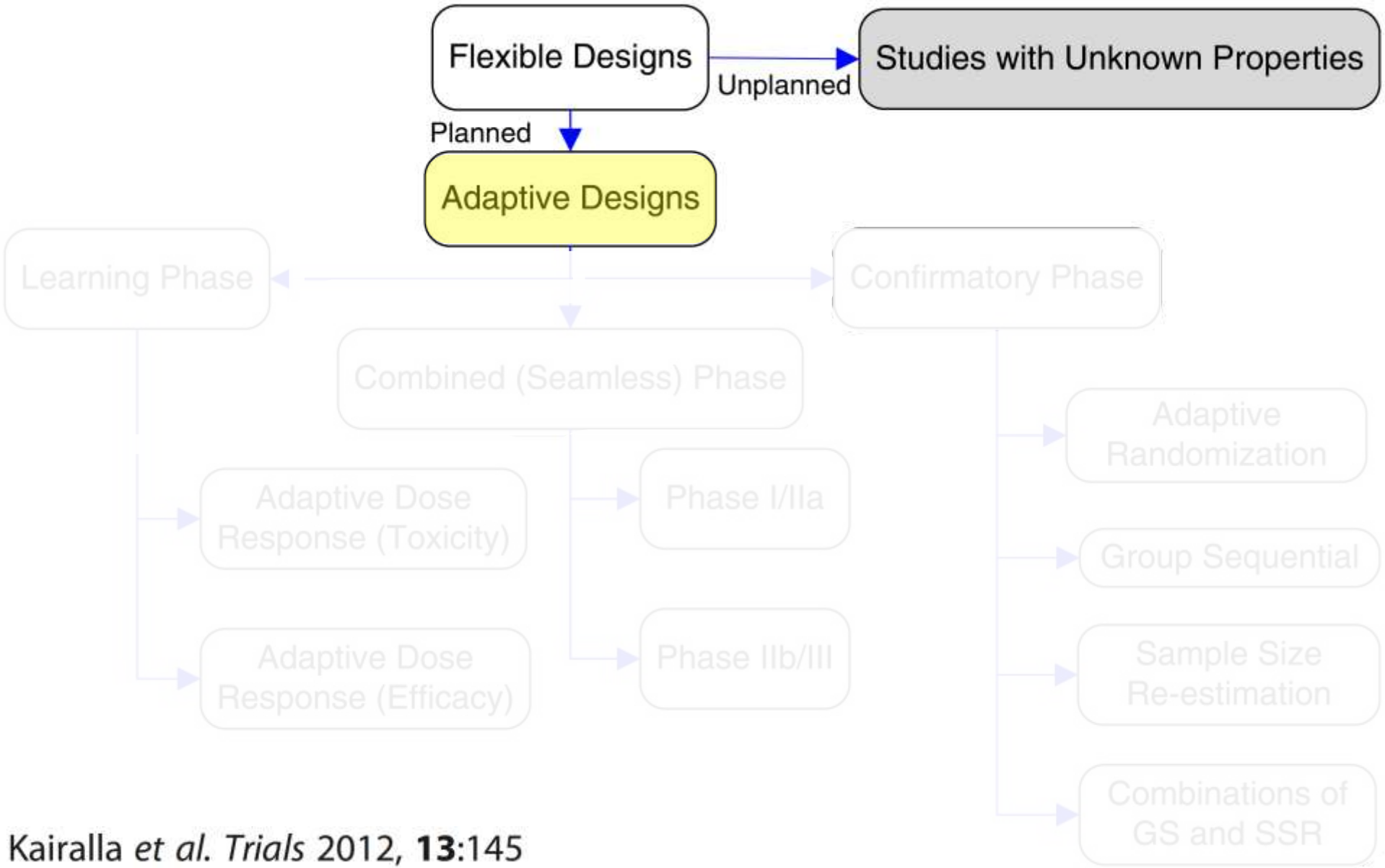
Gli studi convenzionali hanno spesso una componente adattativa

- *Stopping Rules* basate su analisi intermedie
- Modificazioni dei criteri di selezione
- **Modificazioni per conservare la potenza statistica dello studio**

- **Incremento dimensioni**
- **Prolungamento durata**
- **Cambio endpoint primario**

modif. da Paolo Bruzzi, 2015

Summary of different types of adaptive designs for clinical trials.



Kairalla *et al. Trials* 2012, **13**:145

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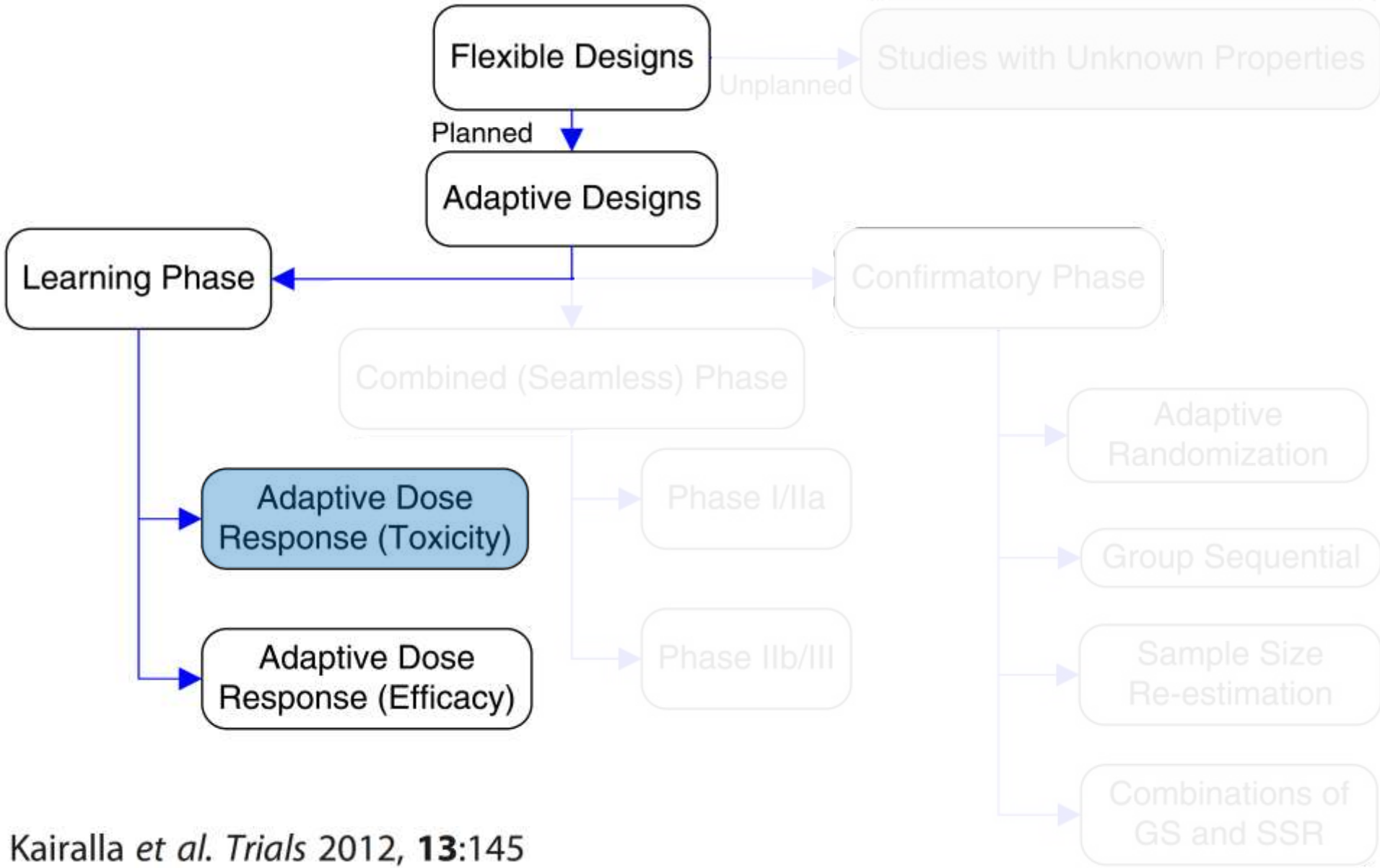


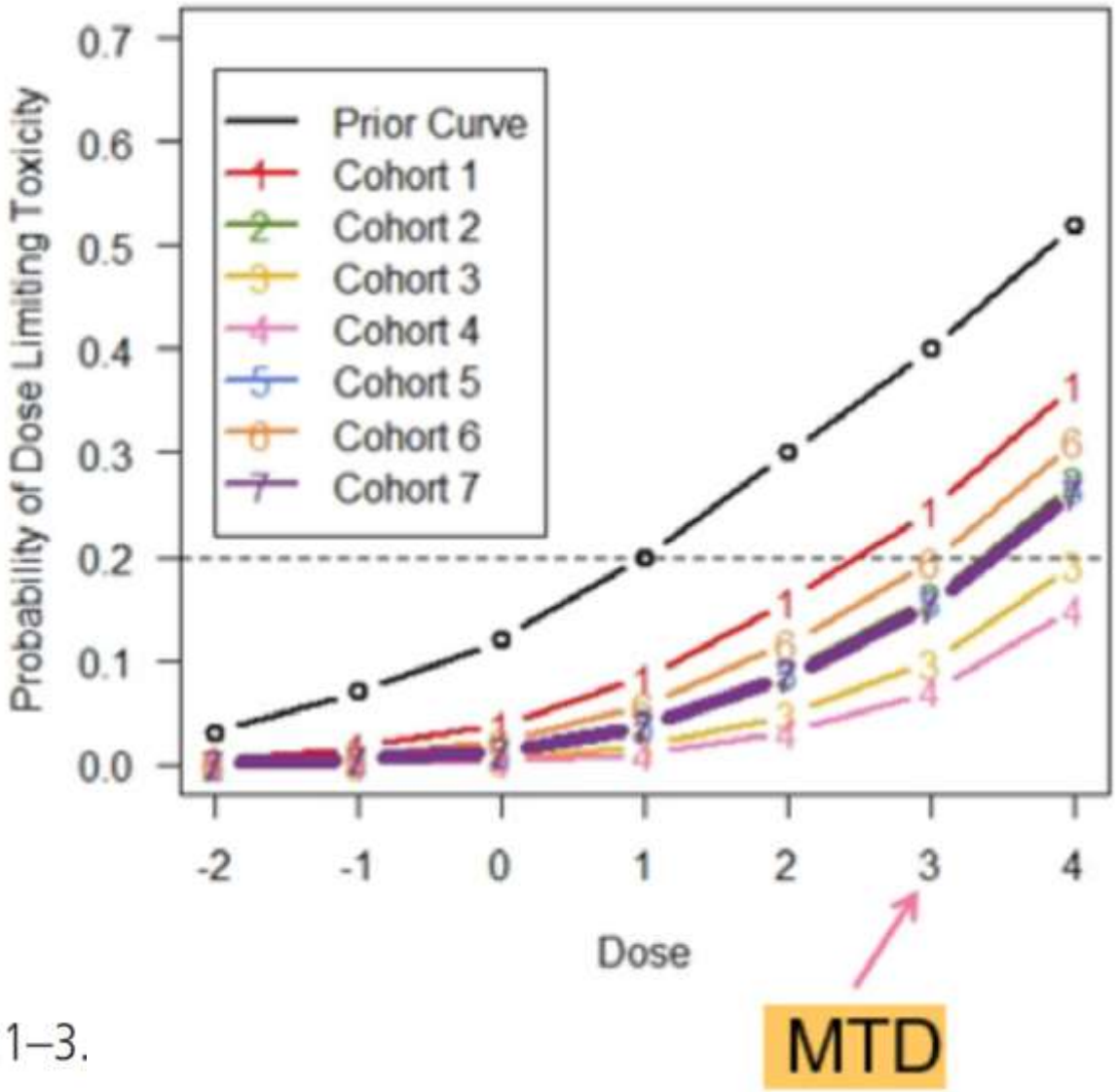
Kairalla *et al. Trials* 2012, **13**:145

WHAT IS THE CONTINUAL REASSESSMENT METHOD?

Unlike rule-based approaches, a continual reassessment method uses a statistical model to estimate the relationship between dose and DLT risk.

With a Bayesian approach, it integrates accumulated observed data in the trial as well as prior information from clinicians and past studies, to recommend a dose with estimated DLT risk closest to the TTL to the next cohort/patient.

The model learns as the trial progresses as the data from every patient already enrolled is included to recommend the best MTD estimate for the next patient.



Millen GC, Yap C. *Arch Dis Child Educ Pract Ed* 2019;**0**:1–3.

	Frequentista	Bayesiano
Significato della Probabilità	Probabilità di un'osservazione	Probabilità di un'ipotesi
	Probability of the observed difference (if the experimental therapy does not work)	*Probability that the experimental therapy works / doesn't work (given observed difference and prior knowledge)*

Bayesian statistics allows to continuously incorporate new evidence into the decision process

Advantages of Bayesian Statistics

- Reflects human reasoning ("common sense")
- It is focused on estimates of effect
- Provides a conceptual framework for medical decision making
- It is transparent
- **It is flexible and promotes flexibility**

Paolo Bruzzi, 2015

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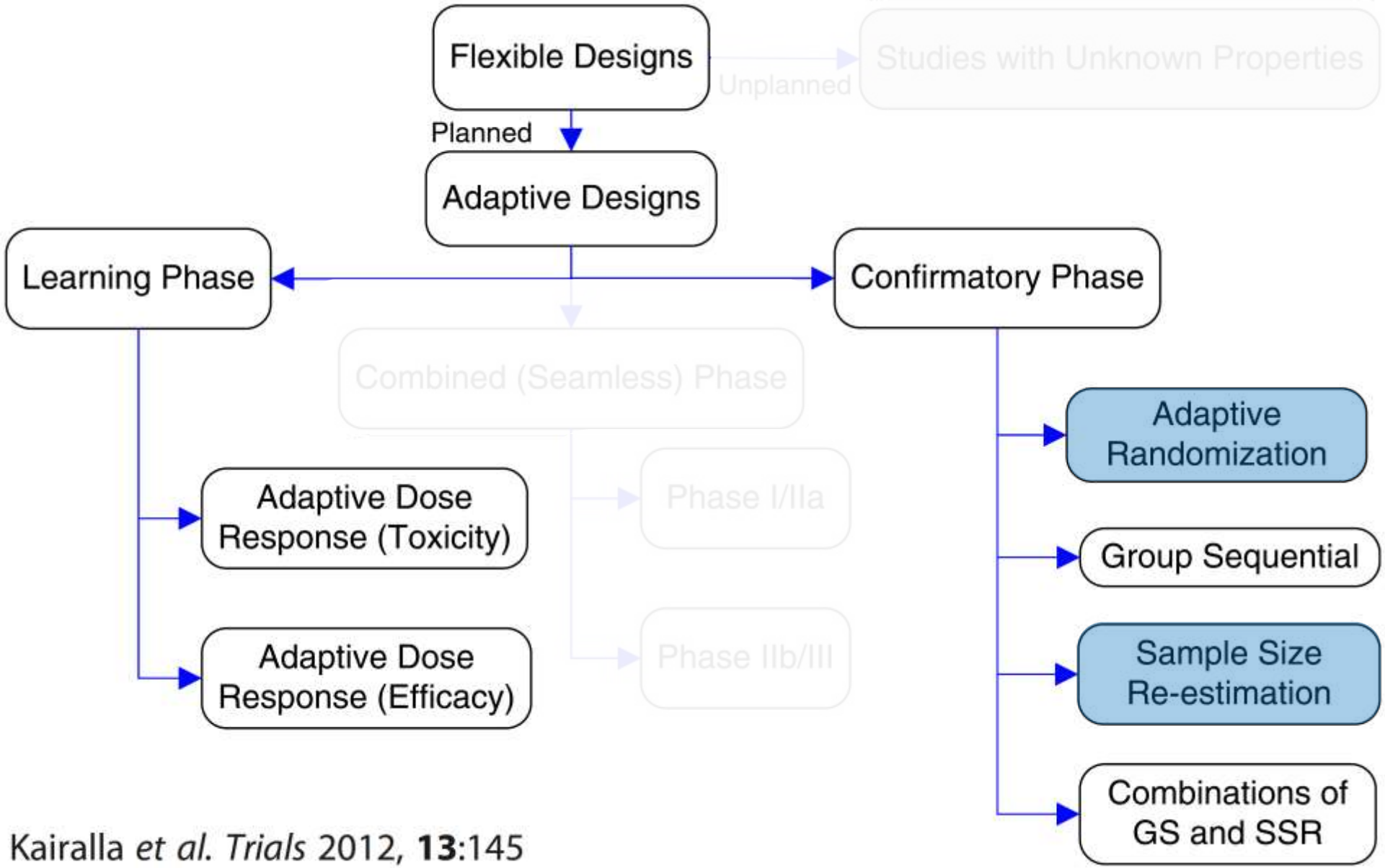

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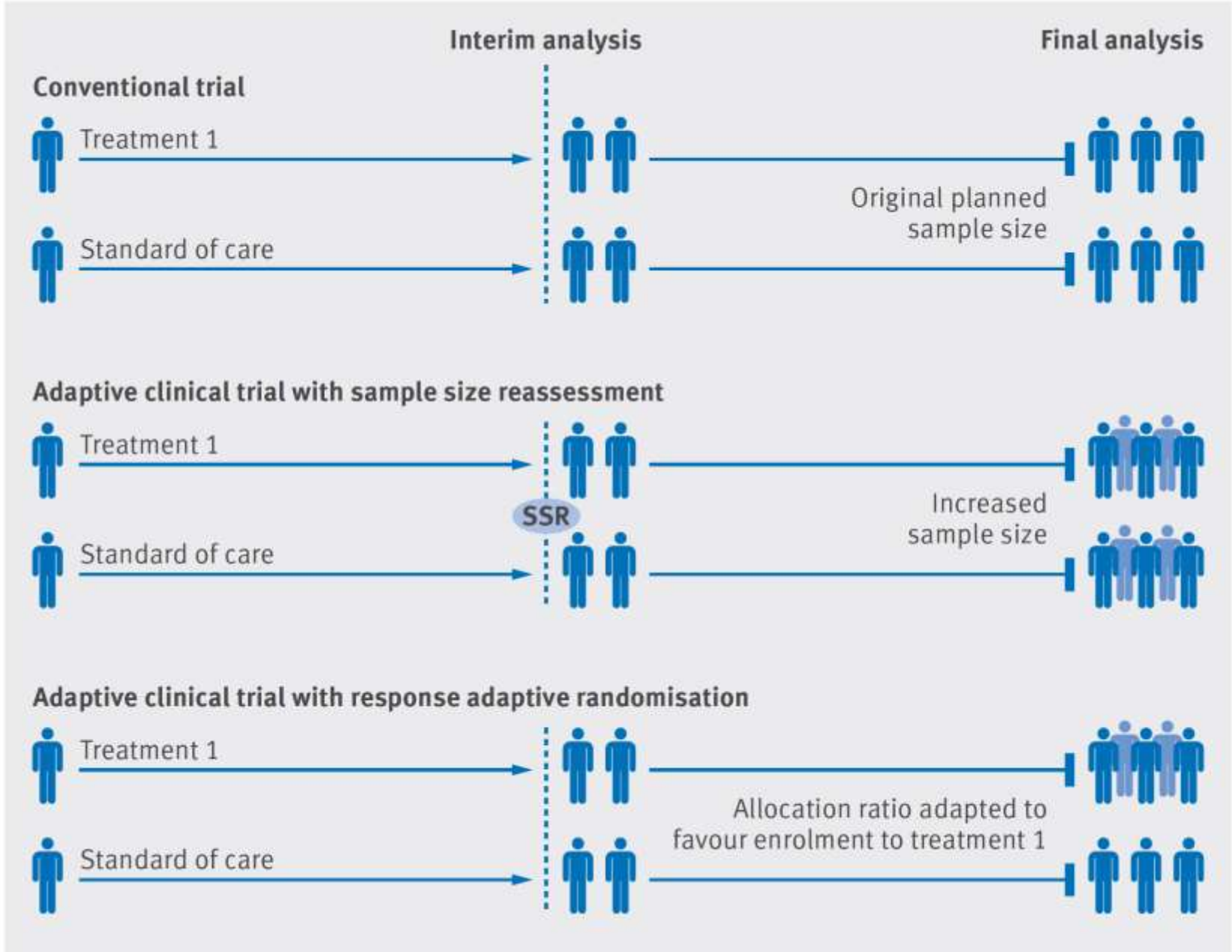
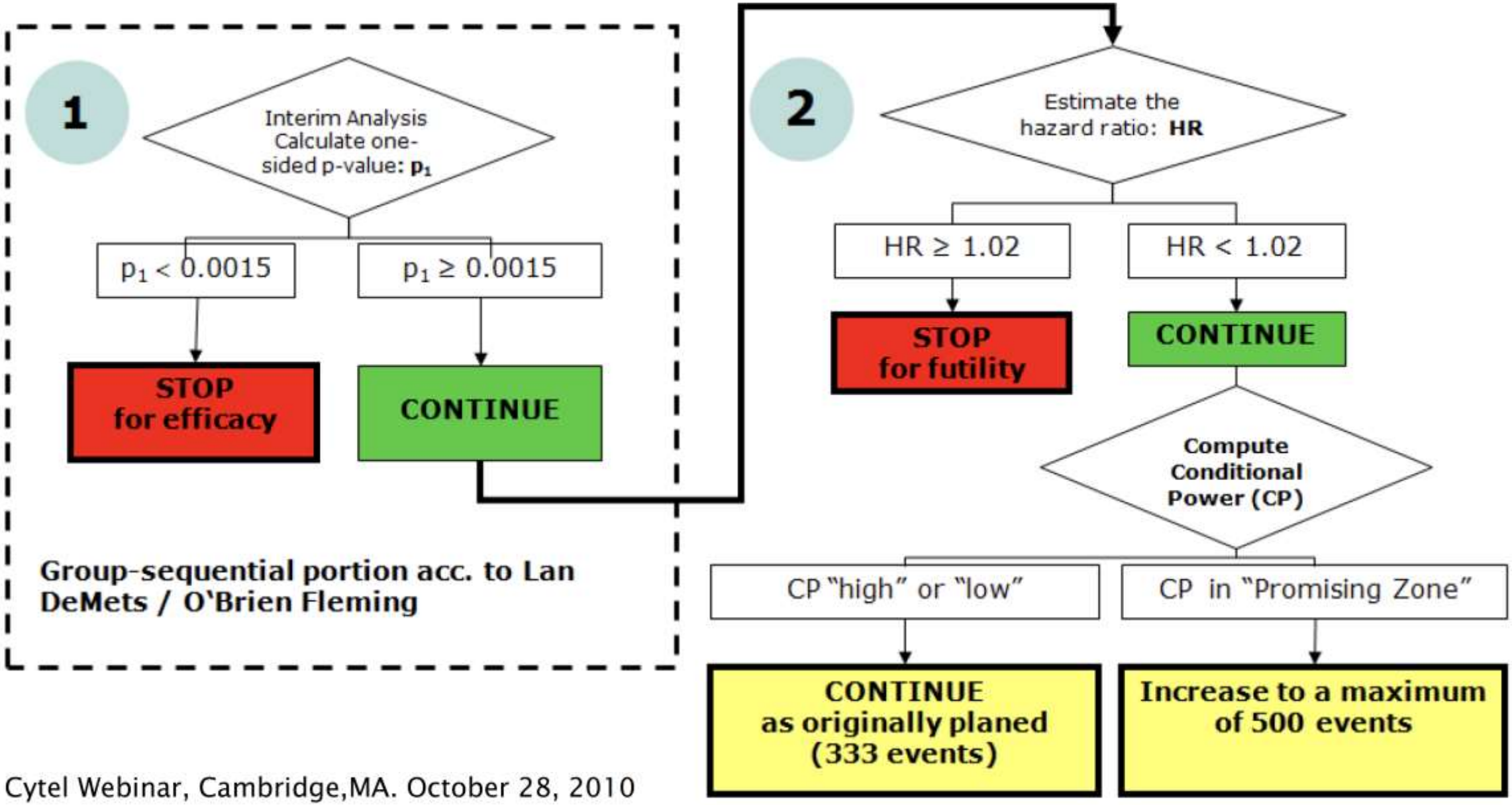
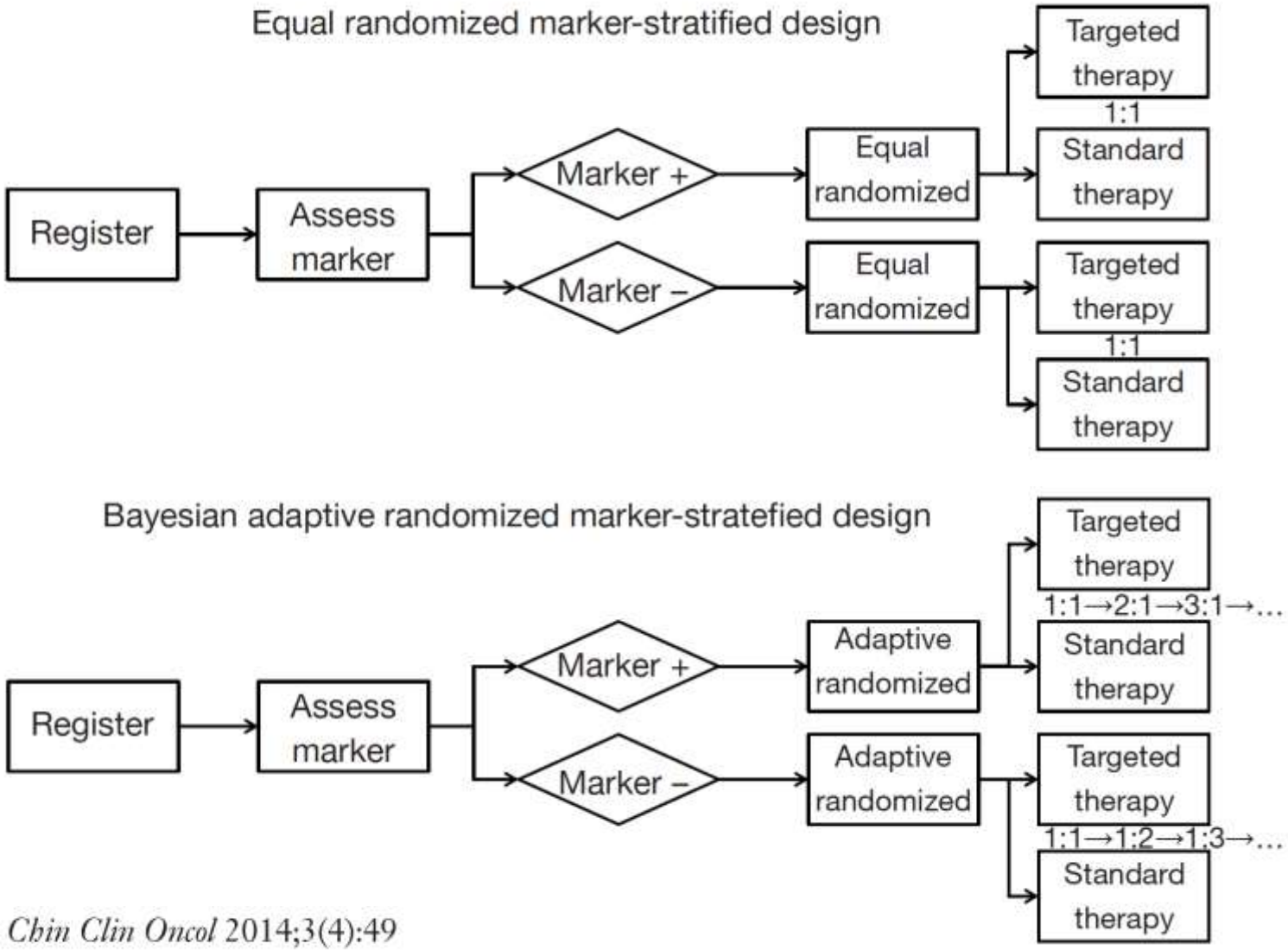


BMJ 2018;360:k698


1
Interim Analysis
Calculate one-sided p-value: p_1
$p_1 < 0.0015$
$p_1 \geq 0.0015$
STOP for efficacy
CONTINUE
Group-sequential portion acc. to Lan DeMets / O'Brien Fleming
2
Estimate the hazard ratio: HR
HR ≥ 1.02
HR < 1.02
STOP for futility
CONTINUE
Compute Conditional Power (CP)
CP "high" or "low"
CP in "Promising Zone"
CONTINUE as originally planed (333 events)
Increase to a maximum of 500 events

Diagrams of the marker-stratified design



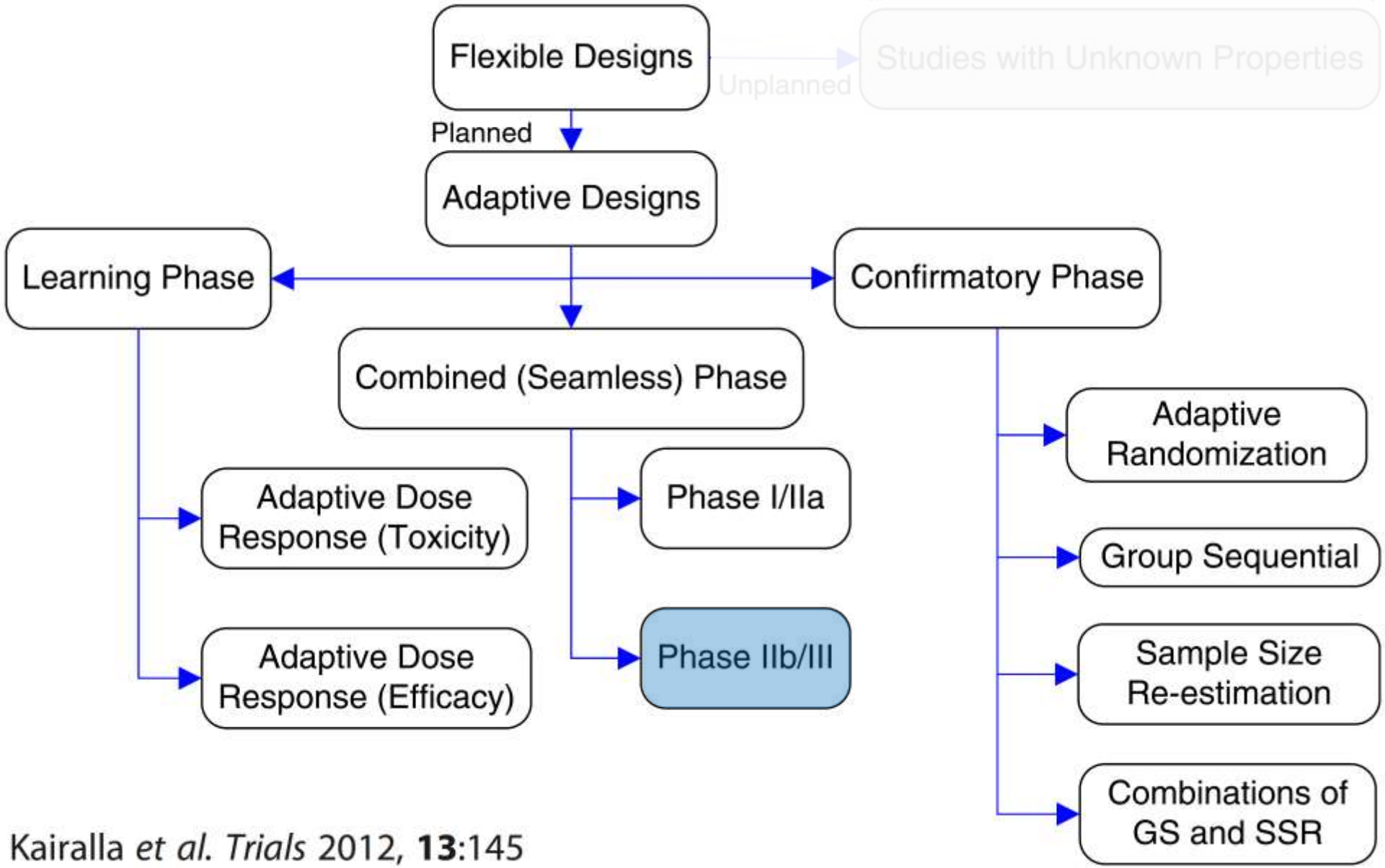
Chin Clin Oncol 2014;3(4):49

Equal randomized marker-stratified design has a fixed 1:1 randomization ratio throughout the trial to assign patients into the targeted therapy and the standard therapy, respectively.

On the other hand, the randomization ratio for the Bayesian adaptive randomized marker-stratified design varies during the trial.

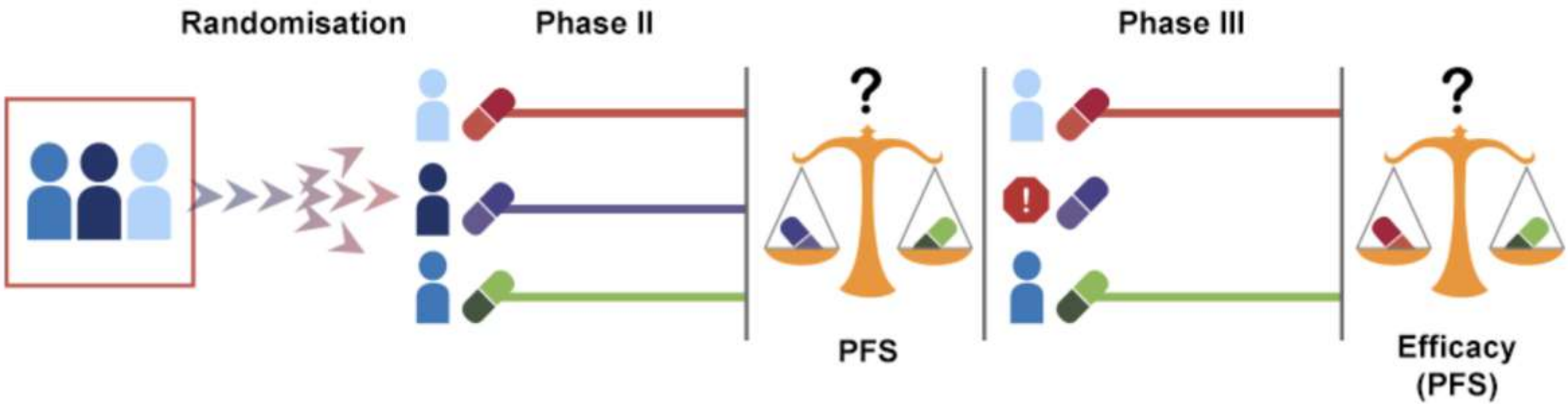
The randomization ratio in the marker positive group could change from 1:1 to 2:1 and to 3:1 while, in the marker negative group, they could change from 1:1 to 1:2 to 1:3 assuming that the targeted therapy is more effective for the marker positive patients and the standard therapy is more effective for the marker negative patients.

Summary of different types of adaptive designs for clinical trials.



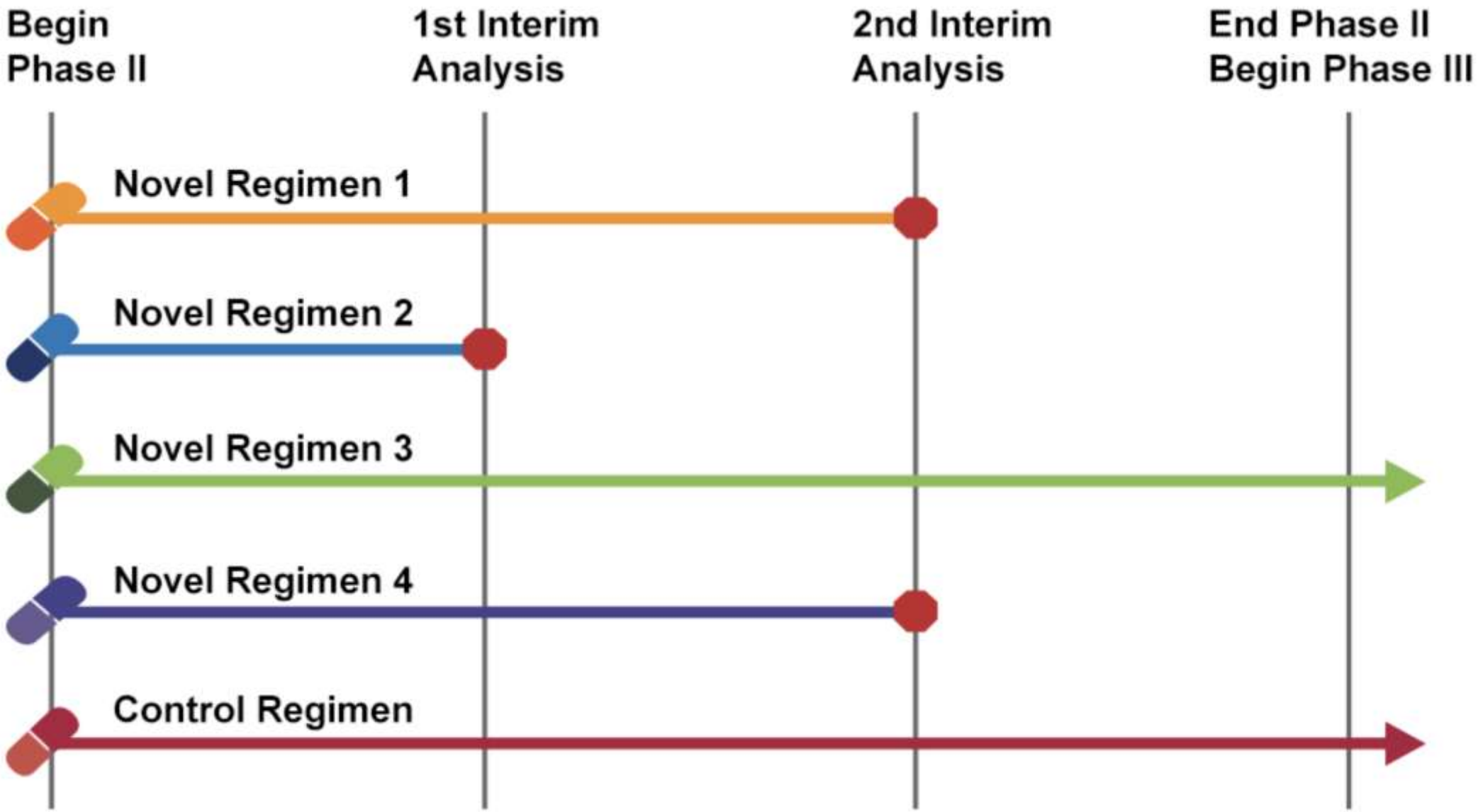
Kairalla *et al. Trials* 2012, **13**:145

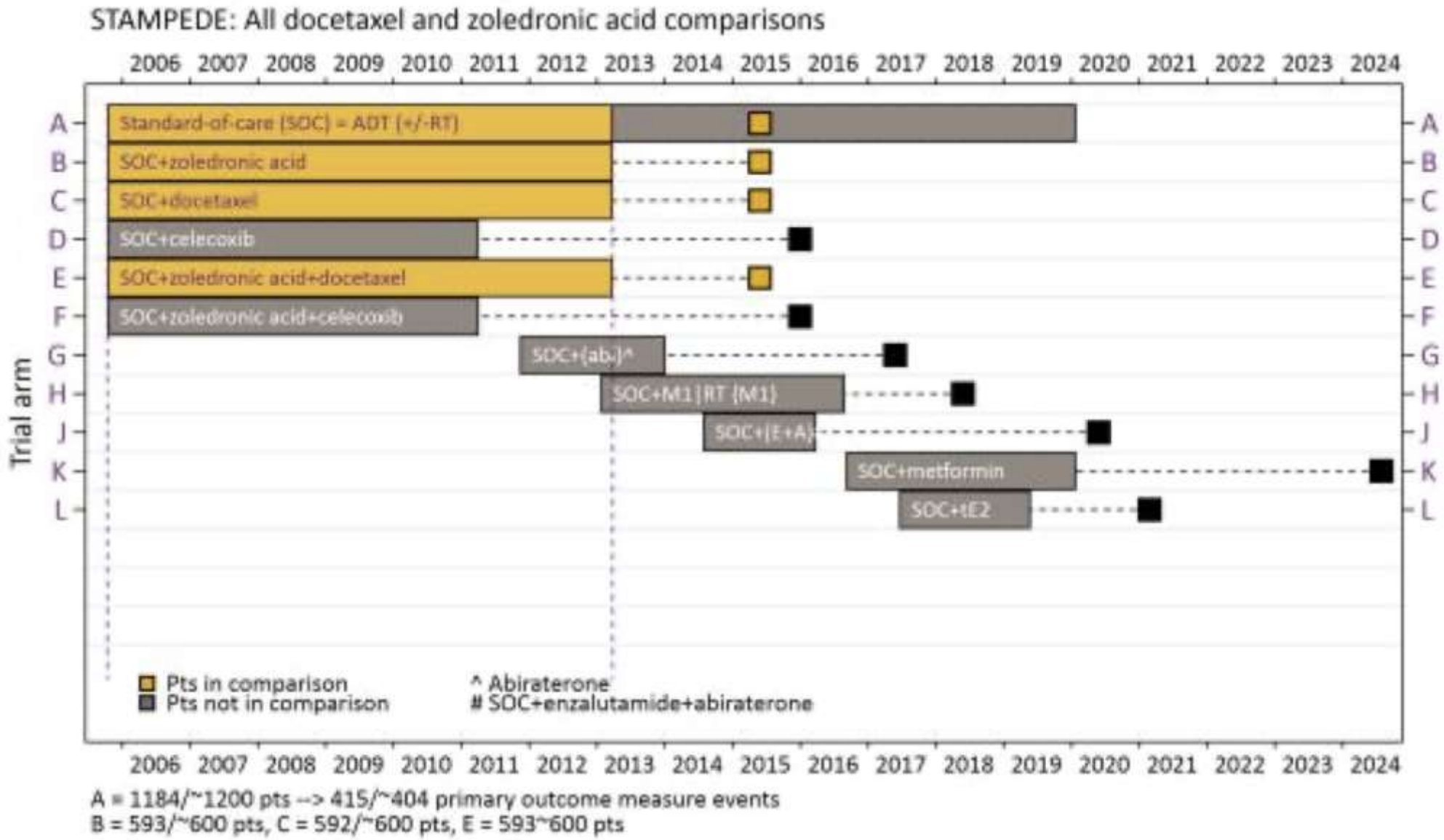
Seamless Phase II/III design



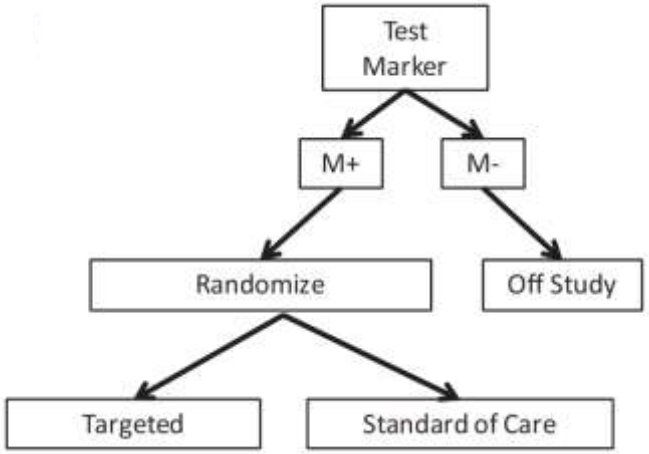
EUPATI
European Patients' Academy
on Therapeutic Innovation
www.eupati.eu

Multi-arm multi-stage (MAMS) design

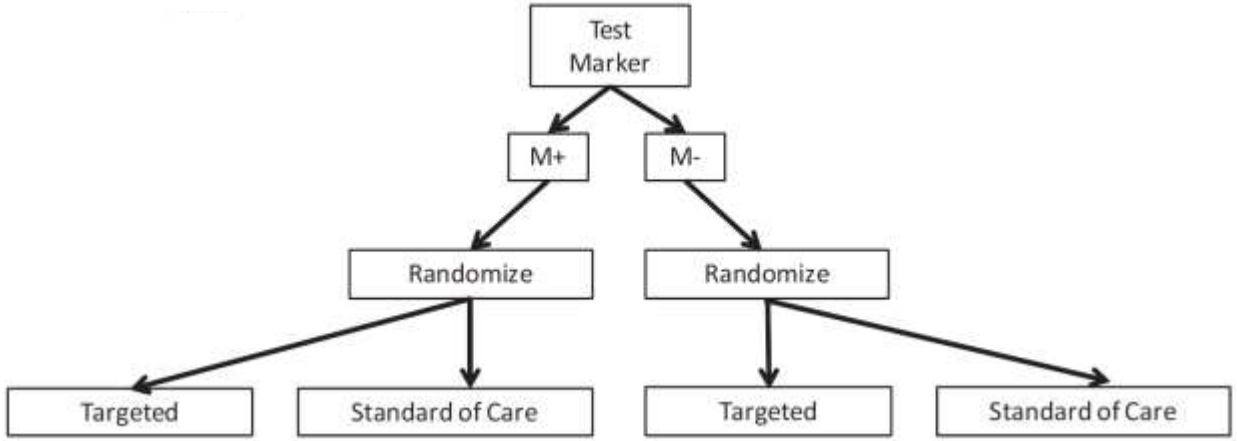




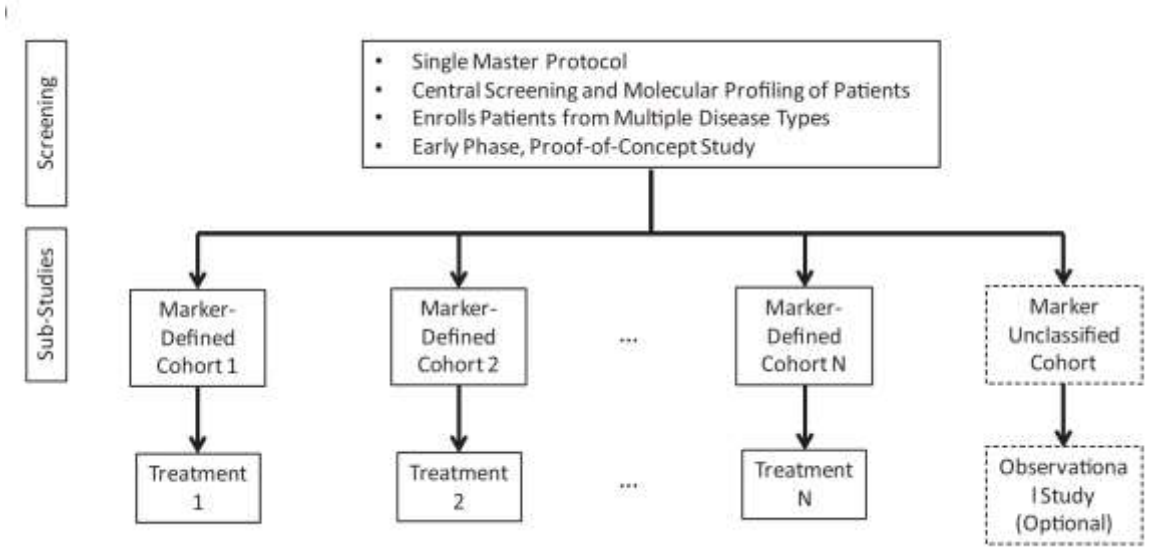
A = 1184/~1200 pts --> 415/~404 primary outcome measure events
B = 593/~600 pts, C = 592/~600 pts, E = 593~600 pts



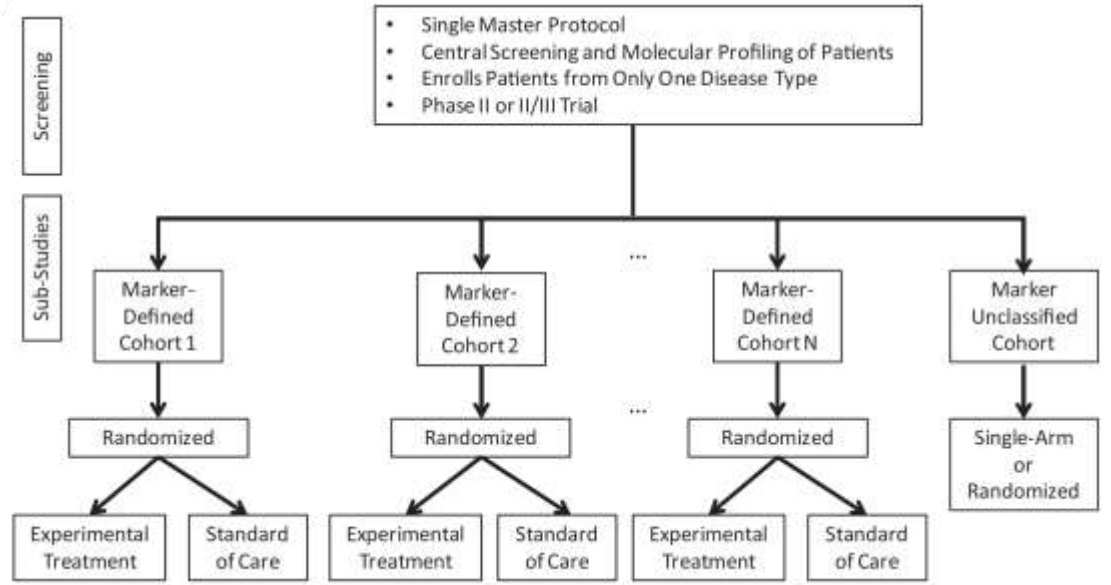
enrichment design



biomarker-by-treatment interaction design

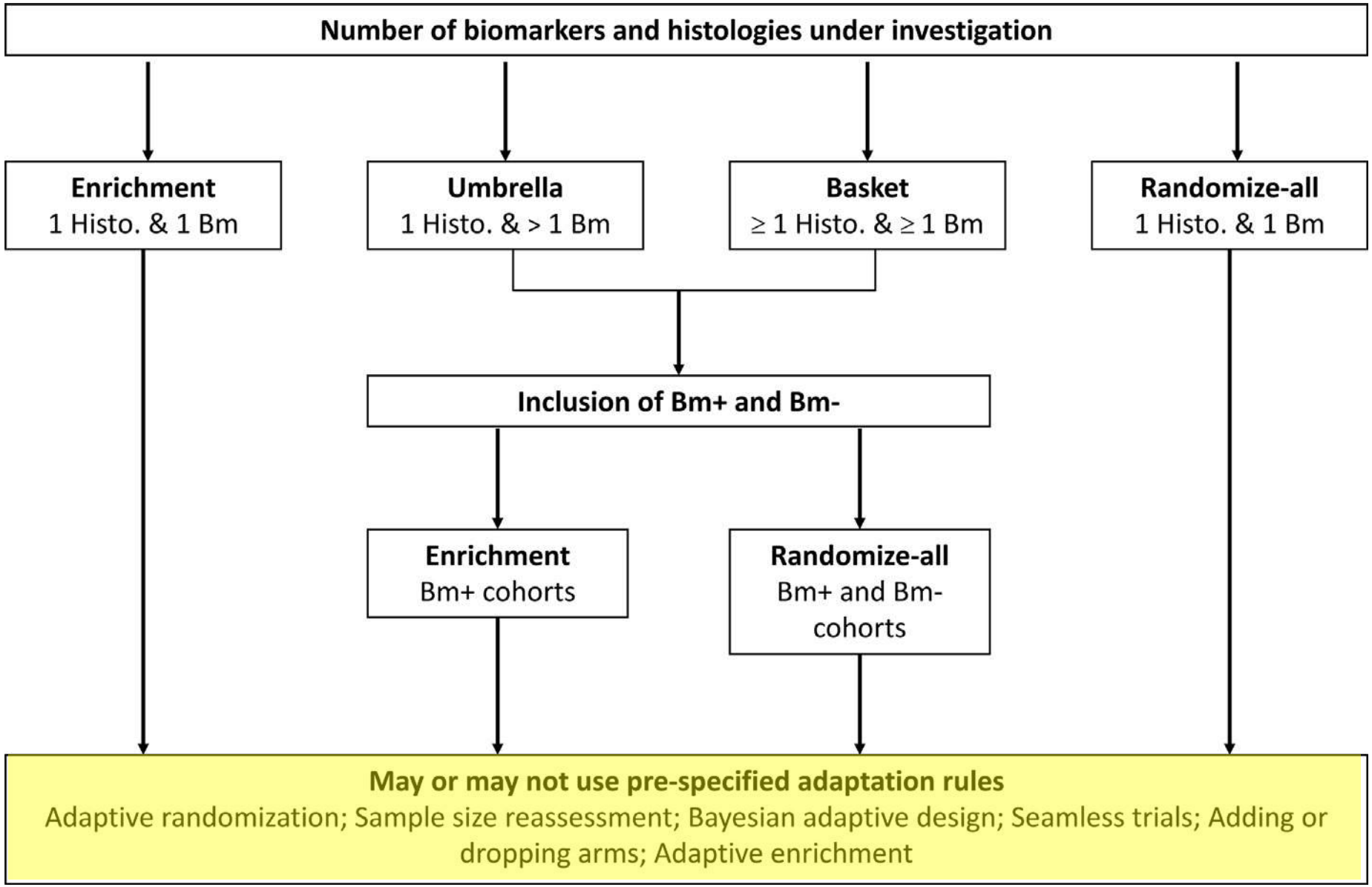


basket trial



umbrella trial

Cancer Treatment Reviews 73 (2019) 20–30



Adaptive designs: The Swiss Army knife among clinical trial designs?

Clinical Trials
2017, Vol. 14(5) 417–424

Frank Bretz[1], Paul Gallo[2] and Willi Maurer[1]

Sometimes, a standard two-armed trial (*scissor*) may be fully sufficient, at other occasions adding an interim analysis for early stopping or sample size review may be appropriate (*regular Swiss Army knife*) and in yet other situations we may want to embark on a more advanced adaptive design with treatment selection at interim (*giant Swiss Army knife*).

However, we need to be careful not to add too much adaptivity and thereby fall into the trap of believing that the more flexible our trial design is, the better it will perform

Adaptive designs: The Swiss Army knife among clinical trial designs?

Clinical Trials
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Frank Bretz[1], Paul Gallo[2] and Willi Maurer[1]

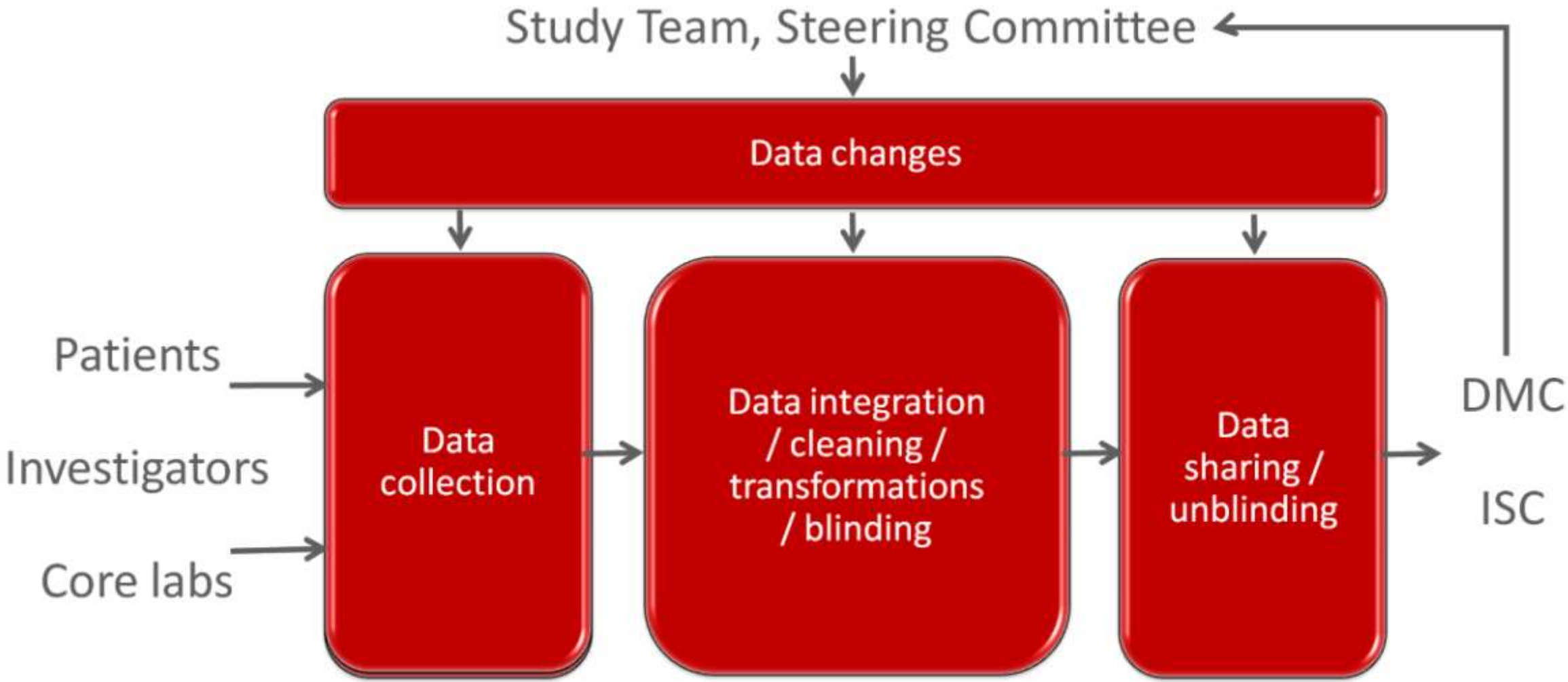
- **Operational Bias**
- **Multiplicity**
- **Sovrastima dell'*effect size***
- **Confusione tra generazione e verifica di ipotesi**

Overview of adaptive designs

Design	Idea
Continual reassessment method	Model-based dose escalation to estimate the maximum tolerated dose
Group-sequential	Include options to stop the trial early for safety, futility or efficacy
Sample size re-estimation	Adjust sample size to ensure the desired power
Multi-arm multi-stage	Explore multiple treatments, doses, durations or combinations with options to 'drop losers' or 'select winners' early
Population enrichment	Narrow down recruitment to patients more likely to benefit (most) from the treatment
Biomarker-adaptive	Incorporate information from or adapt on biomarkers
Adaptive randomisation	Shift allocation ratio towards more promising or informative treatment(s)
Adaptive dose-ranging	Shift allocation ratio towards more promising or informative dose(s)
Seamless phase I/II	Combine safety and activity assessment into one trial
Seamless phase II/III	Combine selection and confirmatory stages into one trial

Pallmann *et al. BMC Medicine* (2018) 16:29

Data architecture and data flow: challenges



Claudio Garutti, PhUSE 2014

Operationally, an adaptive design often requires real-time or near real-time data collection and analysis. In this regard, data standardizations, such as CDISC and electronic data capture (EDC), are very helpful in data cleaning and reconciliation. Note that not all adaptive designs require perfectly clean data at interim analysis, but the cleaner the data are, the more efficient the design is. Adaptive designs require the ability to rapidly integrate knowledge and experiences from different disciplines into the decision-making process and, hence, require a shift to a more collaborative working environment among disciplines.

CLINICAL TRIALS ARENA

12 AUGUST 2015

Adaptive electronic data capture (EDC) at field, patient and study arm levels

PhUSE 2014

Data Challenges in Adaptive Trials