Symposium inter-disciplinaire sur le sepsis
Jeudi 8 septembre 2022

Avancées méthodologiques en recherche clinique

Place et avenir des essais adaptatifs

Pr Sylvie Chevret

Université Paris Cité, Inserm UMR 1153 (ECSTRRA),

Hôpital saint Louis, APHP

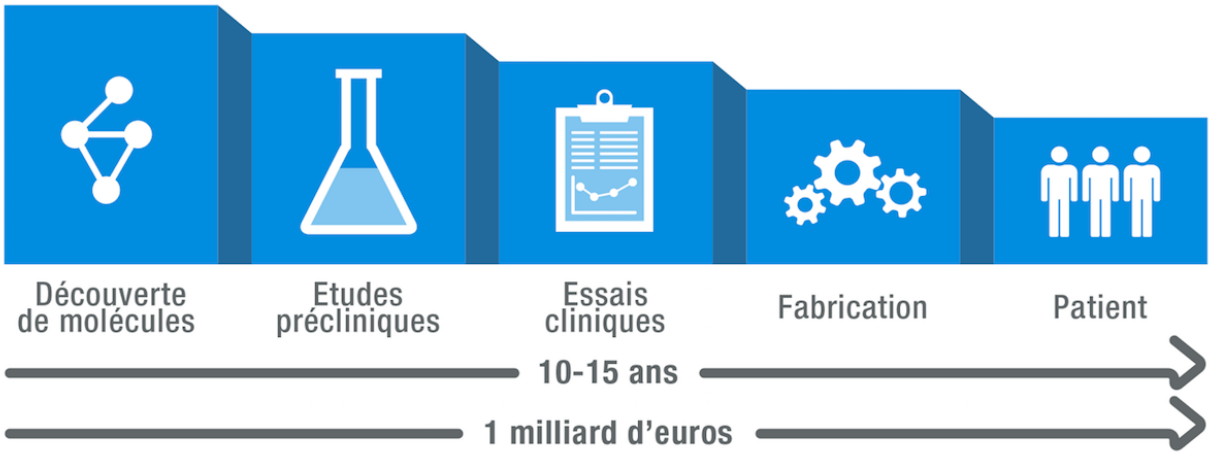
Plan

- Motivations
- Définitions
- Principes, exemples

- Place actuelle
- Avenir ?

Motivations

- Constat
  - Processus long, lent et coûteux



- *Between the years 1963 and 1975, the total cost of bringing a new drug to the market was estimated at $119 million. Recent estimates put the cost of having a drug approved at $802 million dollars*

  - *The dramatic rise in drug development costs is mainly explained by the increase in size and complexity of clinical trials dictated by monopoly national regulatory agencies*

Reducing barriers to the development of high quality, low cost medicines

A proposal for reforming the drug approval process

International Policy Network
Third Floor, Bedford Chambers
The Piazza
London WC2E 8HA UK

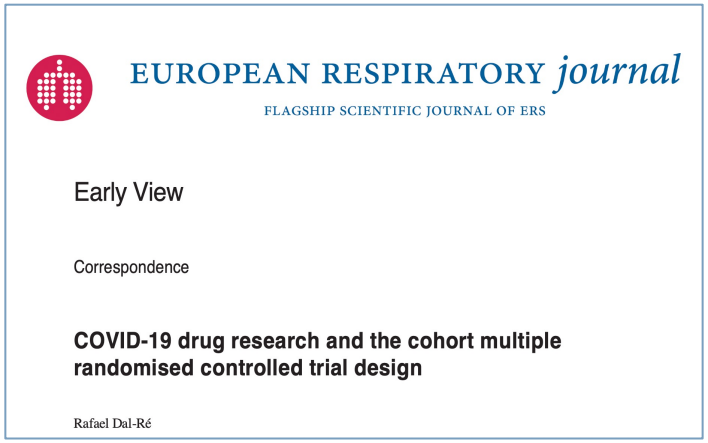
Corinne Sauer
Jerusalem Institute for Market Studies

Robert M. Sauer
Hebrew University of Jerusalem, IZA
Jerusalem Institute for Market Studies

- Constat
  - Processus dispersé …

Exemple : COVID-19

Peu après le début de la pandémie de COVID-19, en mai 2020, plus de 1 300 essais étaient enregistrés dans le monde entier, sont 82 % visaient l'évaluation de médicaments ou de produits biologiques


EUROPEAN RESPIRATORY *journal*

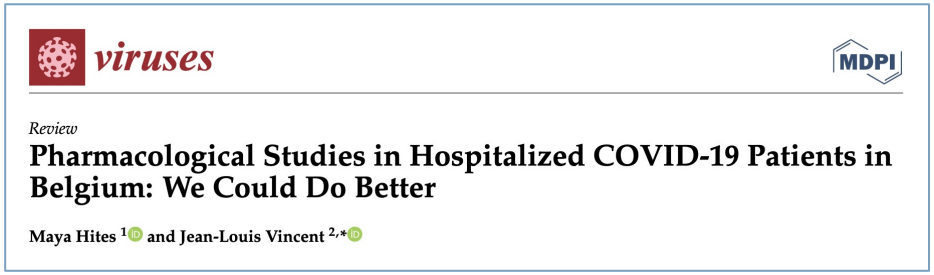
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Correspondence

COVID-19 drug research and the cohort multiple randomised controlled trial design

Rafael Dal-Ré


viruses

MDPI

Review

Pharmacological Studies in Hospitalized COVID-19 Patients in Belgium: We Could Do Better

Maya Hites [1] and Jean-Louis Vincent [2,*]

- Constat
  - Processus incertain dans ses postulats/hypothèses

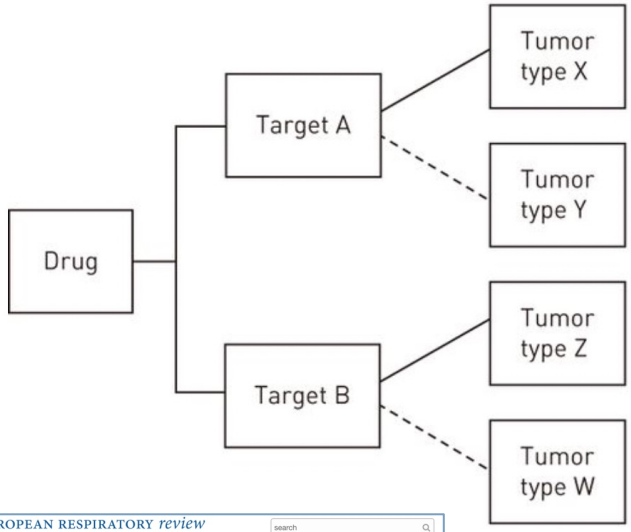
Exemple : Revue de 38 essais en USI

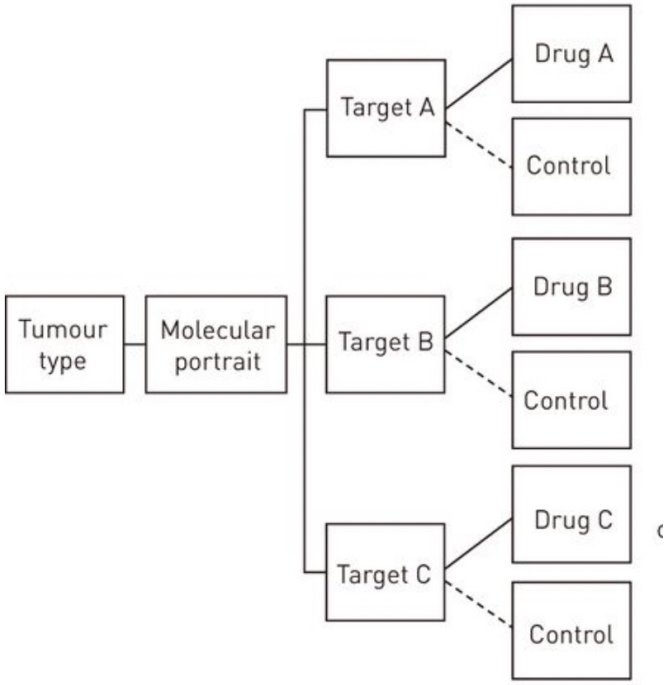
- Moyenne de la différence escomptée 10.1%
- Moyenne de la différence observée 1.4%
  - Essais faussement négatifs
  - Essais inéthiques car non puissants

- Pistes d'amélioration (1)

Répondre à plusieurs questions dans un seul essai : l'exemple des thérapies ciblées en oncologie

➢Basket & Umbrella Trials






EUROPEAN RESPIRATORY *review*

THE RESPIRATORY PROFESSIONAL'S UPDATE ON MEDICINE, SCIENCE AND SURGERY

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New clinical research strategies in thoracic oncology: clinical trial design, adaptive, basket and umbrella trials, new end-points and new evaluations of response

Jessica Menis, Baktiar Hasan, Benjamin Besse

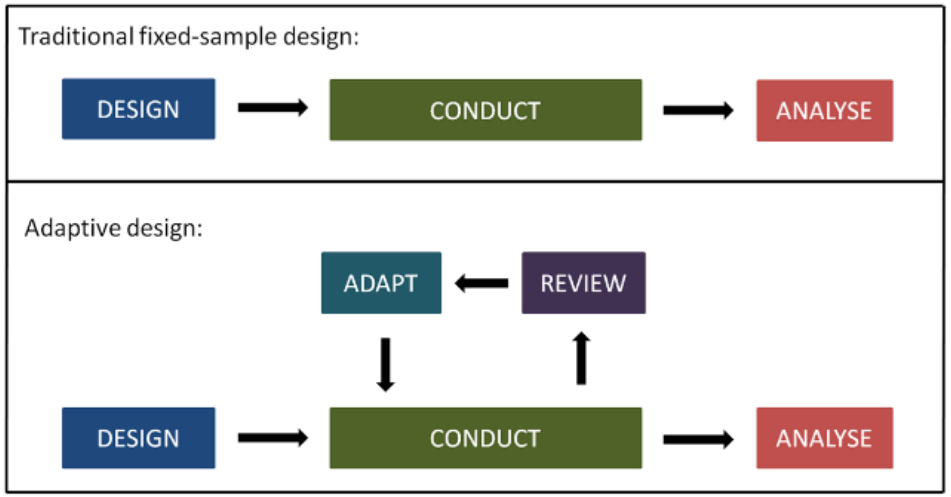
European Respiratory Review 2014 23: 367-378; DOI: 10.1183/09059180.00004214

• Pr Sylvie Chevret

- Pistes d'amélioration (2)

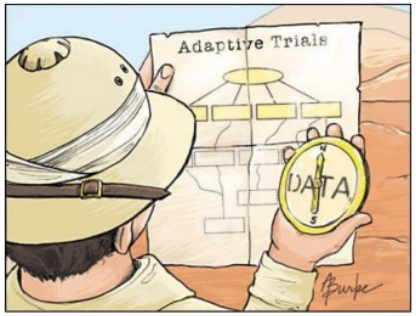
Augmenter la probabilité d'atteindre l'objectif de l'essai en tirant partie des connaissances acquises en cours d'essai

➢Essais adaptatifs ("Adaptive Designs")



Pallmann et al. BMC Medicine (2018) 16:29
https://doi.org/10.1186/s12916-018-1017-7
BMC Medicine
CORRESPONDENCE Open Access

Adaptive designs in clinical trials: why use them, and how to run and report them



JAMA 2006;296:1955-1957.

Définitions

- Schémas définis par

  = "*Changes in design or analyses guided by examination of the accumulated data at an interim point in the trial*"

  Étude **prospective** pré-définissant la possibilité de modifications d'un ou plusieurs aspects de son plan expérimental et des hypothèses postulées

  - à partir de l'analyse (en règle intermédiaire) des données de l'essai

- Aussi (initialement) appelés schémas "flexibles"

(1) FDA Guidance for Industry- Adaptive Design Clinical Trials for Drugs and Biologics- DRAFT GUIDANCE (2010 Feb.)

- Schémas adaptatifs : objectifs ?

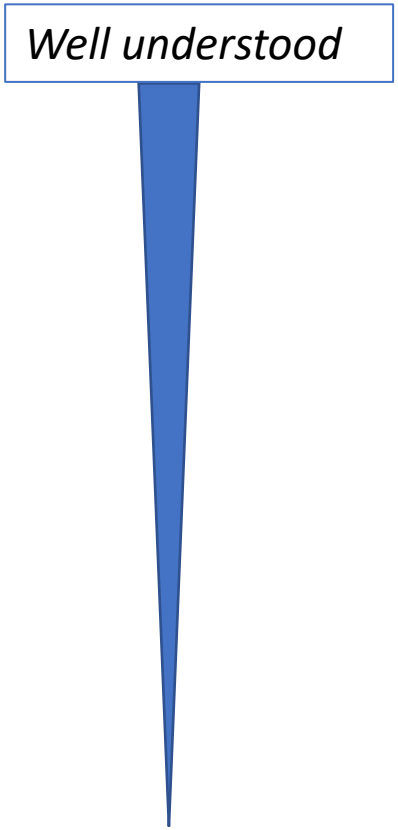
  = "*Changes in design or analyses guided by examination of the accumulated data at an interim point in the trial*"

  "… that may make the studies more efficient (e.g., shorter duration, fewer patients), more likely to demonstrate an effect of the drug if one exists, or more informative (e.g., by providing broader dose-response information)"

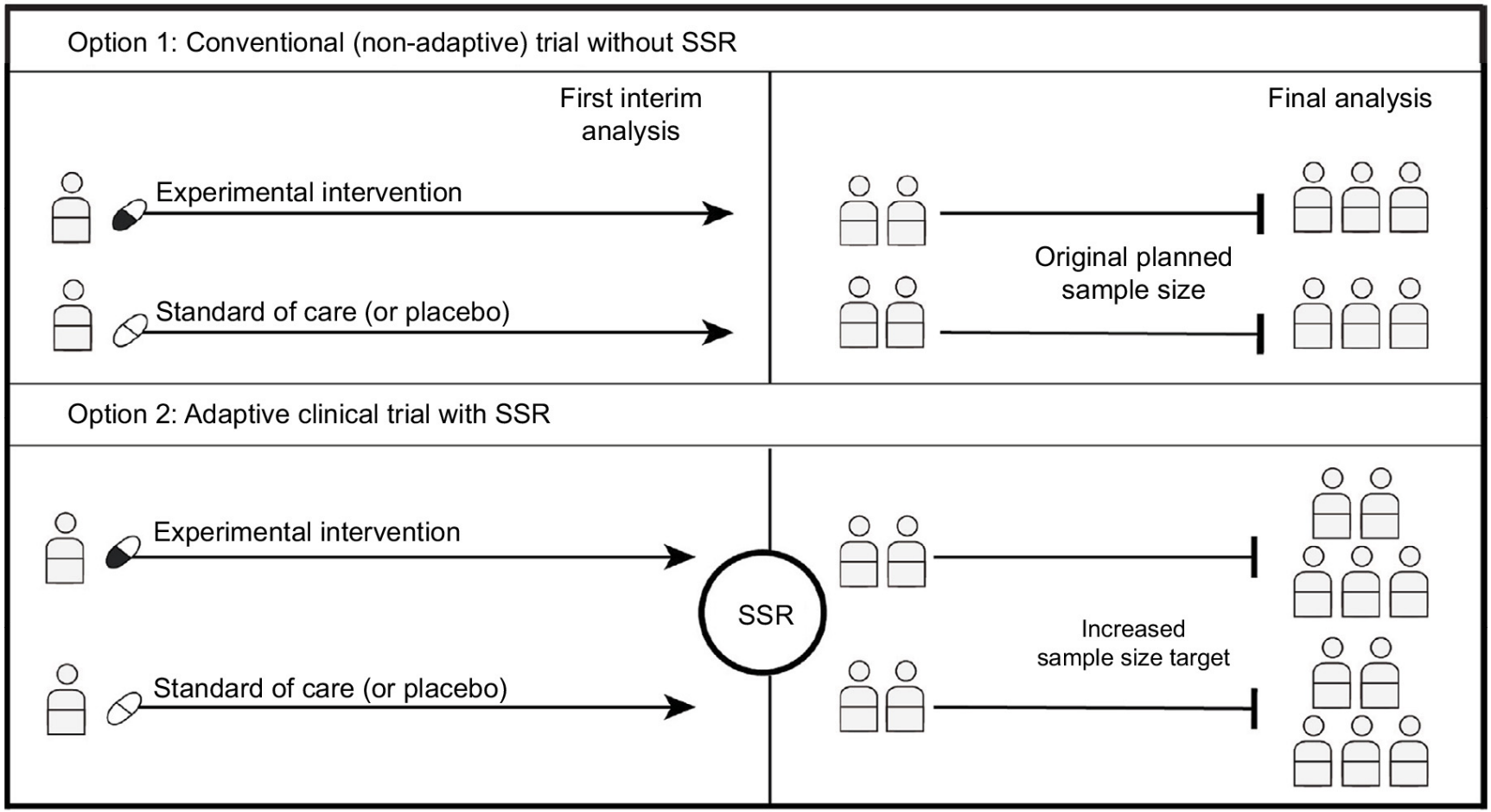
(1) FDA Guidance for Industry- Adaptive Design Clinical Trials for Drugs and Biologics- DRAFT GUIDANCE (2010 Feb.)

- Quelles modifications ?
- Des plus connues (*Well understood*)

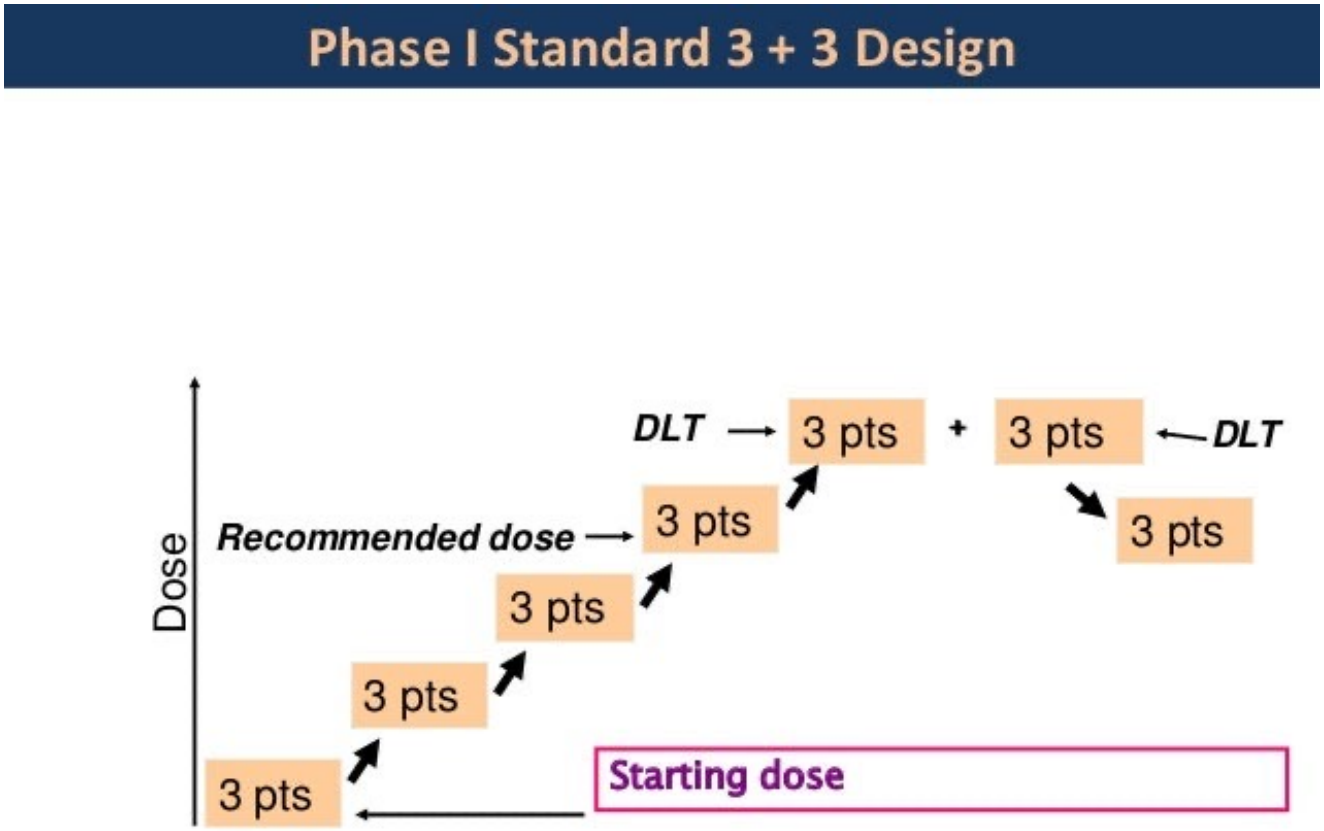
  - Taille de l'échantillon
    - Essais séquentiels groupés
    - **Réévaluation (augmentation) du nombre d'inclus**
  - Traitements (dose, durée, fréquence, …)
    - **Essais de recherche de dose (phase I)**
    - **Essais de phase I/II combinés**
    - Essais de sélection (screening)
  - Procédure de randomisation
    - Essais avec randomisation adaptative
  - Critères d'éligibilité
    - Schémas d'enrichissement de la population



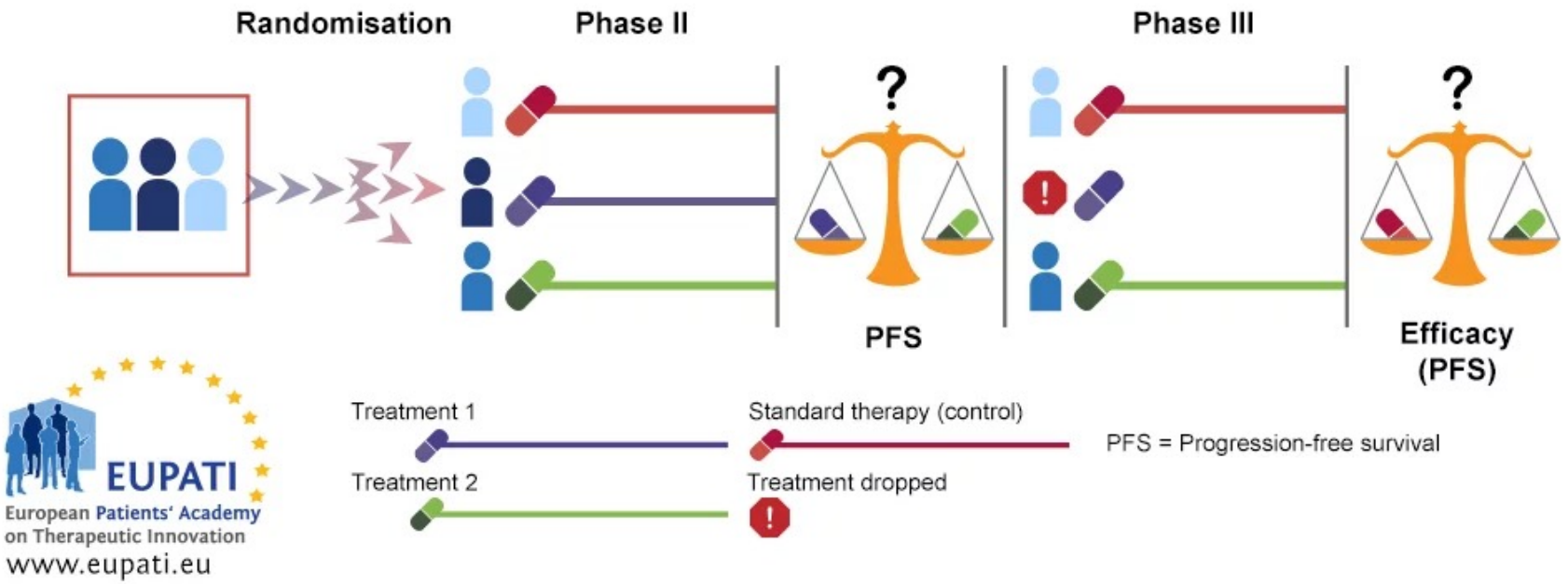
Ex 1: Réévaluation du nombre d'inclus



EX 2: Essais de recherche de dose



EX 3 : Seamless Phase 2-3

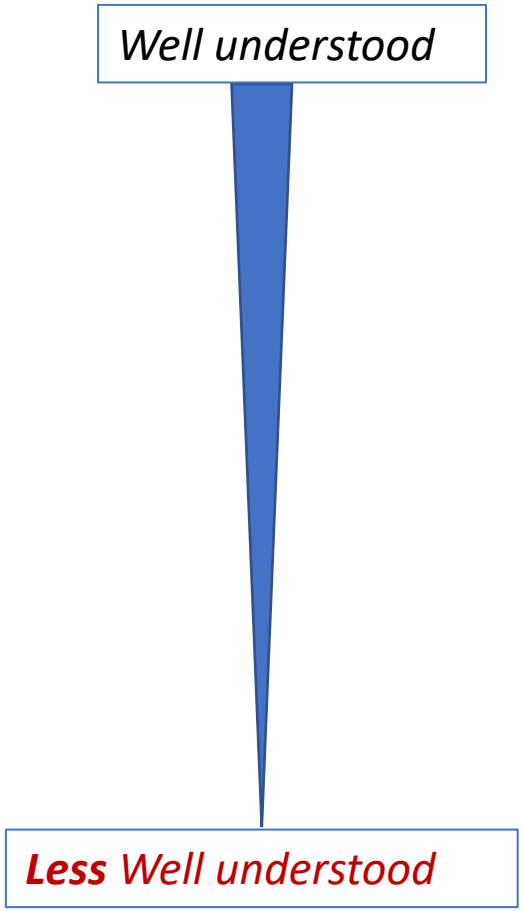


- Quelles modifications ?

aux moins évaluées et utilisées …

- Taille de l'échantillon
  - Essais séquentiels groupés
  - Réévaluation (augmentation) du nombre d'inclus
- Traitements (dose, durée, fréquence, …)
  - Essais de recherche de dose (phase I)
  - Essais de phase I/II combinés
  - **Essais de sélection (screening)**
- Procédure de randomisation
  - **Essais avec randomisation adaptative**
- Critères d'éligibilité
  - **Schémas d'enrichissement de la population**

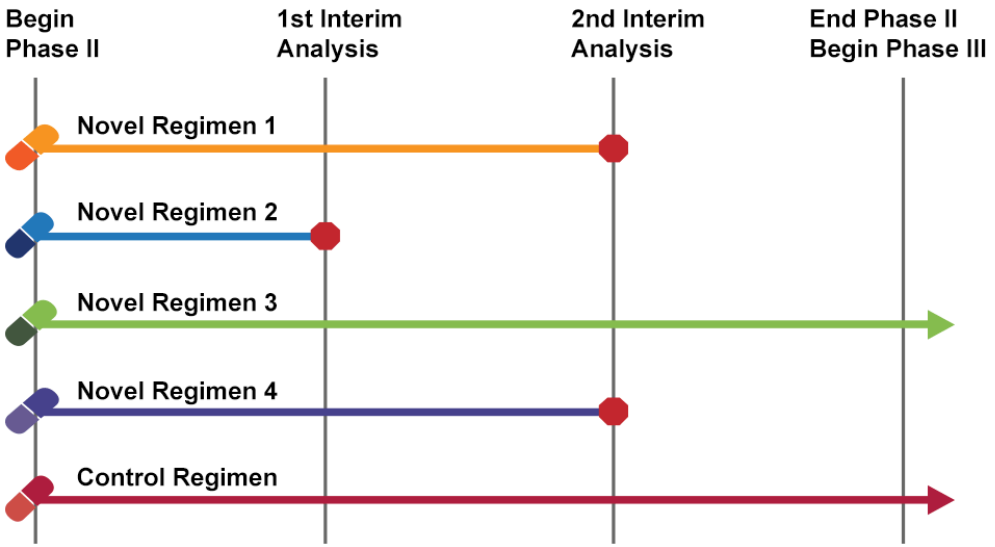
- **Le tout … ?**
  - **Essais plateforme**



Ex 1 : Essais de screening : multi-bras multi-stades (*MultiArm MultiStage*, MAMS)

- But : Evaluer plusieurs traitements expérimentaux contre un traitement contrôle, d'attribution randomisée

*Antérieurement "**Select/Drop** designs"*



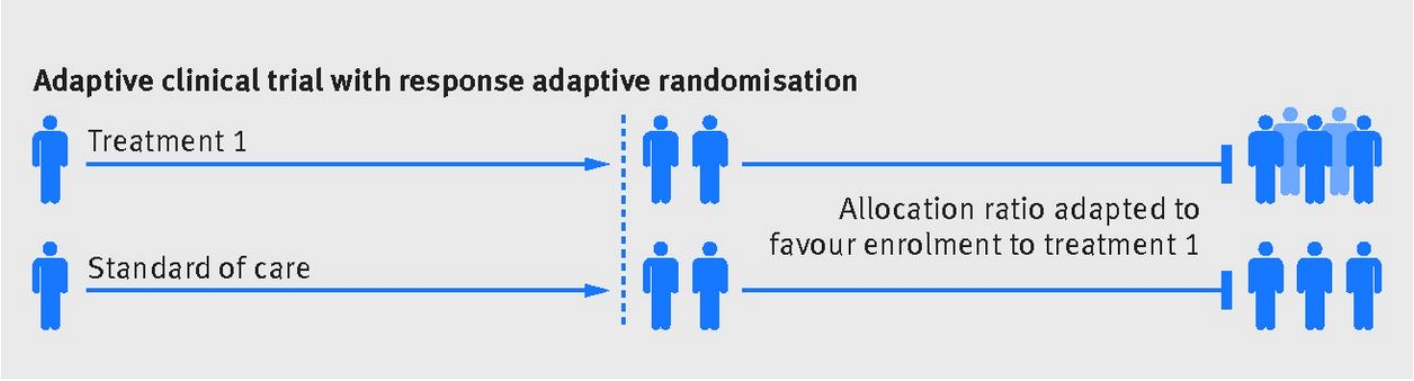
**Wason, Trippa. Statistics Med2014;33:2206-21*
Proschan, Dodd. Statistics Med 2014;33:3241-52

Maggir, Stallard, Jaki. Statistics Med 2014;33:3269-79

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

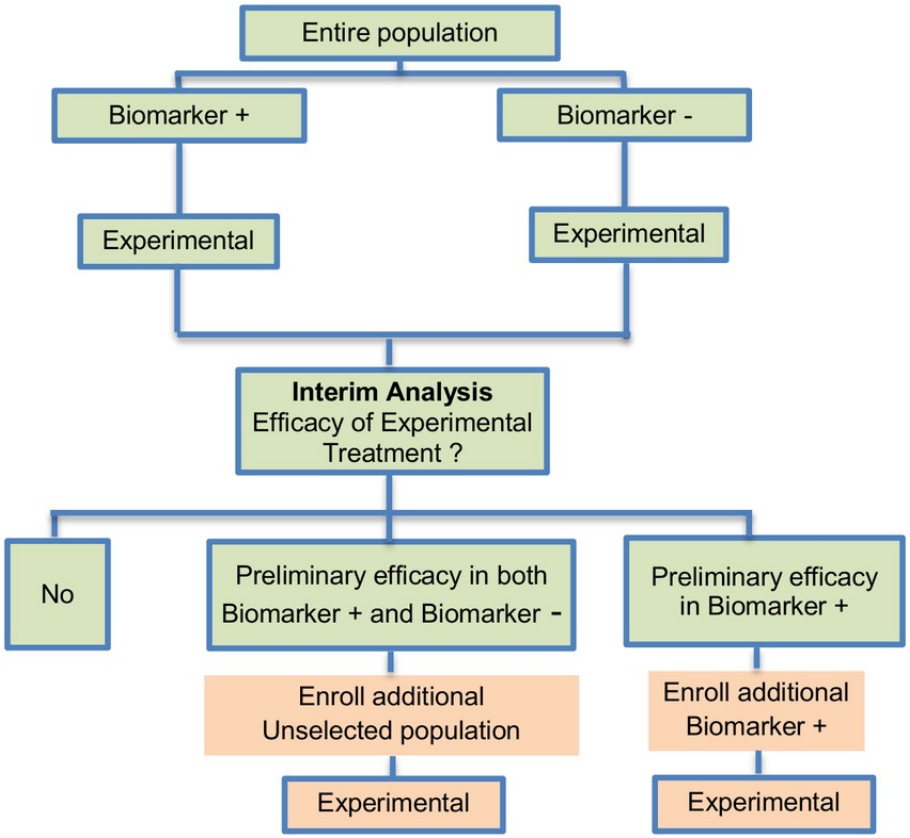
Ex 2 : Schémas de randomisation adaptative

- But : actualiser la proportion de sujets alloués à chaque bras en fonction de la réponse observée

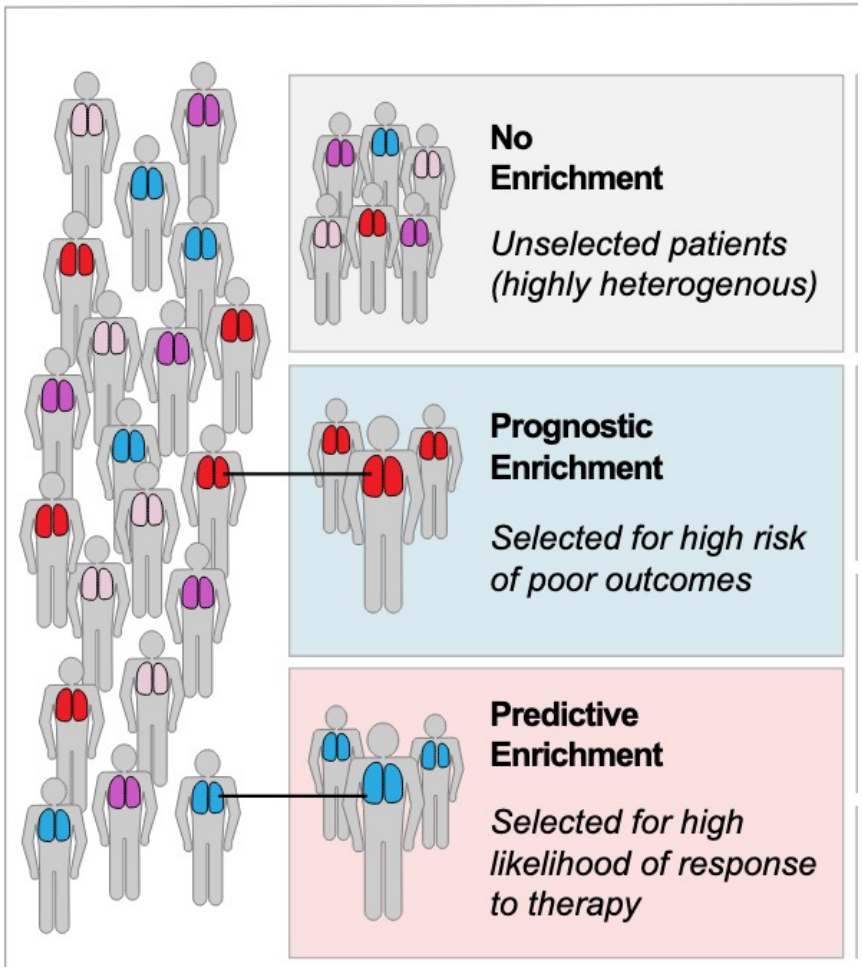


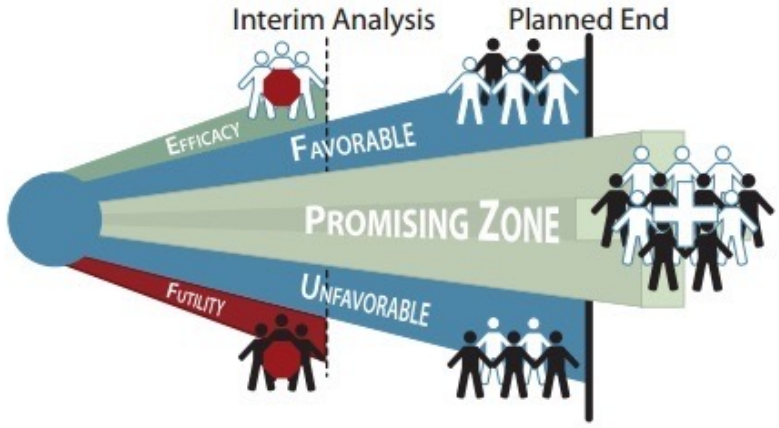
Ex 3 : Biomarker-adaptive randomisation

- But : actualiser la proportion de sujets alloués à chaque bras en fonction du biomarqueur



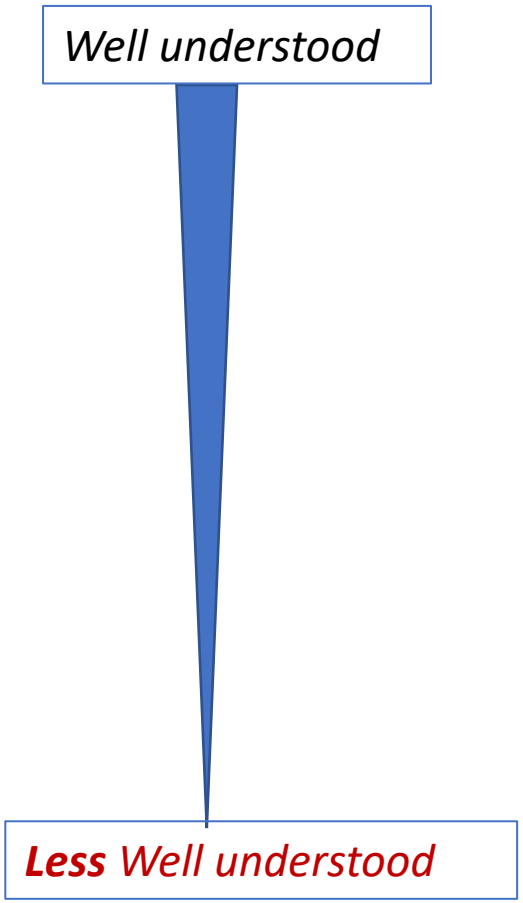
Ex 4: Schémas d'enrichissement de population



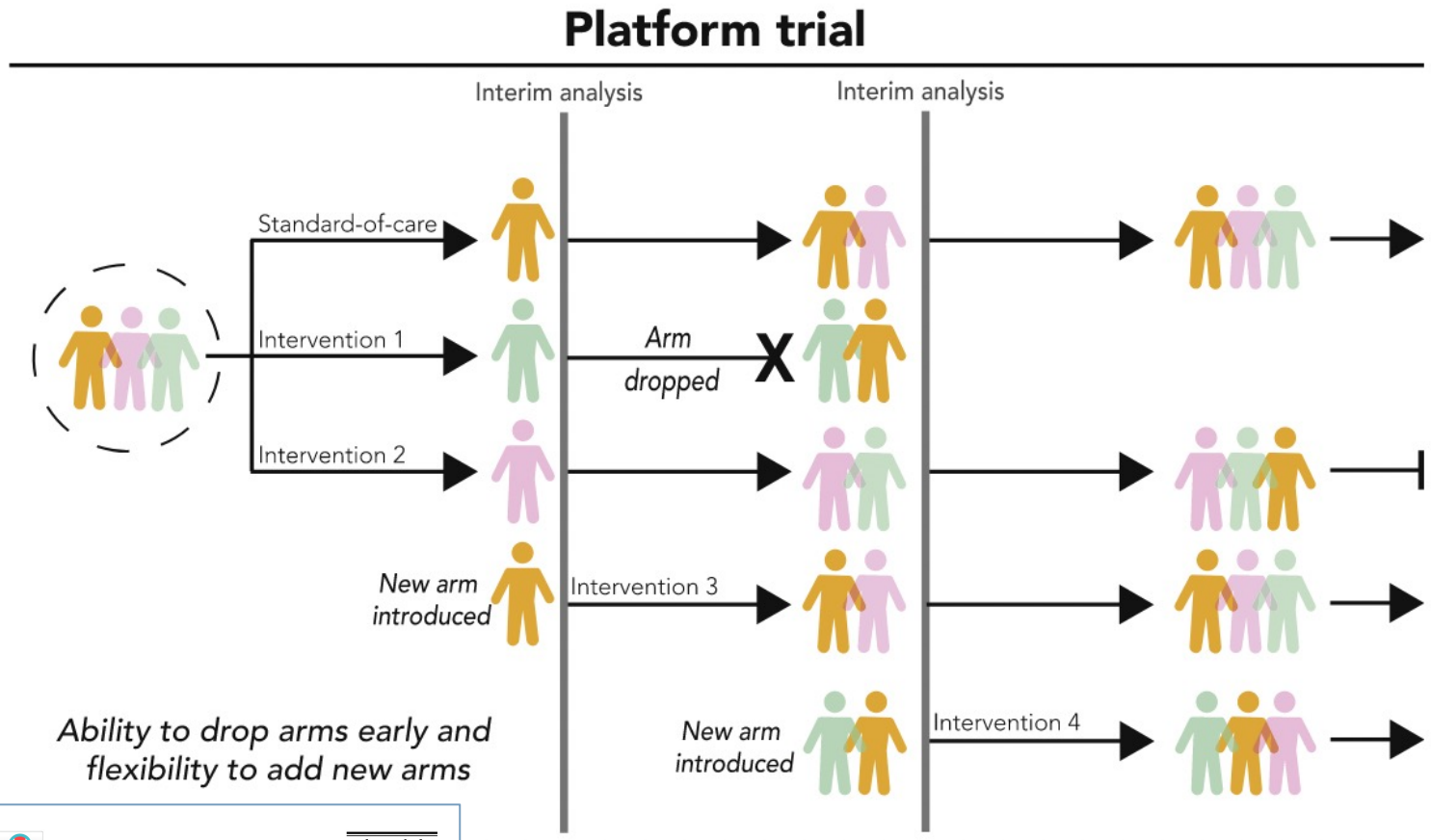


- Taille de l'échantillon
  - Essais séquentiels groupés
  - Réévaluation (augmentation) du nombre d'inclus
- Traitements (dose, durée, fréquence, …)
  - Essais de recherche de dose (phase I)
  - Essais de phase I/II combinés
  - Essais de sélection (screening)
- Procédure de randomisation
  - Essais avec randomisation adaptative
- Critères d'éligibilité
  - **Schémas d'enrichissement de la population**

- **Au maximum : modifier le tout … ?**
  - **Essais plateforme/master Protocols**



Exemple 1



ELSEVIER
Journal of Clinical Epidemiology 125 (2020) 1–8
Journal of Clinical Epidemiology

REVIEW

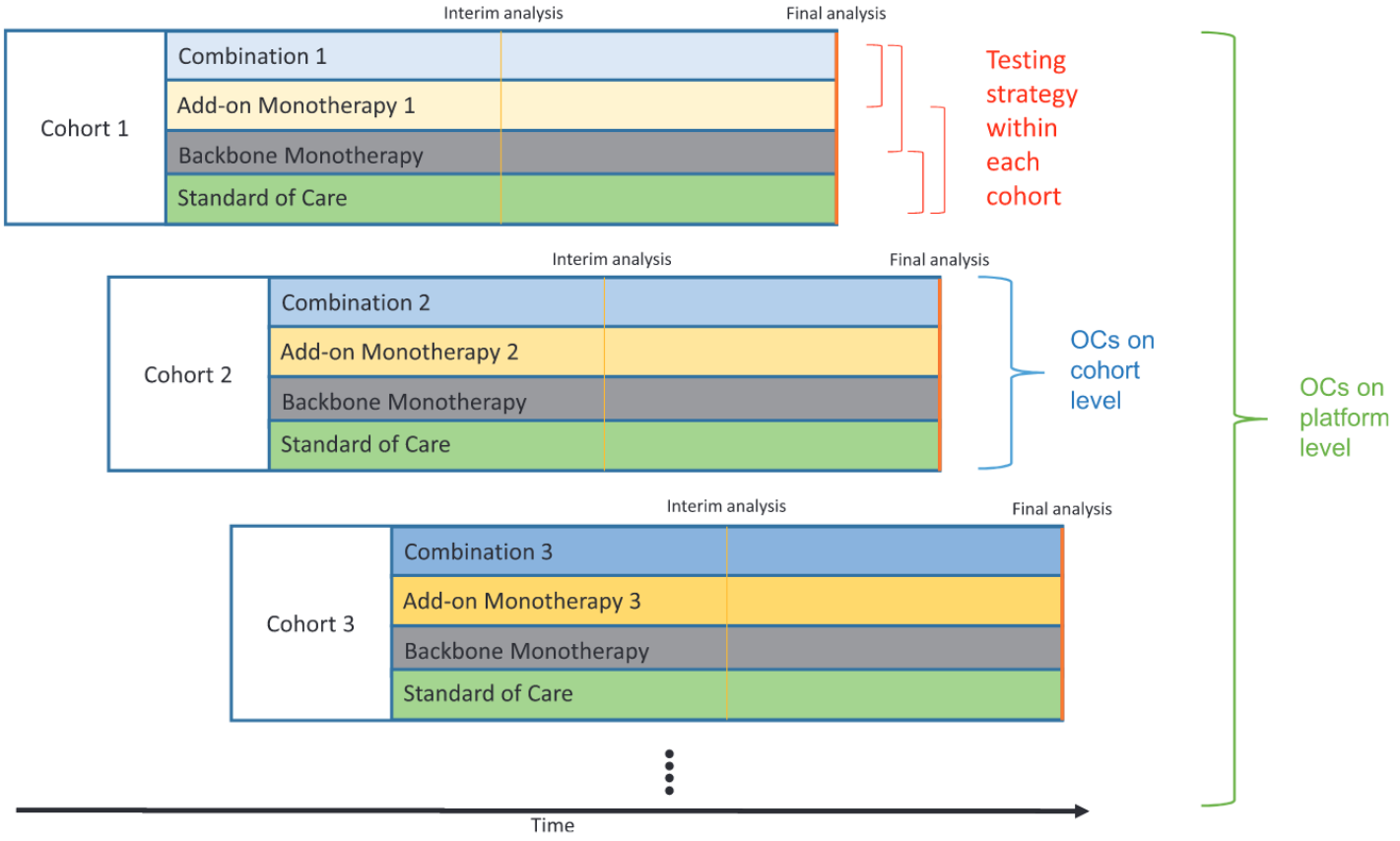
An overview of platform trials with a checklist for clinical readers

Jay J.H. Park[a,b], Ofir Harari[b,c], Louis Dron[b,c], Richard T. Lester[a], Kristian Thorlund[b,c], Edward J. Mills[b,c,*]

[a]Department of Medicine, Experimental Medicine, University of British Columbia, Vancouver, British Columbia, Canada
[b]Cytel, Vancouver, British Columbia, Canada
[c]Department of Health Research Methodology, Evidence, and Impact (HEI), McMaster University, Hamilton, Ontario, Canada

Accepted 22 April 2020; Published online 13 May 2020

Exemple 2



Received: 19 February 2021 | Revised: 29 October 2021 | Accepted: 9 January 2022
DOI: 10.1002/pst.2194

MAIN PAPER

WILEY

Decision rules for identifying combination therapies in open-entry, randomized controlled platform trials

Elias Laurin Meyer[1] | Peter Mesenbrink[2] | Cornelia Dunger-Baldauf[3] | Ekkehard Glimm[3,4] | Yuhan Li[2] | Franz König[1] | EU-PEARL (EU Patient-cEntric clinicAl tRial pLatforms) Consortium

Pr Sylvie Chevret

Principes

"A clinical trial design that uses accumulating data to decide how to modify aspects of the study as it continues, ***without undermining the validity and integrity of the trial****"*

Distinction

- essai confirmatoire / exploratoire
- méthodes maîtrisées ("well understood") / non

Adaptive Designs in Clinical Drug Development : An Executive Summary of the PhRMA Working Group. Journal of Biopharmaceutical Statistics, 16: 275-283, 2006

1- Respecter la validité (interne) de l'essai

"validité approximative avec laquelle nous déduisons qu'une relation entre deux variables est causale" (Campbell, 1966)

- Contrôle des sources de Biais ("opérationnel" +++ : influence sur les investigateurs)

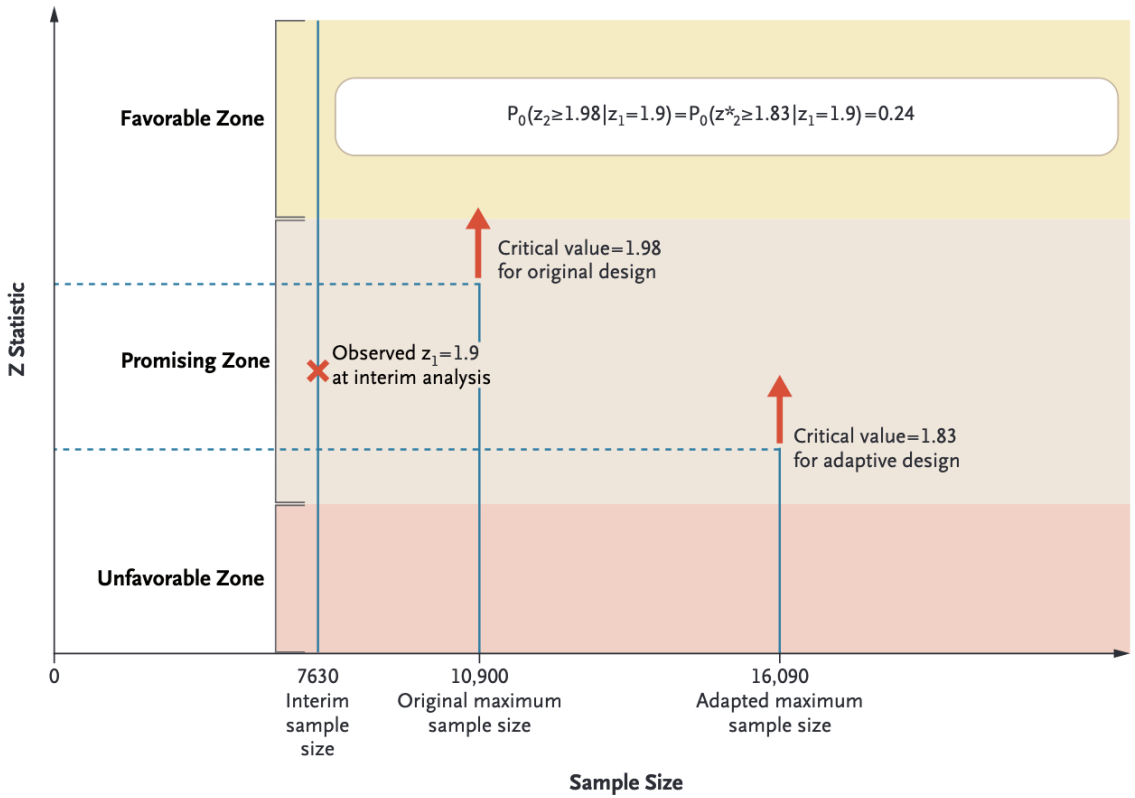
- Contrôle du Risque d'erreur de type I

Plusieurs approches

- **Approches fréquentistes**
- **Approches Bayesiennes**

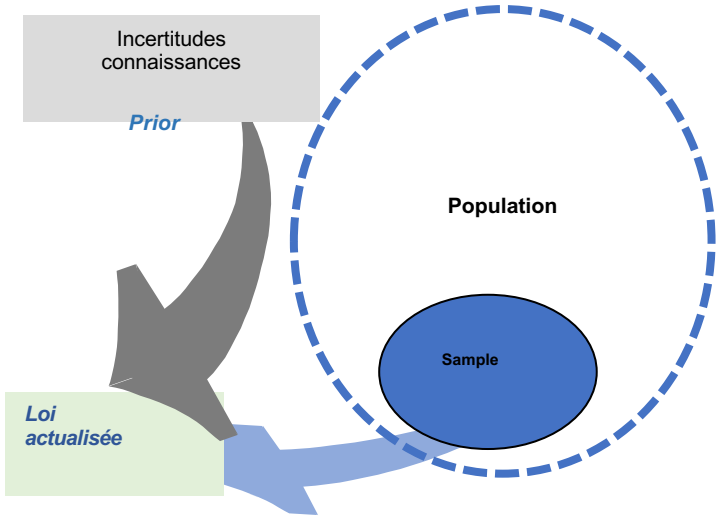
Essais fréquentistes

- Les plus nombreux
- Principe : contrôler l'inflation du risque alpha (faux positifs) par la modification des seuils de signification



Essais bayesiens

Modélisation directe et actualisée de l'incertitude sur l'effet



- Recommandés (FDA) depuis près de 10 ans

2010 Guidance for Industry

Adaptive Design Clinical Trials for Drugs and Biologics

Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials

2015 FDA and Accelerating the Development of New Pharmaceutical Therapies

2017 Bayesian Methods for Making Inferences about Rare Diseases in Pediatric Populations

(1) FDA Guidance for Industry- Adaptive Design Clinical Trials for Drugs and Biologics- DRAFT GUIDANCE (2010 Feb.)

(2) Medicine and Public Issues | Annals of Internal Medicine

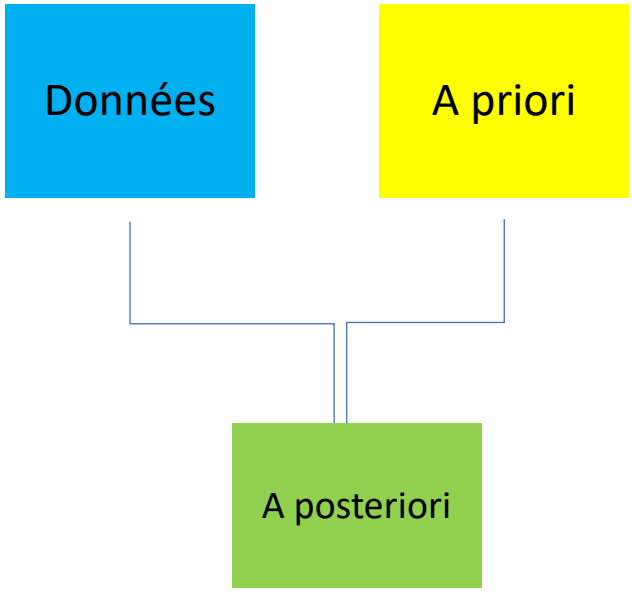
Rethinking Randomized Clinical Trials for Comparative Effectiveness Research: The Need for Transformational Change

Bryan R. Luce, PhD, MBA; Judith M. Kramer, MD, MS; Steven N. Goodman, MD, MHS, PhD; Jason T. Connor, PhD; Sean Tunis, MD, MSc; Danielle Whicher, MHS; and J. Sanford Schwartz, MD

Essais bayesiens

Principe

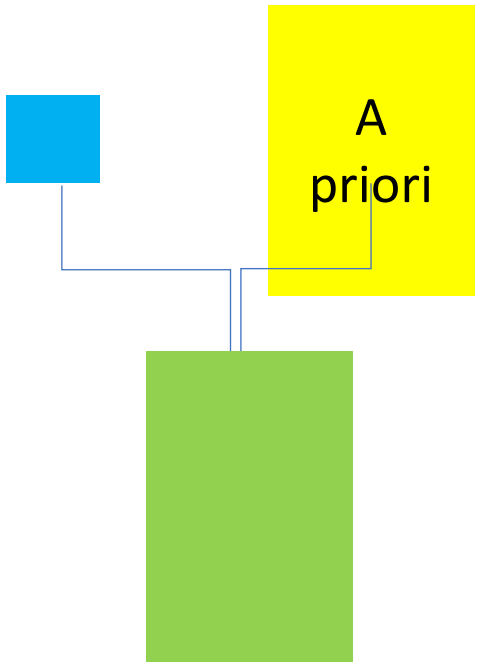
- Permettent de revoir nos croyances grâce à l'observation
    - L'actualisation de nos croyances repose sur le théorème de Bayes
    - Augmentent la quantité d'information en intégrant des informations extérieures à l'essai



Essais bayesiens

Principe

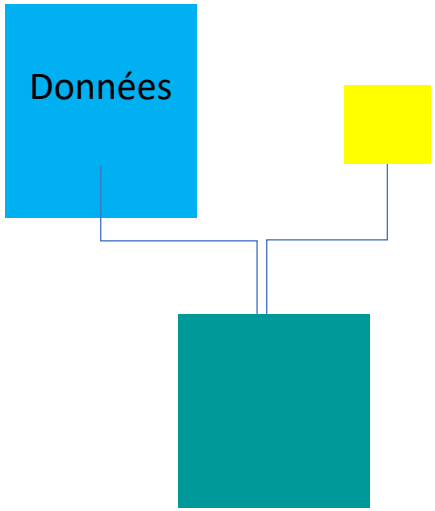
- **Si peu de données, le poids de l'a priori augmente**
    - **D'autant plus que précis**



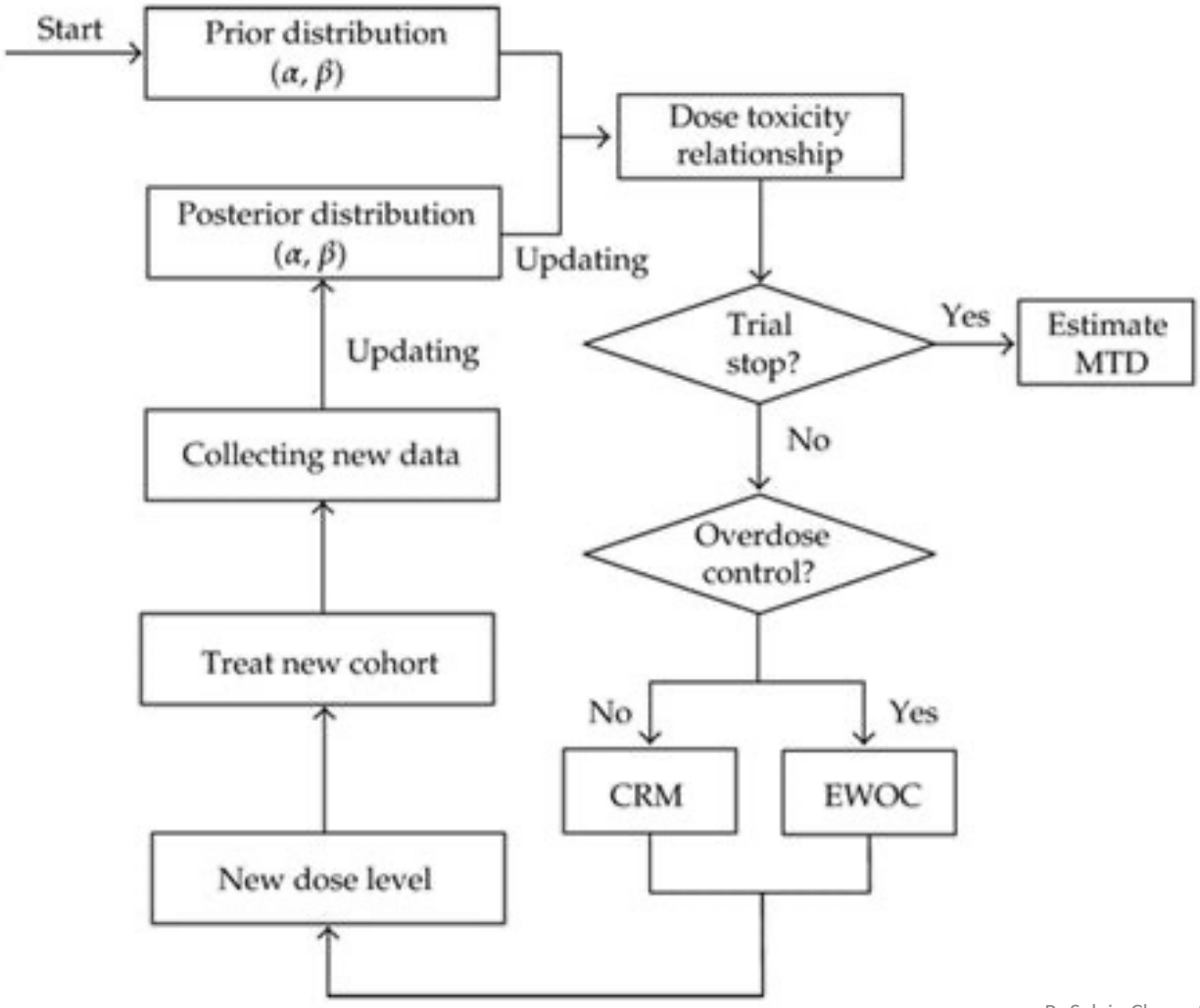
Essais bayesiens

Principe

- **Cette influence est vite “gommée” (“inondée”) par les données**

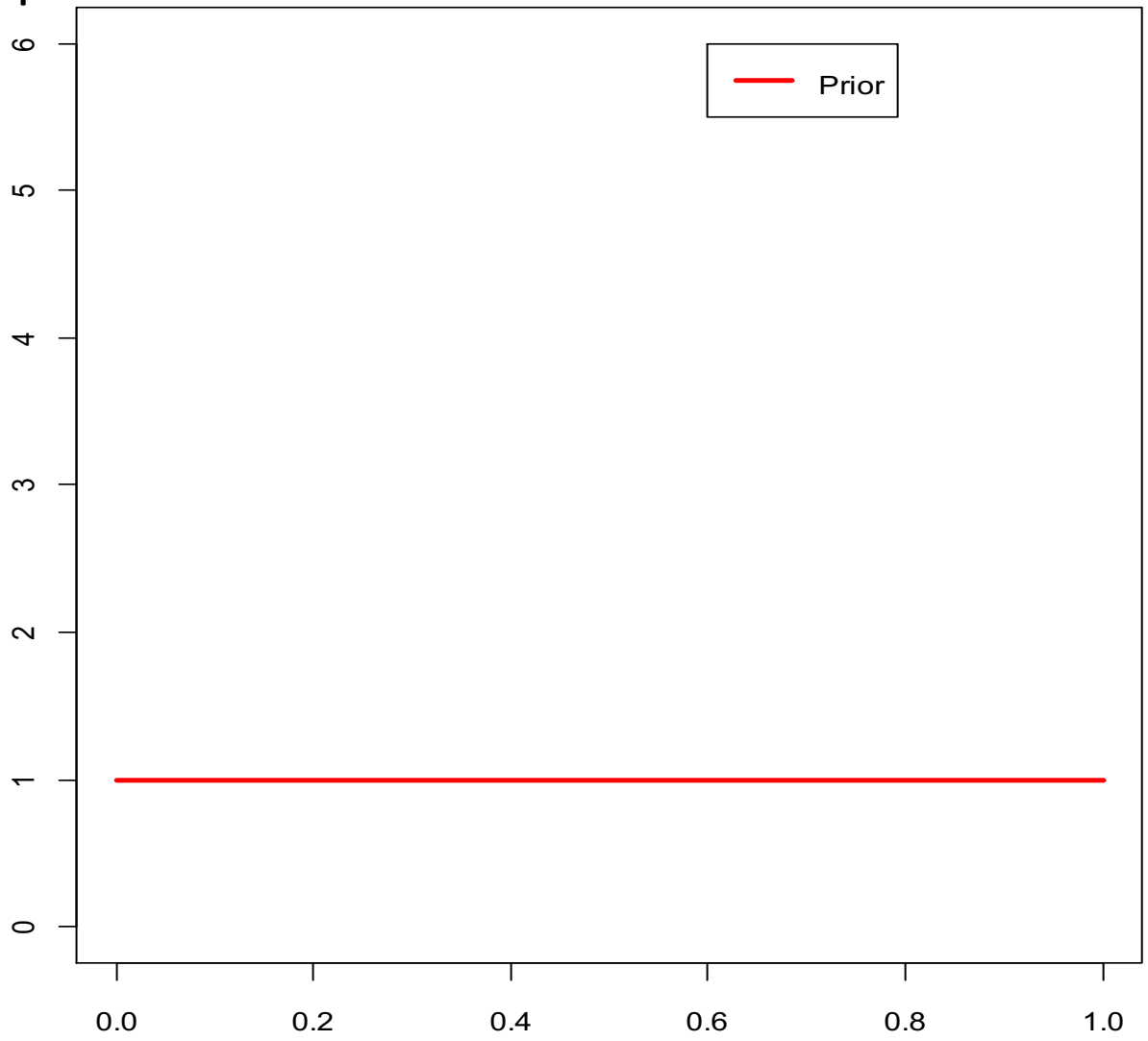


EX 1: Essais bayesiens de recherche de dose

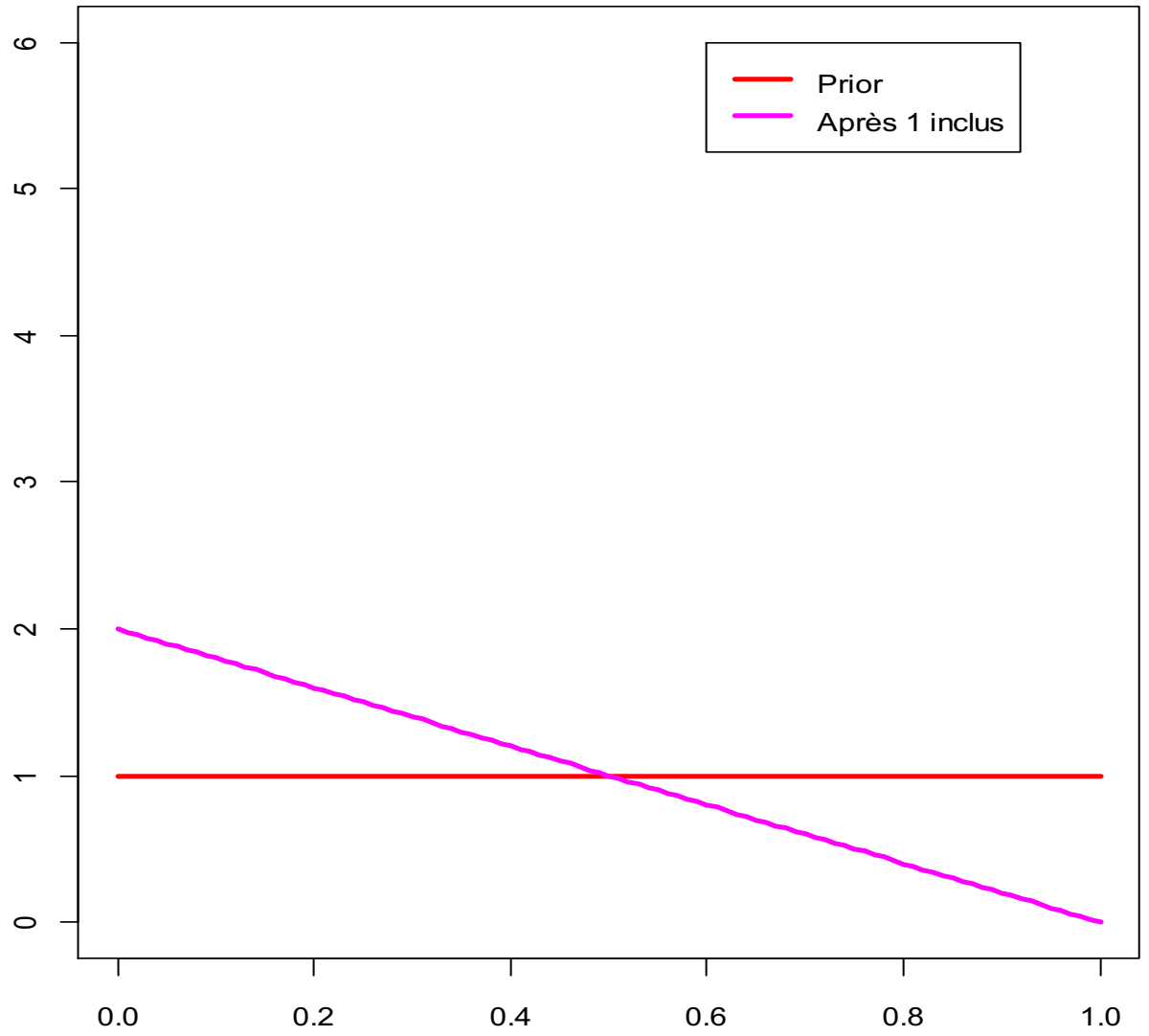


Ex 2 : Essai de phase 2 mono-bras

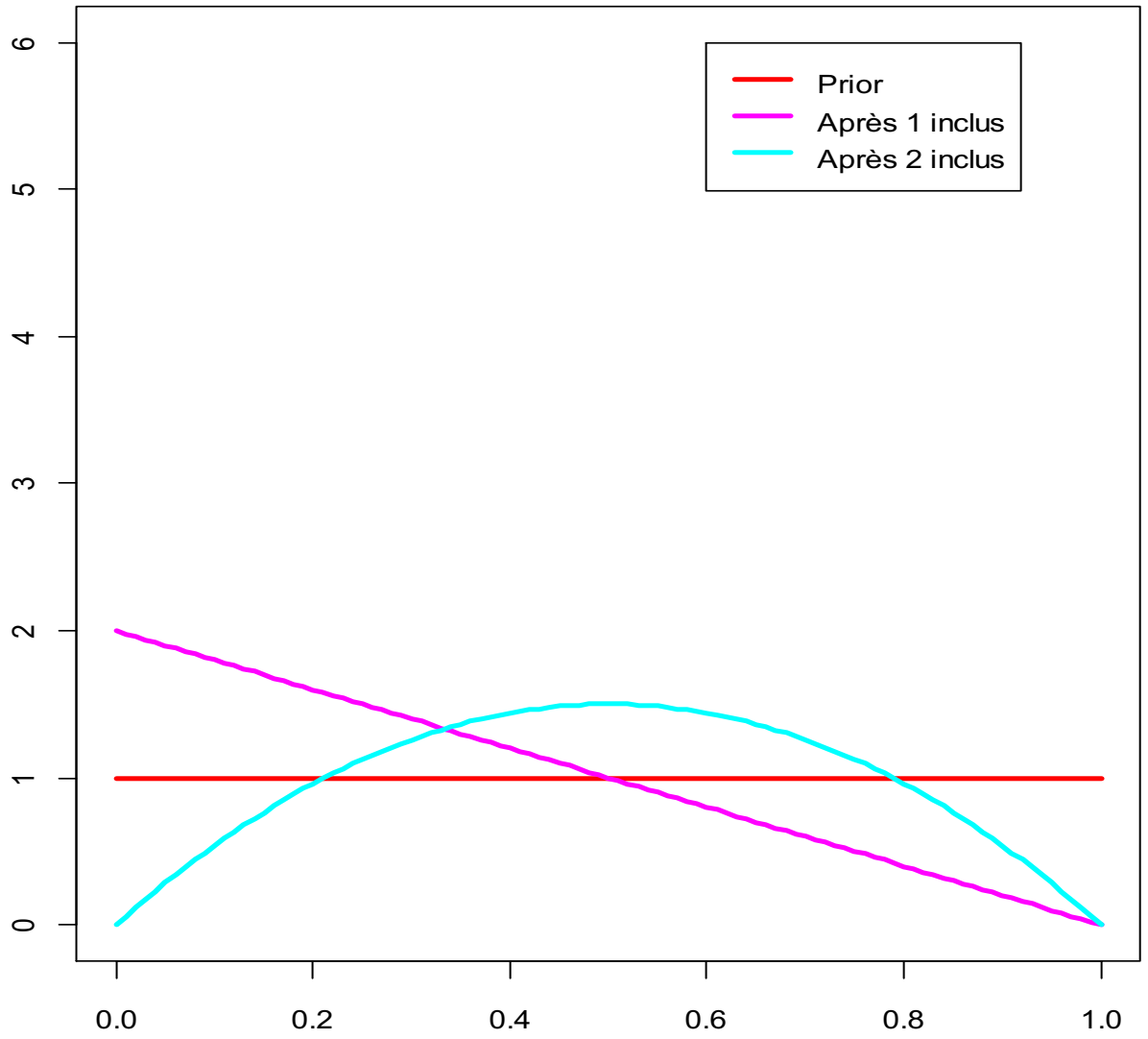
Critère = Pr décès
A priori NON informatif



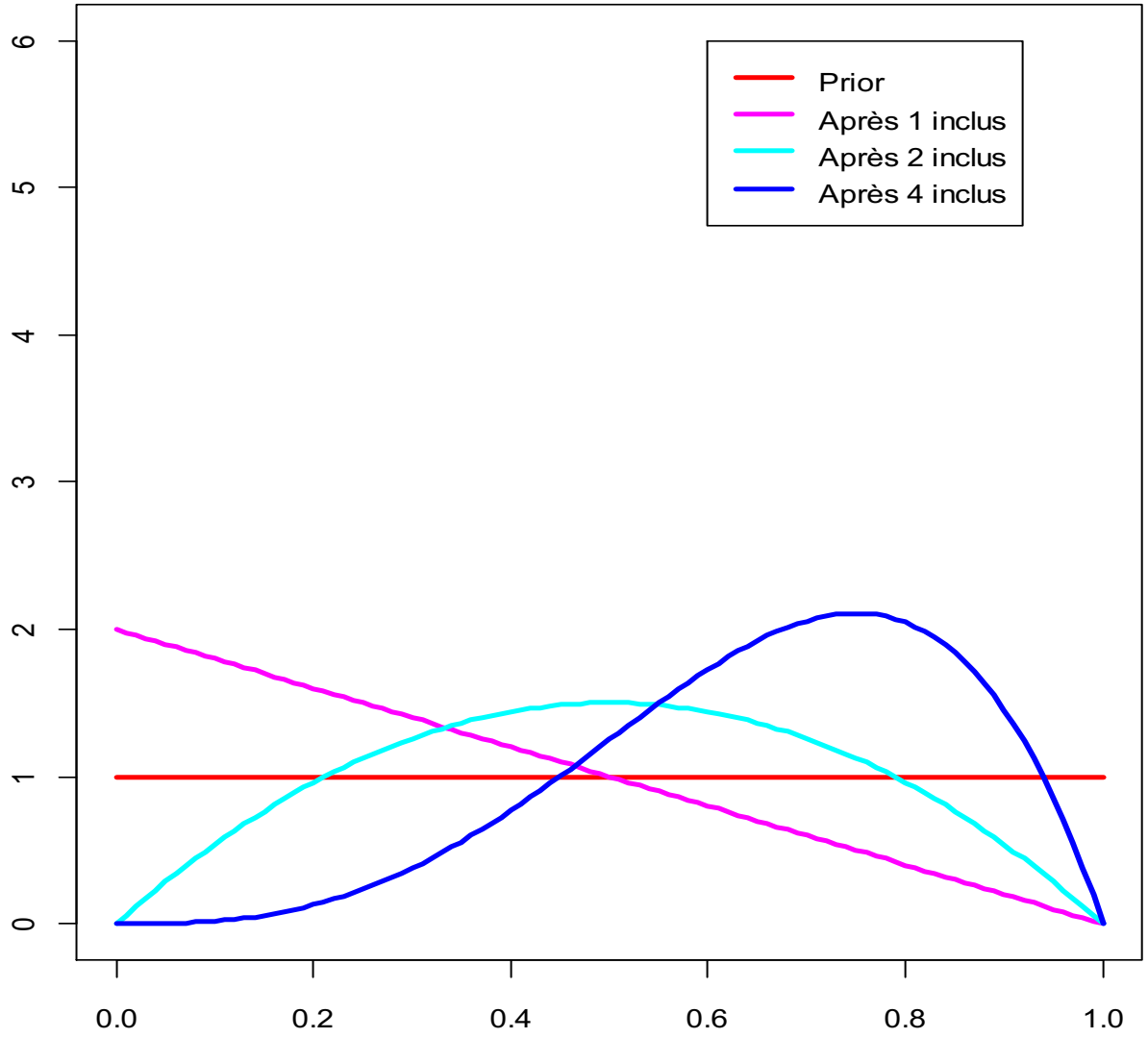
0 décès/1



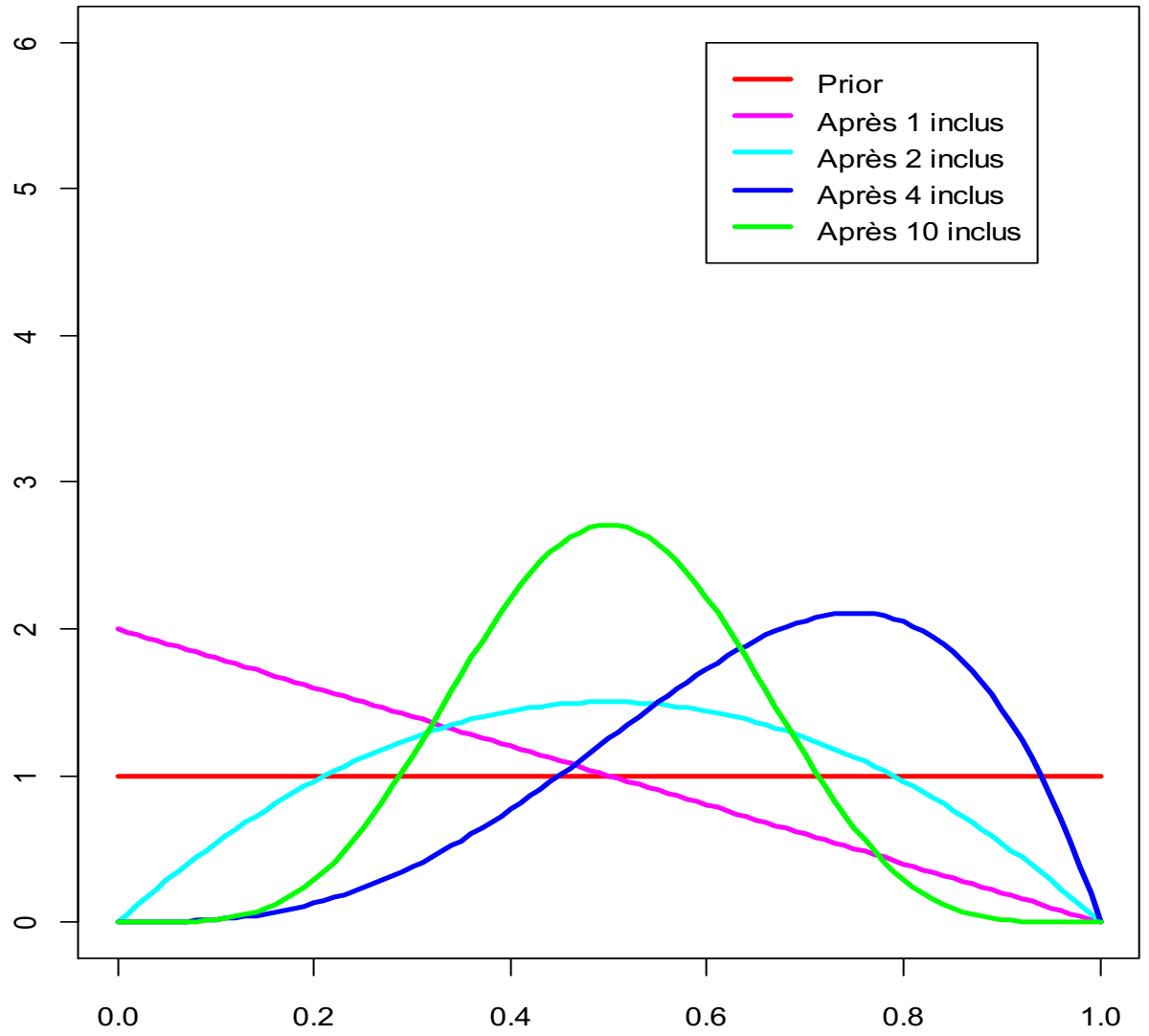
1 décès/2



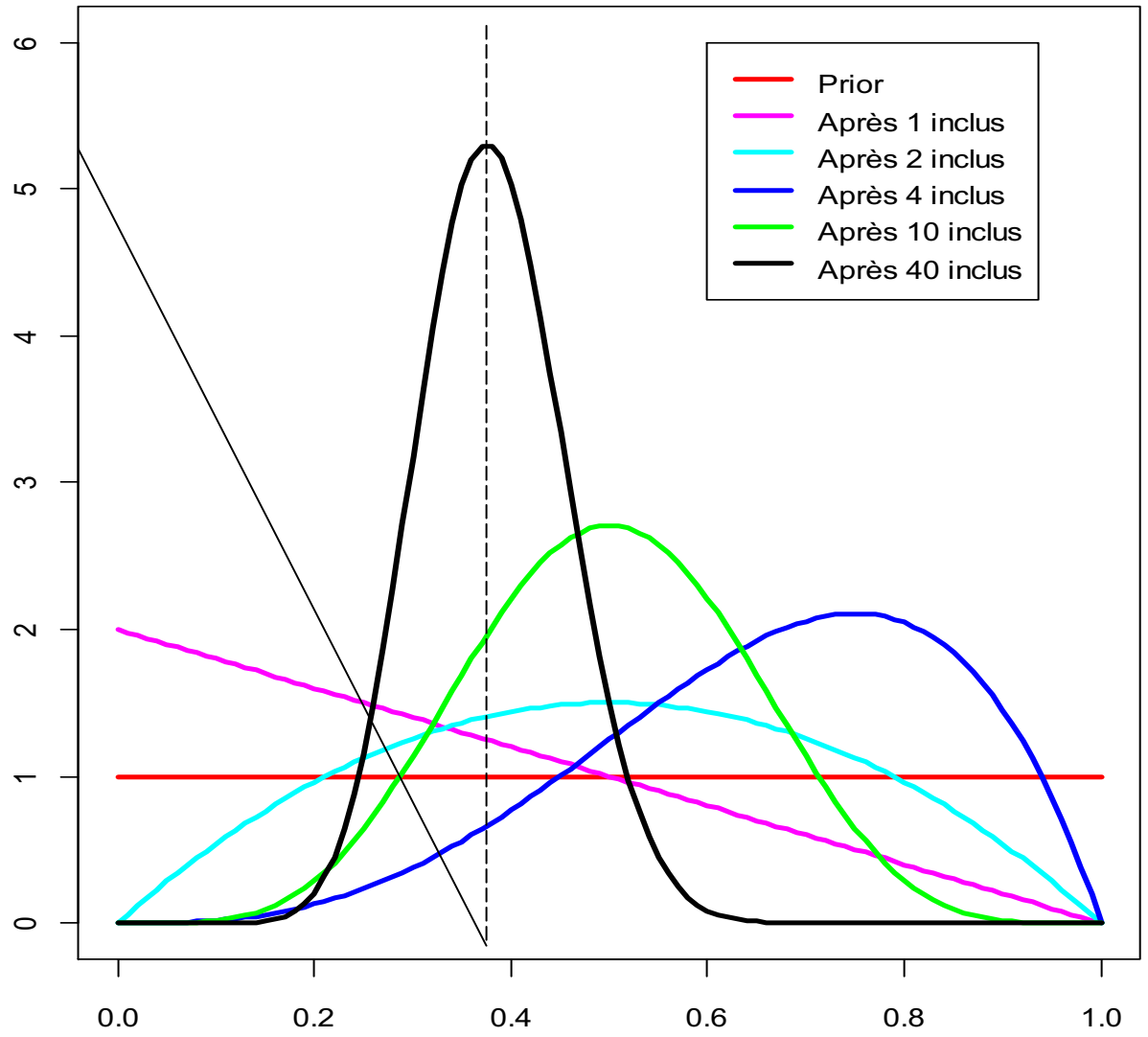
3 décès/4


Prior
Après 1 inclus
Après 2 inclus
Après 4 inclus
0
1
2
3
4
5
6
0.0
0.2
0.4
0.6
0.8
1.0

5 décès/10


Prior
Après 1 inclus
Après 2 inclus
Après 4 inclus
Après 10 inclus
0
1
2
3
4
5
6
0.0
0.2
0.4
0.6
0.8
1.0

15 décès/40: **37,5%**



2- Respecter l'intégrité (scientifique) de l'essai

- Acceptabilité des résultats par la communauté scientifique
- Adaptation planifiée (et détaillée) dans le protocole
- Maintien de la confidentialité des données

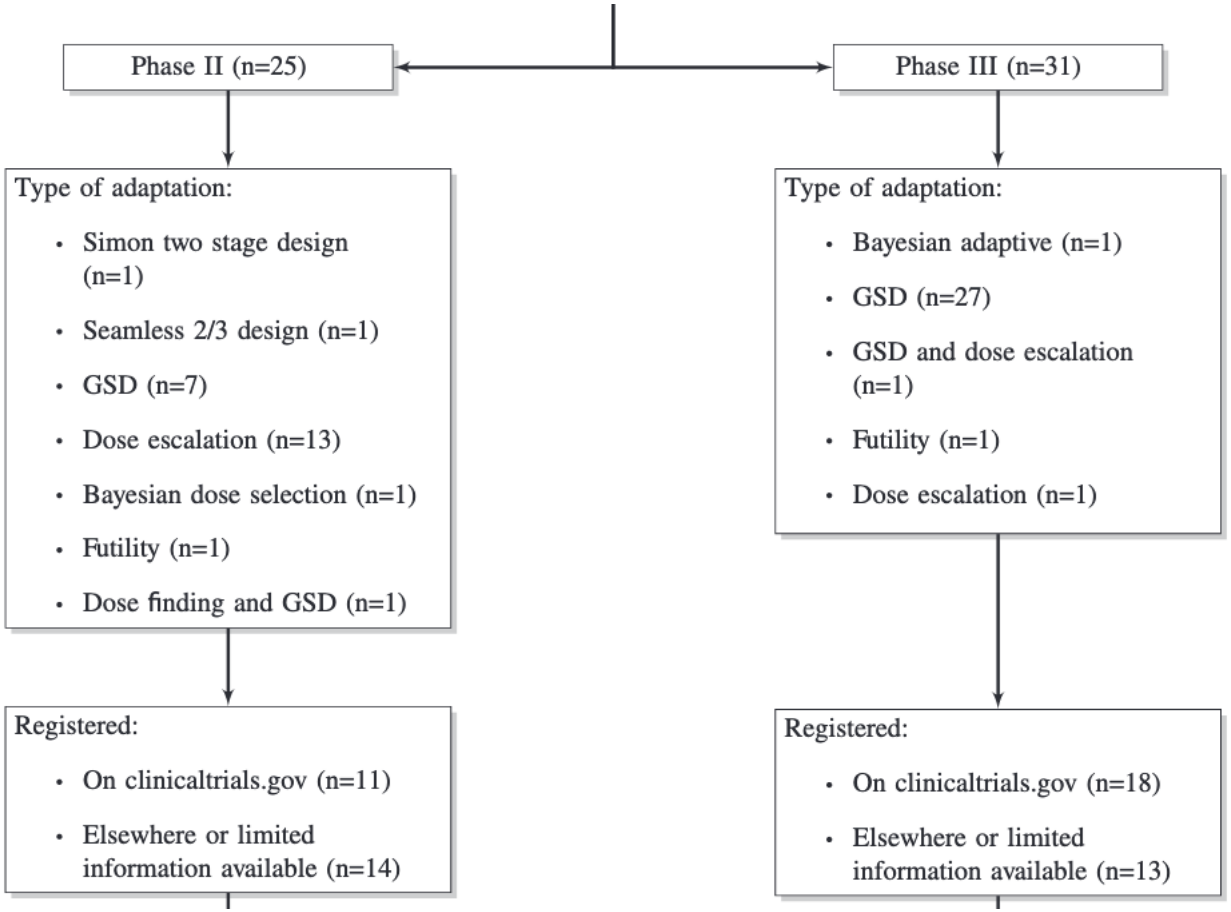
Adaptive Designs in Clinical Drug Development : An Executive Summary of the PhRMA Working Group. Journal of Biopharmaceutical Statistics, 16: 275-283, 2006

En pratique ?

Revues littérature

Quid en réanimation

Revue 2016



Hatfield *et al. Trials* (2016) 17:150
DOI 10.1186/s13063-016-1273-9

Trials

REVIEW Open Access

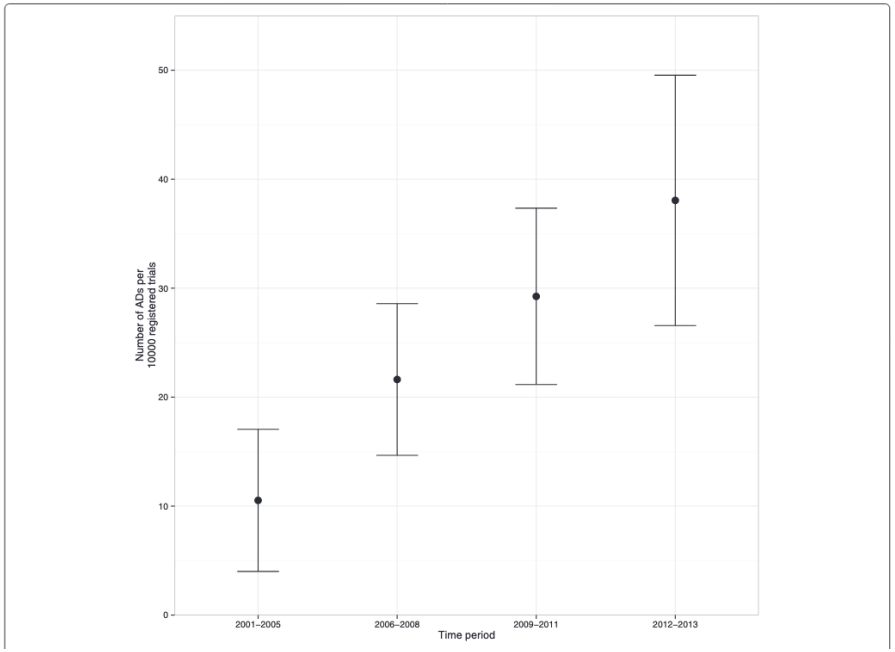
Adaptive designs undertaken in clinical research: a review of registered clinical trials

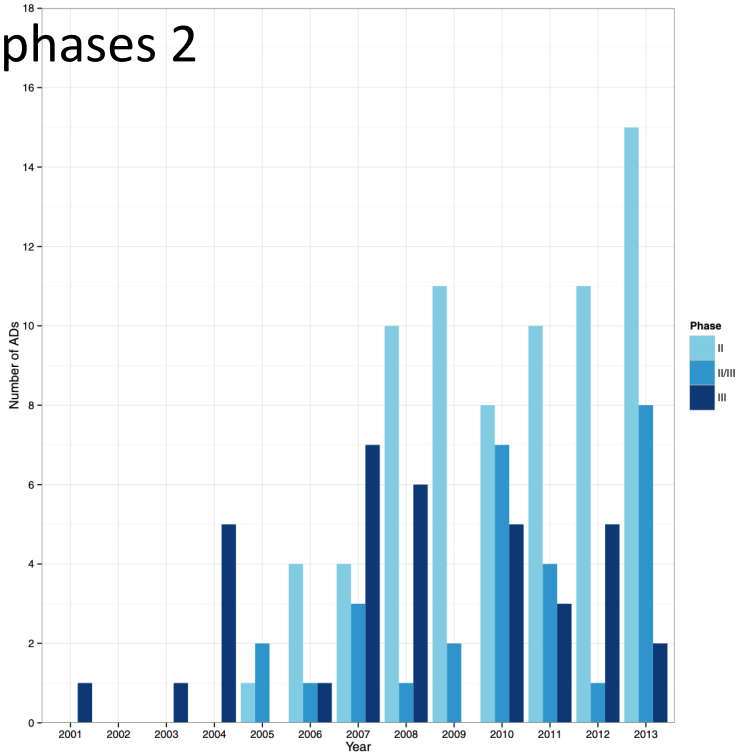
Isabella Hatfield[1,2], Annabel Allison[2,3], Laura Flight[2], Steven A. Julious[2] and Munyaradzi Dimairo[2*]

Group sequential design (GSD)

Revue 2016

- En augmentation, surtout dans les phases 2





Hatfield *et al. Trials* (2016) 17:150
DOI 10.1186/s13063-016-1273-9

Trials

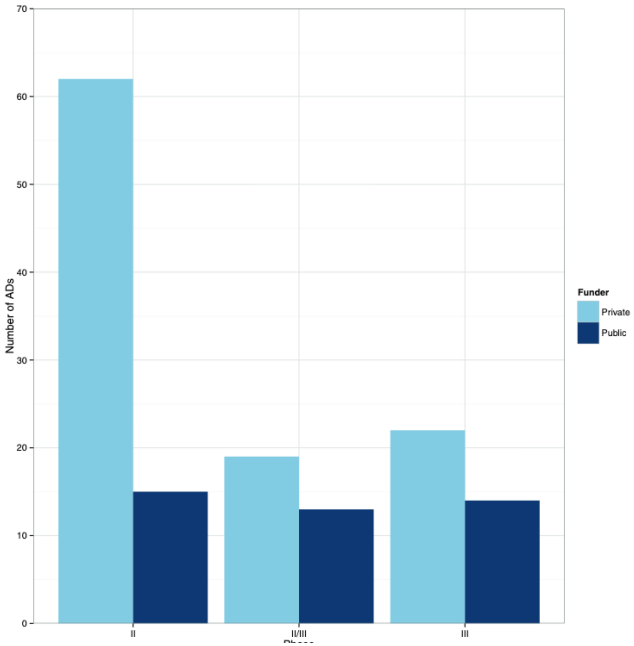
REVIEW Open Access

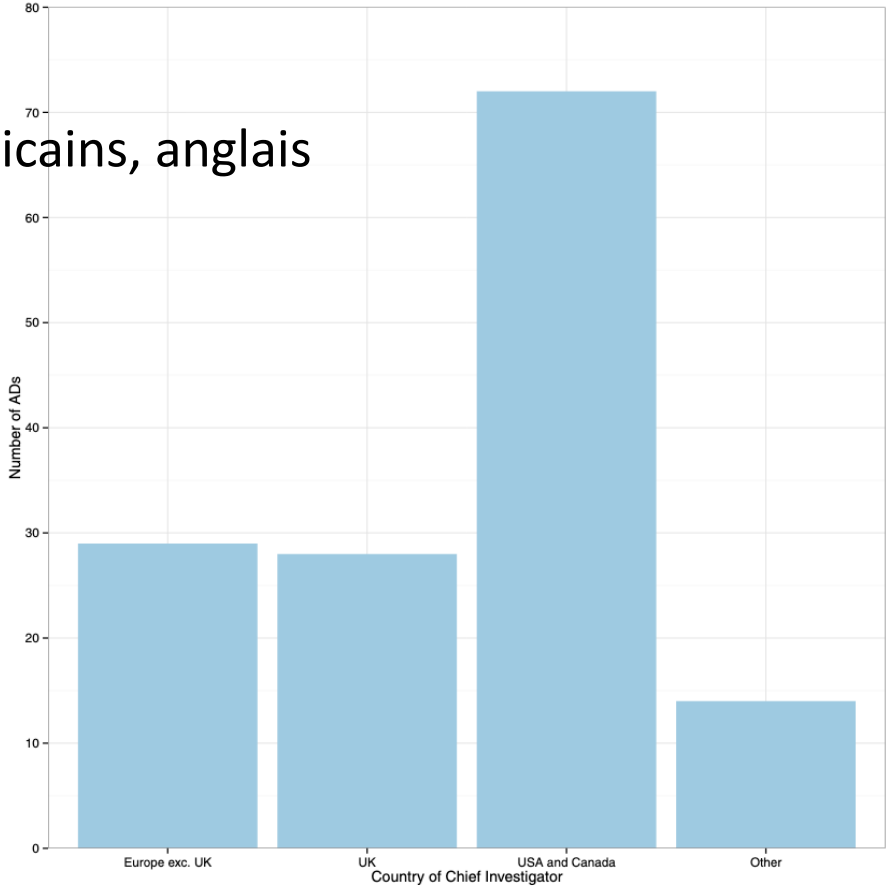
Adaptive designs undertaken in clinical research: a review of registered clinical trials

Isabella Hatfield[1,2], Annabel Allison[2,3], Laura Flight[2], Steven A. Julious[2] and Munyaradzi Dimairo[2*]

Revue 2016

- Promotion industrielle, essais américains, anglais





Hatfield *et al. Trials* (2016) 17:150
DOI 10.1186/s13063-016-1273-9

Trials

REVIEW Open Access

Adaptive designs undertaken in clinical research: a review of registered clinical trials

Isabella Hatfield[1,2], Annabel Allison[2,3], Laura Flight[2], Steven A. Julious[2] and Munyaradzi Dimairo[2*]

Revue 2018 : même constat

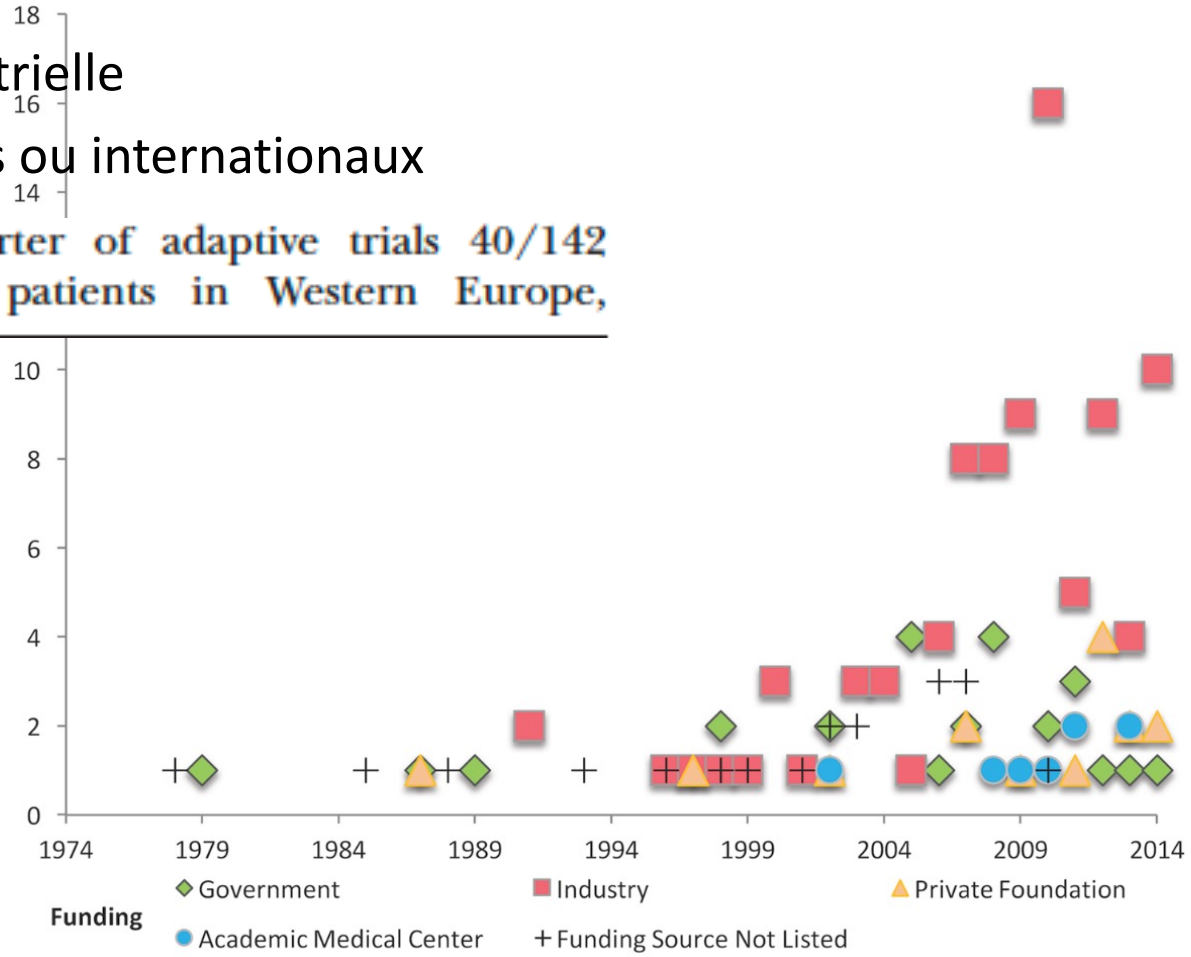
Open Access Research
BMJ Open

Adaptive design clinical trials: a review of the literature and ClinicalTrials.gov

Laura E Bothwell, Jerry Avorn, Nazleen F Khan, Aaron S Kesselheim

- Promotion industrielle
- Essais américains ou internationaux

Approximately one-quarter of adaptive trials 40/142 (28%) only enrolled patients in Western Europe,



Revue 2018

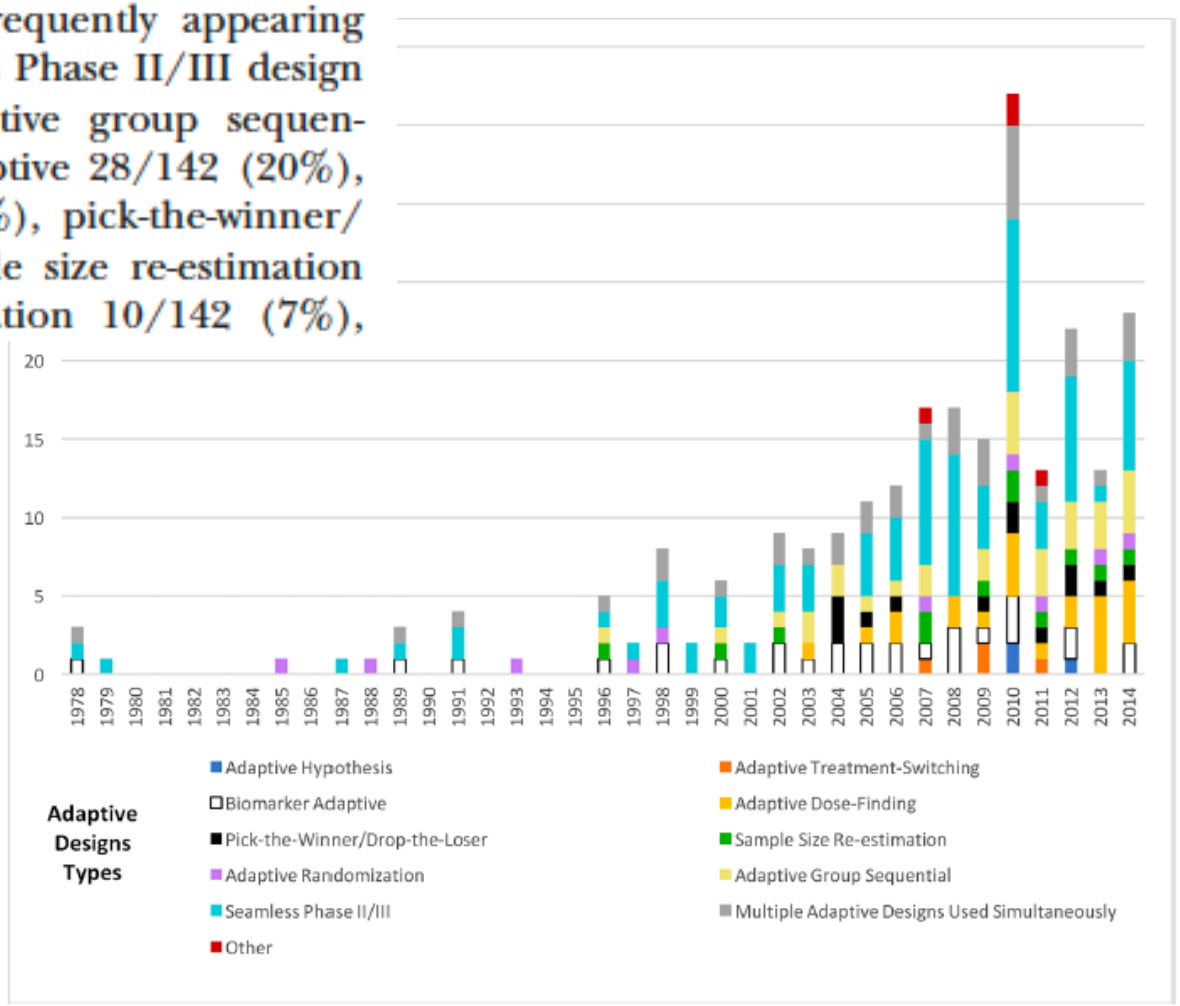
Open Access Research

BMJ Open

Adaptive design clinical trials: a review of the literature and ClinicalTrials.gov

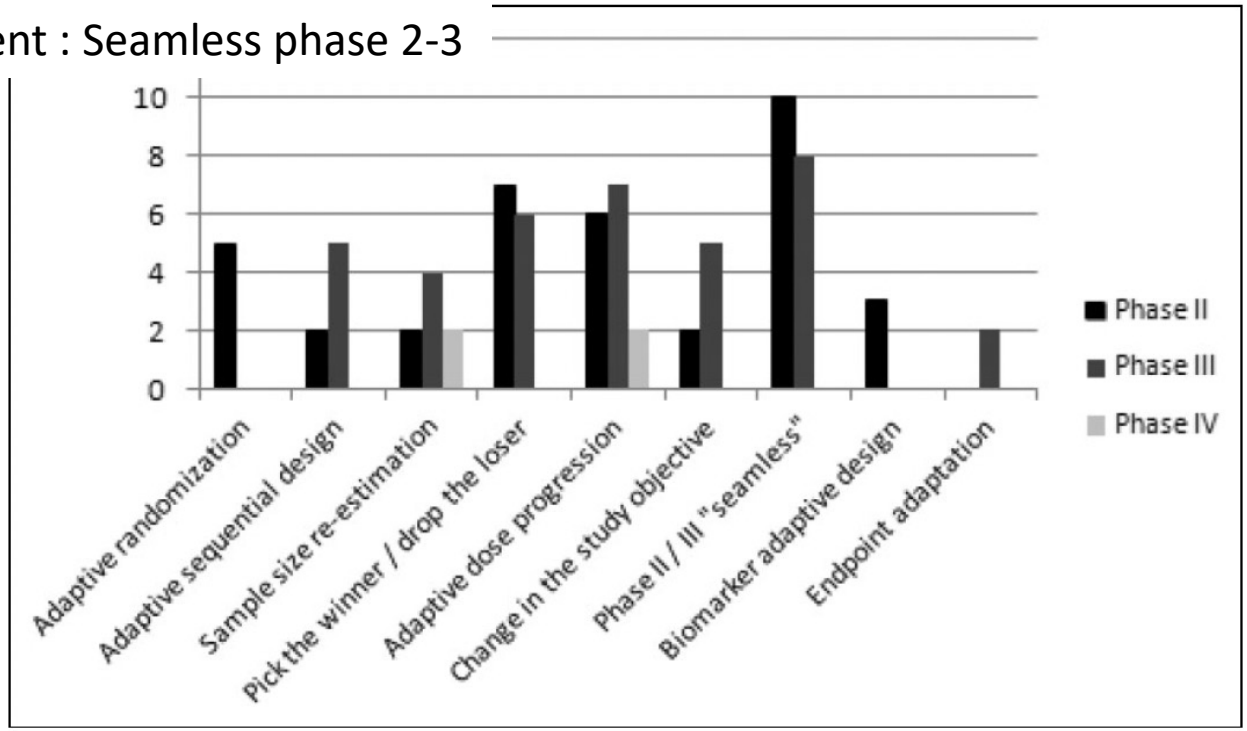
Laura E Bothwell, Jerry Avorn, Nazleen F Khan, Aaron S Kesselheim

Adaptive trials expanded in the scientific literature since the mid-1990s. The most frequently appearing type of adaptation was the seamless Phase II/III design 81/142 (57%), followed by adaptive group sequential 30/142 (21%), biomarker adaptive 28/142 (20%), adaptive dose-finding 23/142 (16%), pick-the-winner/drop-the-loser 13/142 (9%), sample size re-estimation 11/142 (8%), adaptive randomisation 10/142 (7%),



Revue 2020 : confirmation

Schéma le plus fréquent : Seamless phase 2-3



DIA

Review Articles

Therapeutic Innovation & Regulatory Science
2020, Vol. 54(1) 246-258

https://doi.org/10.1007/s43441-019-00052-y

Adaptive Design: A Review of the Technical, Statistical, and Regulatory Aspects of Implementation in a Clinical Trial

Franck Pires Cerqueira, MSc[1,2], Angelo Miguel Cardoso Jesus, PhD[1], and Maria Dulce Cotrim, PhD[2]

Exemples

Pallmann *et al. BMC Medicine* (2018) 16:29
https://doi.org/10.1186/s12916-018-1017-7

BMC Medicine

CORRESPONDENCE Open Access

Adaptive designs in clinical trials: why use them, and how to run and report them

Philip Pallmann[1*], Alun W. Bedding[2], Babak Choodari-Oskooei[3], Munyaradzi Dimairo[4], Laura Flight[5], Lisa V. Hampson[1,6], Jane Holmes[7], Adrian P. Mander[8], Lang'o Odondi[7], Matthew R. Sydes[3], Sofía S. Villar[8], James M. S. Wason[8,9], Christopher J. Weir[10], Graham M. Wheeler[8,11], Christina Yap[12] and Thomas Jaki[1]

Design	Idea	Examples
Continual reassessment method	Model-based dose escalation to estimate the maximum tolerated dose	TRAFIC [136], Viola [137], RomiCar [138]
Group-sequential	Include options to stop the trial early for safety, futility or efficacy	DEVELOP-UK [139]
Sample size re-estimation	Adjust sample size to ensure the desired power	DEVELOP-UK [139]
Multi-arm multi-stage	Explore multiple treatments, doses, durations or combinations with options to 'drop losers' or 'select winners' early	TAILoR [31], STAMPEDE [67, 140], COMPARE [141], 18-F PET study [142]
Population enrichment	Narrow down recruitment to patients more likely to benefit (most) from the treatment	Rizatriptan study [143, 144]
Biomarker-adaptive	Incorporate information from or adapt on biomarkers	FOCUS4 [145], DILfrequency [146]; examples in [147, 148]
Adaptive randomisation	Shift allocation ratio towards more promising or informative treatment(s)	DexFEM [149]; case studies in [150, 151]
Adaptive dose-ranging	Shift allocation ratio towards more promising or informative dose(s)	DILfrequency [146]
Seamless phase I/II	Combine safety and activity assessment into one trial	MK-0572 [152], Matchpoint [153, 154]
Seamless phase II/III	Combine selection and confirmatory stages into one trial	Case studies in [133]

Revue 2022

- Web of Sciences: 371 résultats (topic) dont 271 articles

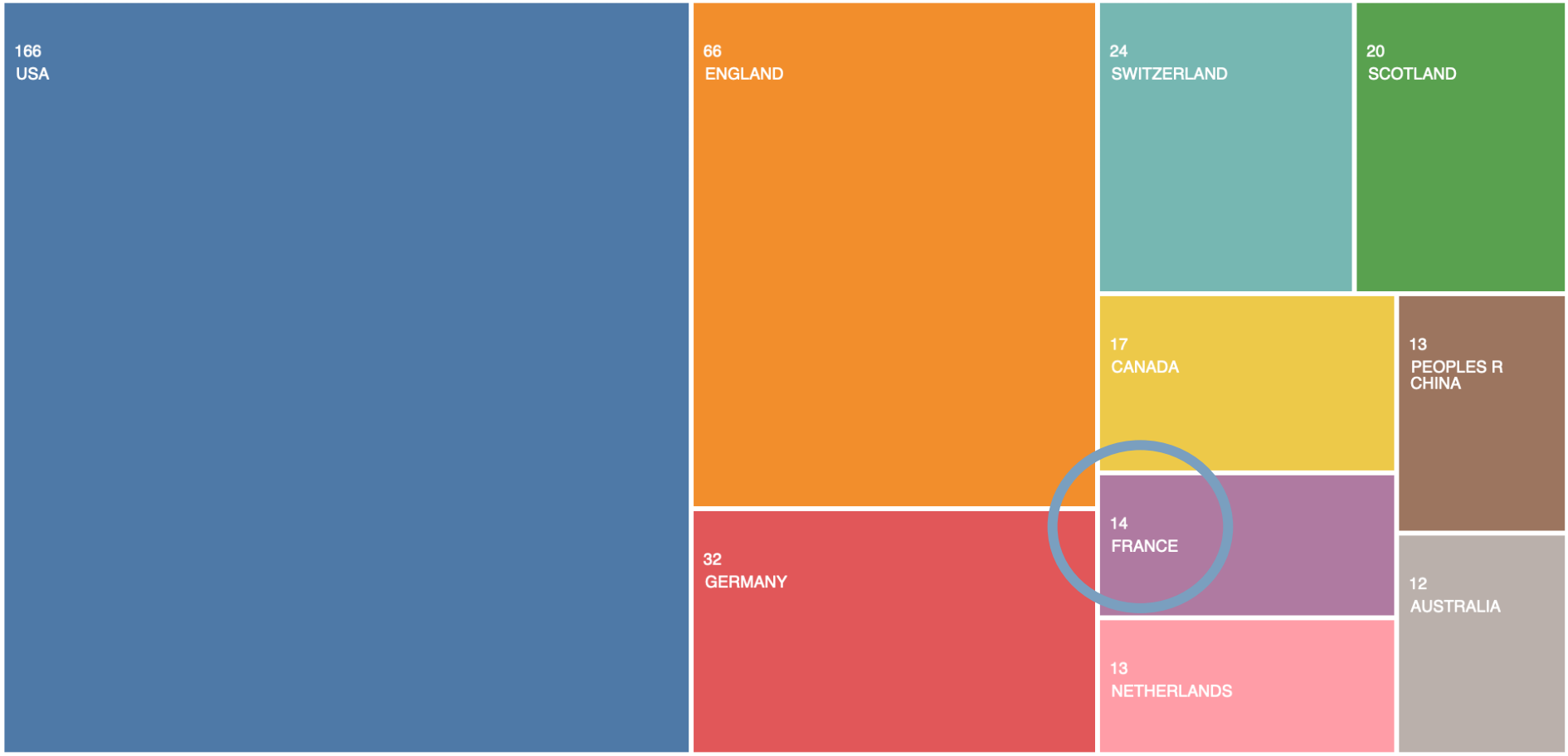


Table 2 Examples of adaptive trials in critically ill patients, all using adaptive sample size only

Study	Population	Intervention	Adaptive rule	Study result
McCloskey et al. [6]	Septic shock with or without GNB	Human monoclonal antibody (HA-1A) vs. placebo	Group sequential design with an interval of 500 GNB patients. Stopping rules: 1) Superiority in patients with GNB, 2) inferiority in patients without GNB. Maximum sample size: 1500 with GNB	Stopped after first interim analysis because of inferiority in patients without GNB ($p = 0.09$). No benefit for patients with GNB
Van Nieuwenhoven et al. [7]	Critically ill patients undergoing mechanical ventilation	Semirecumbent position vs. standard care	Group sequential design with an interval of ten patients. Stopping rules: (1) superiority, (2) futility. Maximum sample size: 252	Stopped after inclusion of 210 patients because of futility
Zhang et al. [8]	Critically ill patients with septic shock and/or ARDS	PiCCO vs. central venous pressure monitoring	Group sequential design with an interval of 50 patients. Stopping rules: (1) superiority, (2) futility. Maximum sample size: 715	Stopped after 350 patients because of futility
Vincent et al. [9]	Patients with severe sepsis	Talactoferrin vs. placebo	Seamless phase II/III design. Decision rule after phase II ($n = 350$): if results suggest benefit, continue enrolment for (phase III). Planned sample size: 1280	Stopped after 305 patients for futility and safety concerns
Welte et al. [10]	Severe community-acquired pneumonia	IGM-enriched immunoglobulin preparation (trimedulin) vs. placebo	Adaptive group sequential design. First interim analysis after 40 patients. Stopping rules: (1) superiority, (2) futility. Adaptation rule: adjust maximum sample size. Original maximum sample size: 82	During first interim analysis original sample size was increased to 160. At second interim analysis (100 patients) no stopping rule reached. Final analysis was inconclusive

ARDS acute respiratory distress syndrome, *GNB* gram-negative bacteraemia, *PiCCO* pulse contour cardiac output

Intensive Care Med (2019) 45:678–682
https://doi.org/10.1007/s00134-018-5426-z

WHAT'S NEW IN INTENSIVE CARE

Adaptive designs in clinical trials in critically ill patients: principles, advantages and pitfalls

C. H. van Werkhoven[1*], S. Harbarth[2,3] and M. J. M. Bonten[1,4]

- Plus larges préoccupations

Intensive Care Med (2019) 45:678–682
https://doi.org/10.1007/s00134-018-5426-z

WHAT'S NEW IN INTENSIVE CARE

Adaptive designs in clinical trials in critically ill patients: principles, advantages and pitfalls

C. H. van Werkhoven[1*], S. Harbarth[2,3] and M. J. M. Bonten[1,4]

Rationale and Design of an Adaptive Phase 2b/3 Clinical Trial of Selepressin f Adults in Septic Shock. Selepressin Evaluation Programme for Sepsis-induced Shock—Adaptive Clinical Trial

Roger J. Lewis [1,2,3,4], Derek C. Angus [5,6], Pierre-François Laterre [7], Anne Louise Kjølbye [8], Egbert van der Meulen
Allan Blemings [8], Todd Graves [4], James A. Russell [9], Jan E. Carlsen [10], Karsten Jacobsen [8], Donald M. Yealy [11], Shc...

Intensive Care Med (2021) 47:1303–1311
https://doi.org/10.1007/s00134-021-06501-3

Mebazaa *et al. Journal of Intensive Care* (2016) 4:24
DOI 10.1186/s40560-016-0151-6

Journal of Intensive Care

ORIGINAL

High dose coupled plasma filtration and adsorption in septic shock patients. Results of the COMPACT-2: a multicentre, adaptive, randomised clinical trial

Elena Garbero[1], Sergio Livigni[2], Fiorenza Ferrari[3,4], Stefano Finazzi[1], Martin Langer[5], Paolo Malacarne[6], Manlio Cosimo Claudio Meca[7], Sabino Mosca[2], Carlo Olivieri[8], Marco Pozzato[9], Carlotta Rossi[1*], Mario Tavola[10], Marina Terzitta[11], Bruno Viaggi[12] and Guido Bertolini[1] on behalf of the GiViTI

REVIEW Open Access

Designing phase 3 sepsis trials: application of learned experiences from critical care trials in acute heart failure

Alexandre Mebazaa[1,2,3*], Pierre François Laterre[4], James A. Russell[5], Andreas Bergmann[6], Luciano Gattinoni[7], Etienne Gayat[8], Michael O. Harhay[9], Oliver Hartmann[6], Frauke Hein[6], Anne Louise Kjolbye[10], Matthieu Legrand[11], Roger J. Lewis[12], John C. Marshall[13], Gernot Marx[14], Peter Radermacher[15], Mathias Schroedter[6], Paul Scigalla[6], Wendy Gattis Stough[16], Joachim Struck[6], Greet Van den Berghe[17], Mehmet Birhan Yilmaz[18] and Derek C. Angus[19,20]

REVIEW Open Access

Perspective on optimizing clinical trials in critical care: how to puzzle out recurrent failures

Bruno François[1,2*], Marc Clavel[1], Philippe Vignon[1] and Pierre-François Laterre[3]

Intensive Care Med (2020) 46:2153–2156
https://doi.org/10.1007/s00134-020-06232-x

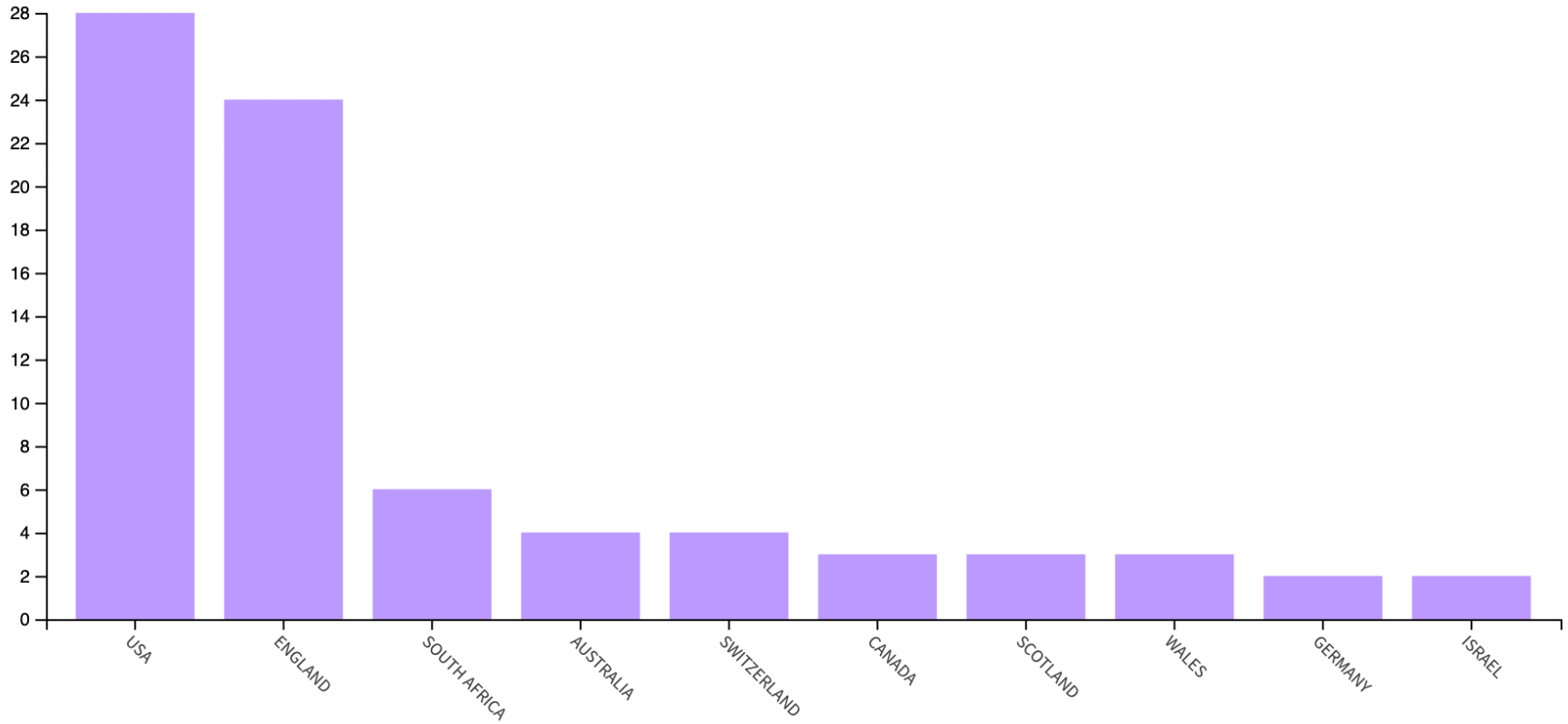
NARRATIVE REVIEW

Designing an ARDS trial for 2020 and beyond: focus on enrichment strategies

Lorraine B. Ware[1*], Michael A. Matthay[2] and Alexandre Mebazaa[3]

Revue 2022: Platform trials?

- Web of Sciences: 101 résultats (titre) dont 48 articles



Platform trials 2022?

- Web of Sciences: 101 résultats (titre) dont 48 articles

RECOVERY: Essai plateforme, COVID-19

BMJ 2020;369:m1626 doi: 10.1136/bmj.m1626 (Published 28 April 2020)

FEATURE

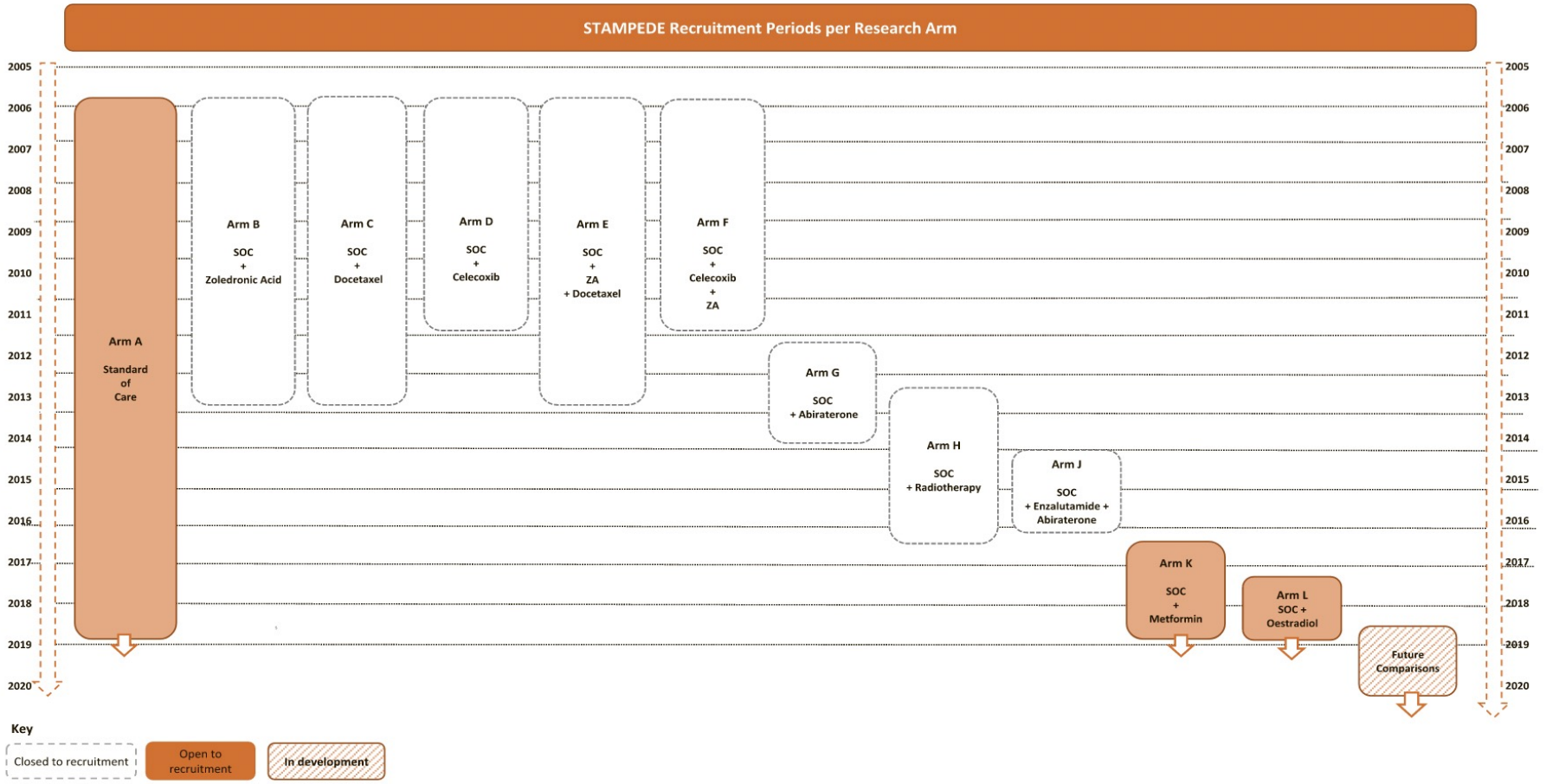
MEDICAL RESEARCH

RECOVERY trial: the UK covid-19 study resetting expectations for clinical trials

Emma Wilkinson talks to the researchers who recruited 7000 NHS patients in a few weeks

Emma Wilkinson

STAMPEDE: Essai plateforme, cancer prostate



REMAP-CAP: Essai plateforme, pneumopathies

REMAP-CAP

Home About REMAP-CAP COVID-19 The REMAP-CAP Team Resources Contact Us

REMAP-CAP

A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia

20,627	18,069	57
Patient randomisations	Patient randomisations with suspected or proven COVID-19	Current or completed interventions in 17 Domains
11,657	10,000	326
Total patients	Patients with suspected or proven	

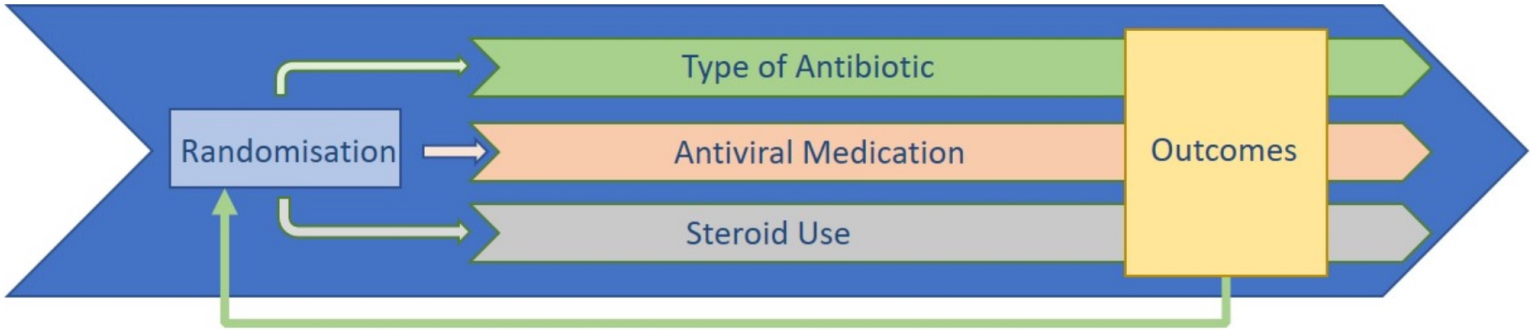
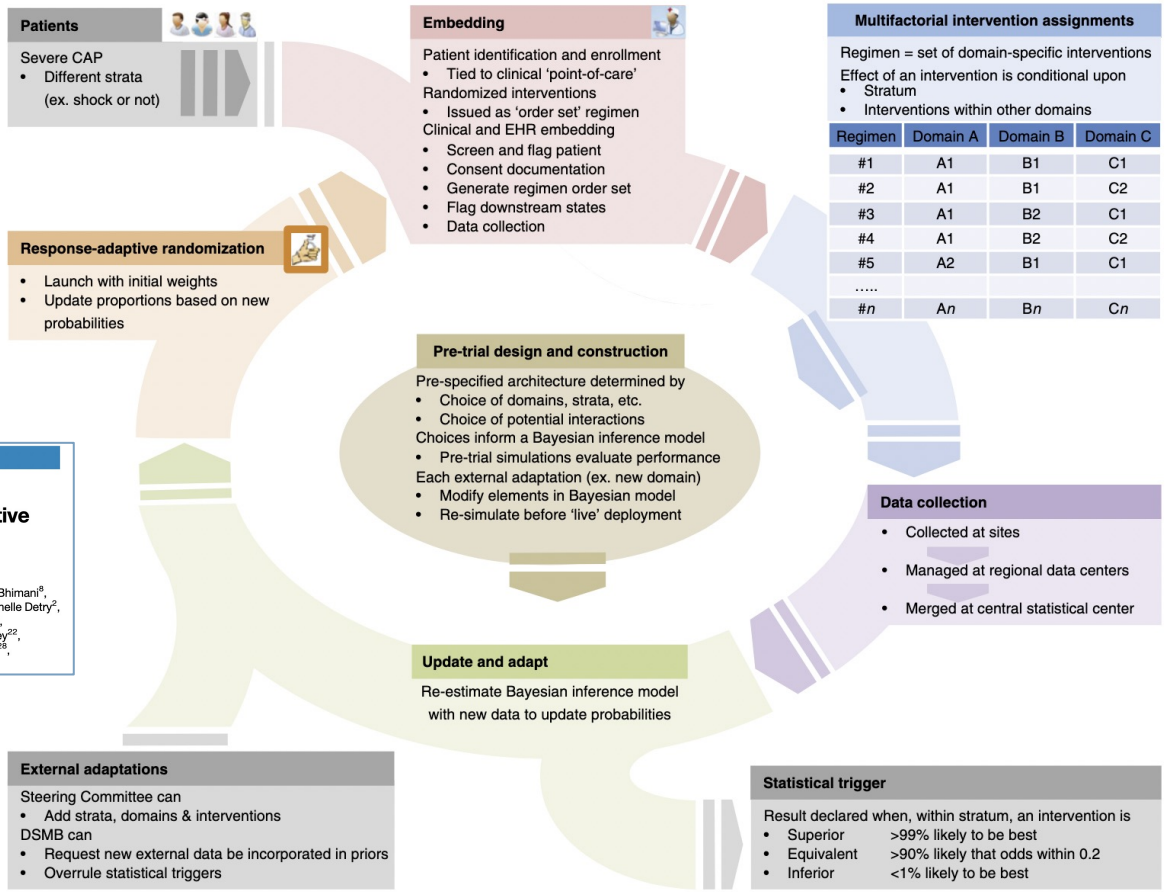


Schéma de randomisation adaptative

- But : actualiser la proportion de sujets alloués à chaque bras



CLINICAL STUDY DESIGN

The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study

Rationale and Design

Derek C. Angus[1], Scott Berry[2], Roger J. Lewis[2,3,4], Farah Al-Beidh[5], Yaseen Arabi[6], Wilma van Bentum-Puijk[7], Zahra Bhimani[8], Marc Bonten[7,9], Kristine Broglio[2], Frank Brunkhorst[10], Allen C. Cheng[11,12], Jean-Daniel Chiche[13], Menno De Jong[14], Michelle Detry[2], Herman Goossens[15], Anthony Gordon[5], Cameron Green[12], Alisa M. Higgins[12], Sebastiaan J. Hullegie[7], Peter Kruger[16], Francois Lamontagne[17], Edward Litton[18], John Marshall[8,19], Anna McGlothlin[2], Shay McGuinness[12,20,21], Paul Mouncey[22], Srinivas Murthy[23], Alistair Nichol[12,24,25], Genevieve K. O'Neill[12], Rachael Parke[20,21,26], Jane Parker[12], Gernot Rohde[27,28], Kathryn Rowan[22], Anne Turner[21], Paul Young[21,29], Lennie Derde[7,30], Colin McArthur[21,31], and Steven A. Webb[12,18,32]

Revue 2022: Platform trials?

- Web of Sciences: 101 résultats (titre) dont 48 articles: 2 « intensive care »

Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

RECOVERY Collaborative Group*

Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

Oxford, UK

Christopher C Butler, Ly-Mee Yu, Jienchi Dorward, Oghenekome Gbinigie, Gail Hayward, Benjamin R Saville, Oliver Van Hecke, Nicholas Berry, Michelle A Detry, Christina Saunders, Mark Fitzgerald, Victoria Harris, Ratko Djukanovic, Stephan Gadola, John Kirkpatrick, Simon de Lusignan, Emma Ogburn, Philip H Evans, Nicholas P B Thomas, Mahendra G Patel, F D Richard Hobbs, on behalf of the PRINCIPLE Trial Collaborative Group*

Perspectives?

Essais adaptatifs en réanimation

Nombreux articles de réflexion/théorie

Wason *et al. BMC Medicine* (2022) 20:254
https://doi.org/10.1186/s12916-022-02445-7

BMC Medicine

CORRESPONDENCE Open Access

Practical guidance for planning resources required to support publicly-funded adaptive clinical trials

James M. S. Wason[1*], Munyaradzi Dimairo[2], Katie Biggs[2], Sarah Bowden[3], Julia Brown[4], Laura Flight[5], Jamie Hall[2], Thomas Jaki[6,7], Rachel Lowe[8], Philip Pallmann[9], Mark A. Pilling[9], Claire Snowdon[10], Matthew R. Sydes[11], Sofía S. Villar[6], Christopher J. Weir[12], Nina Wilson[1], Christina Yap[10], Helen Hancock[13] and Rebecca Maier[13]

Hague *et al. Trials* (2019) 20:294
https://doi.org/10.1186/s13063-019-3322-7

Trials

METHODOLOGY Open Access

Changing platforms without stopping the train: experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons

Dominic Hague[1,2*], Stephen Townsend[1,2], Lindsey Masters[1,2], Mary Rauchenberger[1,2], Nadine Van Looy[1,2], Carlos Diaz-Montana[1,2], Melissa Gannon[1,2], Nicholas James[4], Tim Maughan[5], Mahesh K. B. Parmar[1,2], Louise Brown[1,2], Matthew R. Sydes[1,2] and for the STAMPEDE and FOCUS4 investigators

Lee *et al. Trials* (2021) 22:203
https://doi.org/10.1186/s13063-021-05150-7

Trials

COMMENTARY Open Access

Statistical consideration when adding new arms to ongoing clinical trials: the potentials and the caveats

Kim May Lee[1,2*], Louise C. Brown[3], Thomas Jaki[1,4], Nigel Stallard[5] and James Wason[1,6]

Contemporary Clinical Trials 106 (2021) 106438

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Short Communication

Moving forward in clinical research with master protocols

Jay J.H. Park [a,*], Louis Dron [b], Edward J. Mills [b]

[a] *Experimental Medicine, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada*
[b] *Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada*

Received: 19 February 2021 | Revised: 29 October 2021 | Accepted: 9 January 2022
DOI: 10.1002/pst.2194

MAIN PAPER

WILEY

Decision rules for identifying combination therapies in open-entry, randomized controlled platform trials

Elias Laurin Meyer[1] | Peter Mesenbrink[2] | Cornelia Dunger-Baldauf[3] | Ekkehard Glimm[3,4] | Yuhan Li[2] | Franz König[1] | EU-PEARL (EU Patient-cEntric clinicAl tRi

Wilson *et al. BMC Medicine* (2021) 19:251
https://doi.org/10.1186/s12916-021-02124-z

BMC Medicine

RESEARCH ARTICLE Open Access

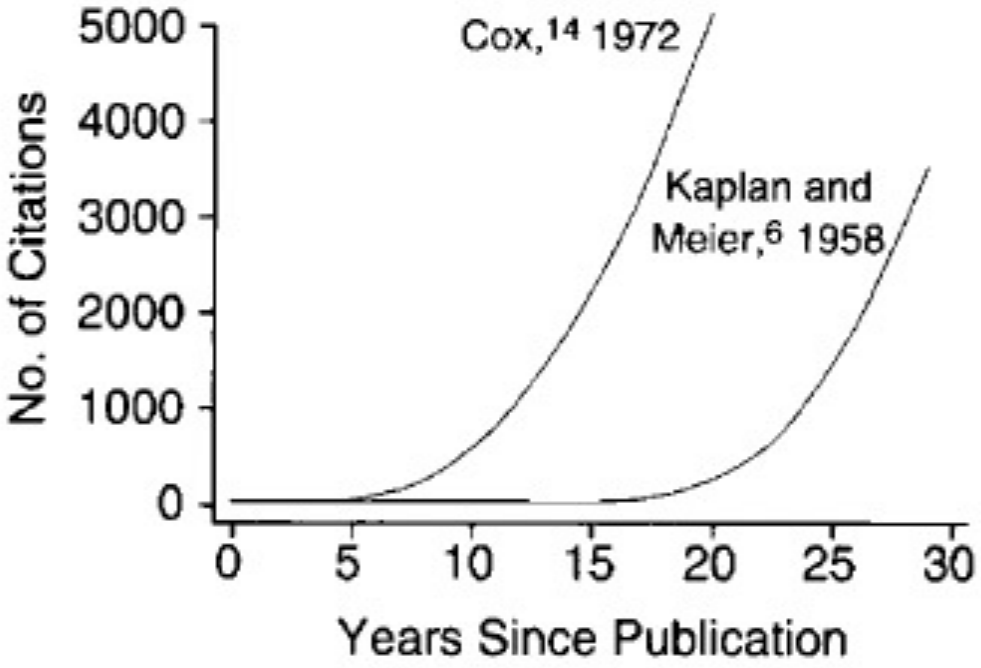
Costs and staffing resource requirements for adaptive clinical trials: quantitative and qualitative results from the Costing Adaptive Trials project

Nina Wilson[1], Katie Biggs[2], Sarah Bowden[3], Julia Brown[4], Munyaradzi Dimairo[2], Laura Flight[2], Jamie Hall[2], Anna Hockaday[4], Thomas Jaki[5,6], Rachel Lowe[7], Caroline Murphy[8], Philip Pallmann[7], Mark A. Pilling[9], Claire Snowdon[10], Matthew R. Sydes[11], Sofía S. Villar[5], Christopher J. Weir[12], Jessica Welburn[2], Christina Yap[10], Rebecca Maier[1,13], Helen Hancock[1,13] and James M. S. Wason[1*]

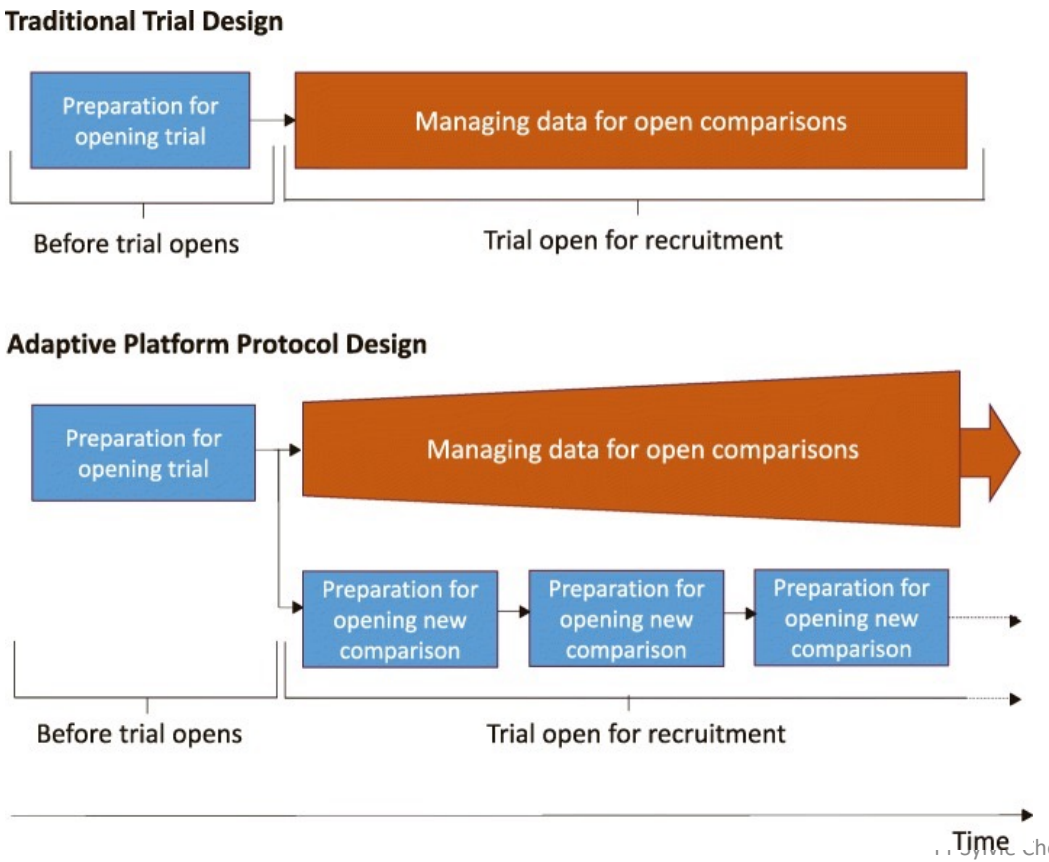
Transfer of Technology From Statistical Journals to the Biomedical Literature

Past Trends and Future Predictions

Douglas G. Altman, Steven N. Goodman, MD, PhD



- Améliorer la compréhension et mise en œuvre de ces essais, notamment en France
  - Plus grande complexité de conduite (et d'analyse)



Aide scientifique : à généraliser ?

"*Committee for Human Medicinal Products*" (CHMP)

- Proposition d'une aide scientifique sur ces essais (1)
- Revue de 59 demandes (2)
  - 46% en oncologie, critère binaire (34%)/censuré (47%)

Type of adaptations planned (multiple answers possible)	Sample size reassessment	43 (73%)
	Population enrichment	5 (8%)
	Dropping of treatment arms	19 (32%)
	Other adaptations	4 (7%)
CHMP raised issues regarding type I error rate control		19 (32%)
Categorization of the CHMP advice regarding the adaptive study design	Accepted	15 (25%)
	Accepted conditionally (concerns to be addressed)	32 (54%)
	Not accepted	12 (20%)

(1) EMEA. Qualification of novel methodologies for drug development: guidance to applicants EMA/CHMP/SAWP/72894/2008 (Revision 3, 2014 nov, 12)

(2) Elsäßer *et al. Trials* 2014, **15**:383
http://www.trialsjournal.com/content/15/1/383

TRIALS

RESEARCH Open Access

Adaptive clinical trial designs for European marketing authorization: a survey of scientific advice letters from the European Medicines Agency

Essais Plateforme

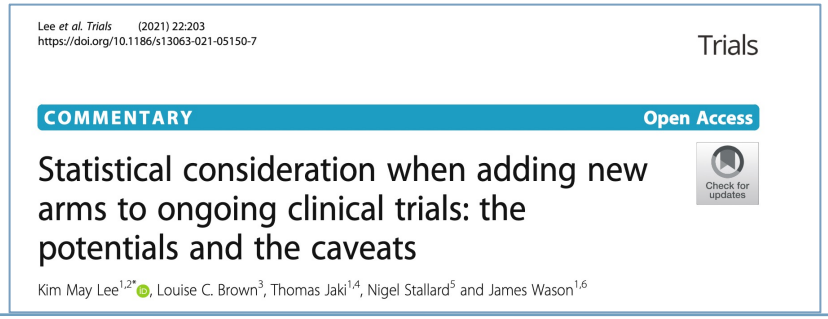
Abstract

Background: Platform trials improve the efficiency of the drug development process through flexible features such as adding and dropping arms as evidence emerges. The benefits and practical challenges of implementing novel trial designs have been discussed widely in the literature, yet less consideration has been given to the statistical implications of adding arms.

Main: We explain different statistical considerations that arise from allowing new research interventions to be added in for ongoing studies. We present recent methodology development on addressing these issues and illustrate design and analysis approaches that might be enhanced to provide robust inference from platform trials. We also discuss the implication of changing the control arm, how patient eligibility for different arms may complicate the trial design and analysis, and how operational bias may arise when revealing some results of the trials. Lastly, we comment on the appropriateness and the application of platform trials in phase II and phase III settings, as well as publicly versus industry-funded trials.

Conclusion: Platform trials provide great opportunities for improving the efficiency of evaluating interventions. Although several statistical issues are present, there are a range of methods available that allow robust and efficient design and analysis of these trials.

Keywords: Adding arms, Bias, Error rates, Multiplicity, Platform trials



Lee *et al. Trials* (2021) 22:203
https://doi.org/10.1186/s13063-021-05150-7

Trials

COMMENTARY Open Access

Statistical consideration when adding new arms to ongoing clinical trials: the potentials and the caveats

Kim May Lee[1,2*], Louise C. Brown[3], Thomas Jaki[1,4], Nigel Stallard[5] and James Wason[1,6]

REVUE DES DEUX MONDES
REVUE MENSUELLE FONDÉE EN 1829

Yvon Lebranchu
Juil 11, 2022

« Si la patrie de Pasteur reste le premier pays de l'Union européenne pour les essais cliniques enregistrés dans la base de données Clinicaltrials.gov, ceux auxquels elle procède sont **majoritairement d'origine académ**ique. Elle perd en revanche du terrain depuis dix ans en matière d'essais à promotion industrielle.

…

« Les causes du recul de la recherche clinique médicamenteuse française sont multiples. Certaines ont été prises en compte par les pouvoirs publics. C'est le cas des **lourdeurs administratives** et des capacités réduites d'inclusion de patients dans les essais dans les délais impartis. D'autres, comme le **manque d'incitation des investigateurs** et les difficultés actuelles de l'hôpital public, devront l'être dans les meilleurs délais. »