Istituti Clinici Scientifici Maugeri

THE EUROPEAN MEDICINES REGULATORY NETWORK: PRESENT AND FUTURE

X Foresight Training Course,

Pavia, 27-28 October 2017

Gain Evidence from Innovative Study Designs for Clinical Trials

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Scientific Direction

Istituti Clinici Scientifici Maugeri SpA Società Benefit

The context

- About 4.000 CTs per year in EU
- About 700 CTs per year in Italy
- Main area: oncology

Area terapeutica (classificazione MedDRA)	2015		
	SC	%	% cumulata
Neoplasie	249	37,1	37,1
Malattie del sistema nervoso	49	7,3	44,3
Malattie del sistema cardiovascolare	42	6,3	50,6
Malattie virali	40	6,0	56,5
Malattie del sistema ematico e linfatico	35	5,2	61,8
Malattie del metabolismo e della nutrizione	34	5,1	66,8
Malattie delle vie respiratorie	32	4,8	71,6
Malattie del sistema muscoloscheletrico	27	4,0	75,6
Malattie del sistema immunitario	26	3,9	79,5
Malattie dell'occhio	21	3,1	82,6
Malattie dell'apparato digerente	17	2,5	85,1
Malattie e anomalie neonatali	16	2,4	87,5

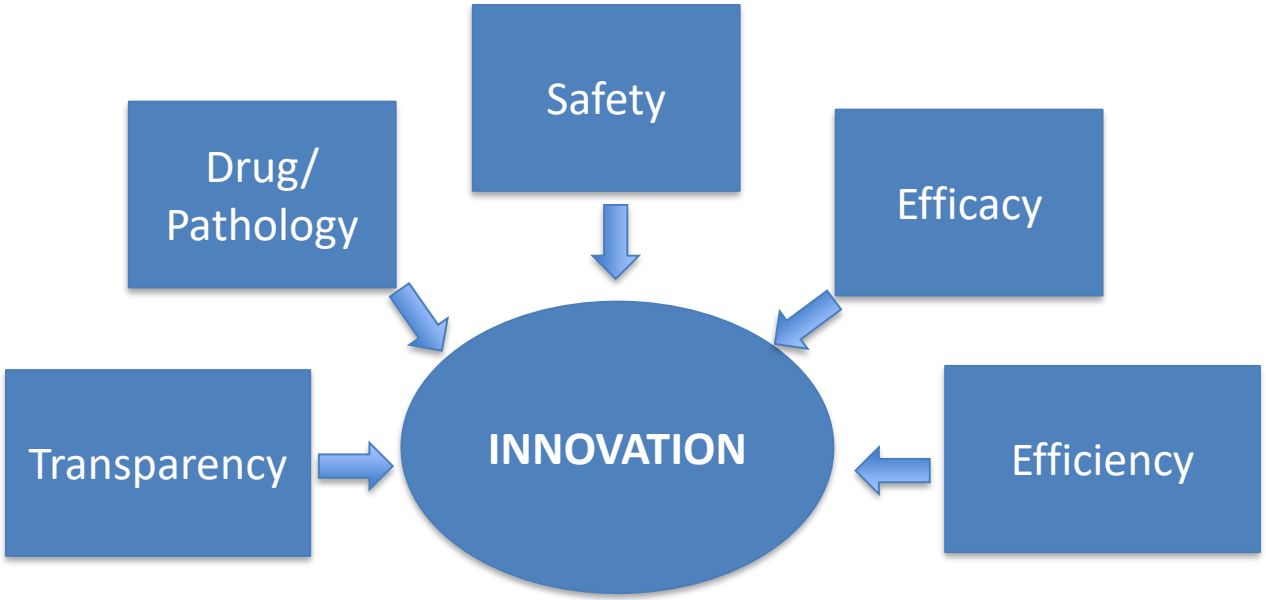
The context of clinical research

- Rapidly changing scientific and methodology environment
- Need to address the increasing complexity of clinical research

- (Italy) 4% of CTs with ‘complex design’

Clinical Trial Regulation EU 536/2014

- It is meant to be the main response to these changes in clinical research
- Within an innovation scenario moving fast, there is a strong need to find adequate responses to the changes introduced by scientific and technologic innovation

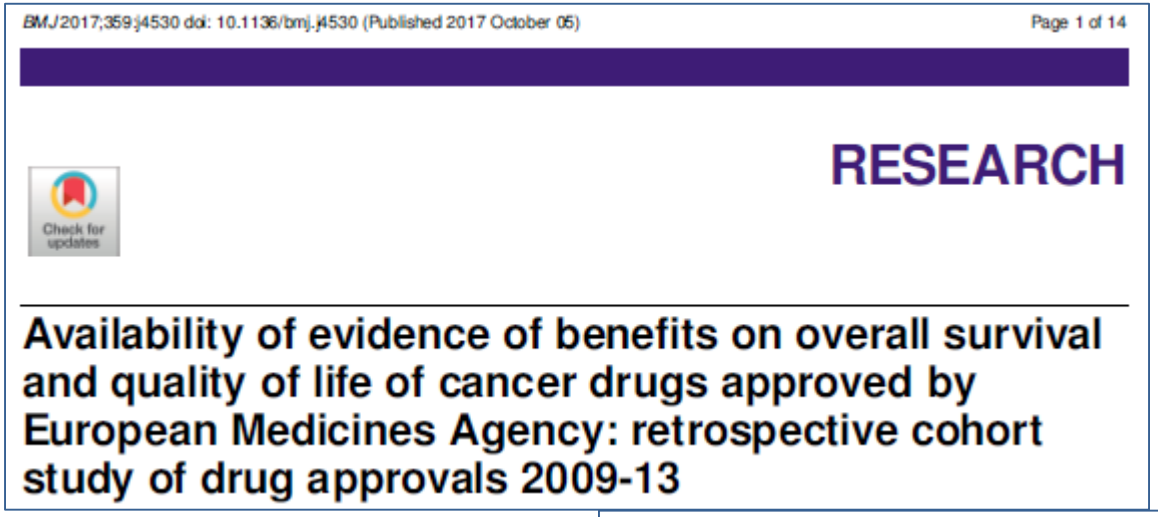


Clinical Research in 2017

Issues to deal with

- *Evolution of anticancer treatments*
  - From drugs for the population to personalized medicine
  - Treatment optimization through ‘biomarker discovery’ and validation
- *Patients’ expectancies*
- *Economic burden of drugs*
  - Prioritization

Scientific literature debate



BMJ 2017;359:j4530 doi: 10.1136/bmj.j4530 (Published 2017 October 05)

RESEARCH

Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13

thebmj

BMJ 2017;359:j4543 doi: 10.1136/bmj.j4543 (Published 2017 October 05)

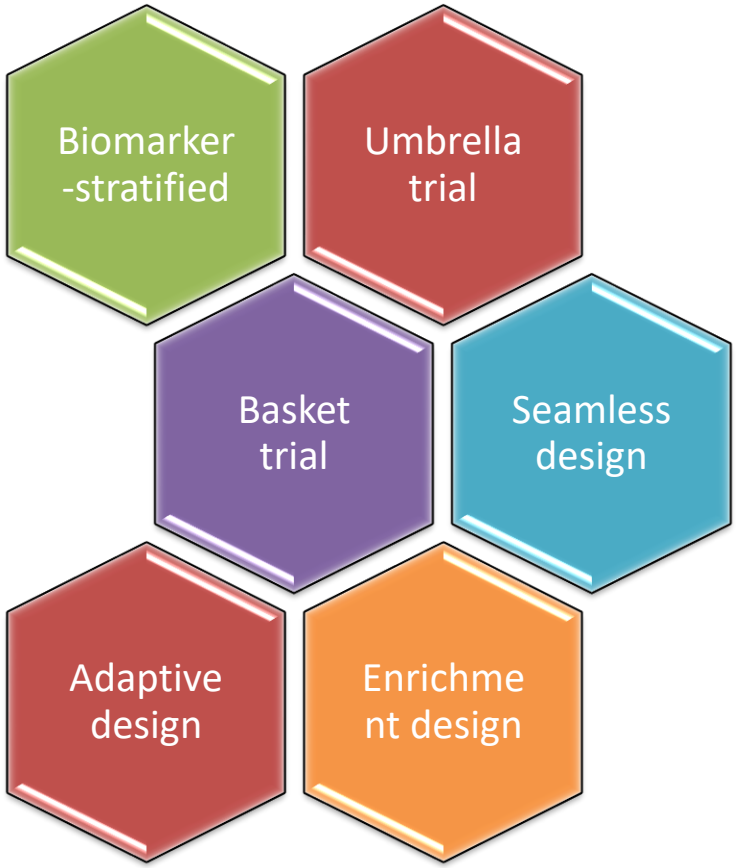
FEATURE

DRUG REGULATION

Cancer drugs: high price, uncertain value

A study published in The BMJ this week shows how most new cancer drugs are failing to deliver any clinically meaningful benefit. It's time for Europe to raise the evidence bar before market approval, finds Deborah Cohen

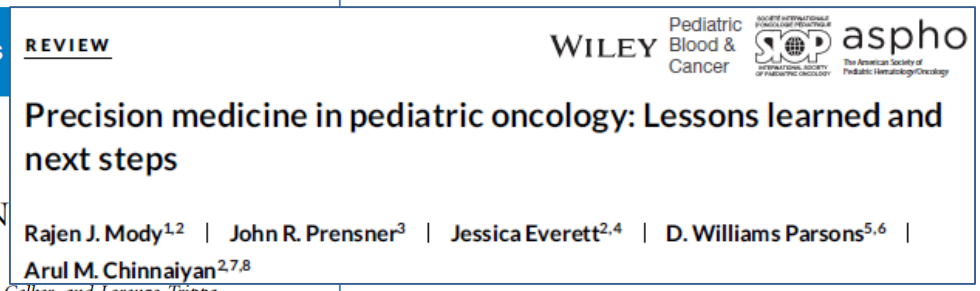
New trial designs may play a role



POTENTIAL ADVANTAGES

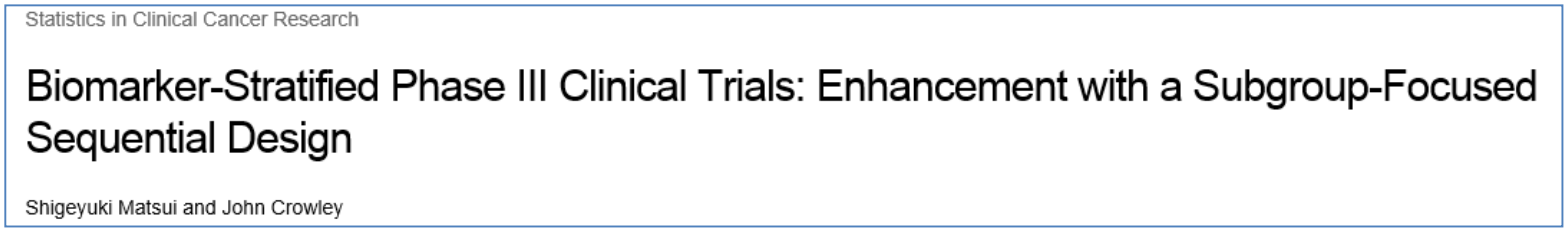
- Increasing efficiency in screening/recruitment
- Trial tailored for individual patient need
- Faster development process
- Increased study power
- Lower costs


VOLUME 35 · NUMBER 27 · SEPTEMBER 20, 2017
JOURNAL OF CLINICAL ONCOLOGY
STATISTICS
Designing Clinical Trials That Accept N
in Metastatic Breast Cancer
Steffen Ventz, Brian M. Alexander, Giovanni Parmigiani, Richard D. Gelber, and Lorenzo Trippa


REVIEW
WILEY Pediatric Blood & Cancer
aspho
Precision medicine in pediatric oncology: Lessons learned and next steps
Rajen J. Mody[1,2] | John R. Prensner[3] | Jessica Everett[2,4] | D. Williams Parsons[5,6] | Arul M. Chinnaiyan[2,7,8]


The NEW ENGLAND JOURNAL of MEDICINE
REVIEW ARTICLE
THE CHANGING FACE OF CLINICAL TRIALS
Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., Editors
Adaptive Designs for Clinical Trials
Deepak L. Bhatt, M.D., M.P.H., and Cyrus Mehta, Ph.D.


inical research strategies in
ic oncology: clinical trial design,
ve, basket and umbrella trials, new
ints and new evaluations of response
is[1], Baktiar Hasan[2] and Benjamin Besse[3]
the Series "Topics in Thoracic Oncology"
Zalcman and N. Girard


Statistics in Clinical Cancer Research
Biomarker-Stratified Phase III Clinical Trials: Enhancement with a Subgroup-Focused Sequential Design
Shigeyuki Matsui and John Crowley

Innovative approaches to CT design

- Data-dependent designs
  - *Adaptive design*
- Identify responders and increase statistical power
  - *"enrichment" approach*
- Identify large and meaningful differences in small, molecularly selected groups of patients
  - *Basket trials, Umbrella trials*

Adaptive design

Modifications of some aspects of the trial can be prospectively planned so that "adaptations" may take place while the study is ongoing

Type of design	Features
Adaptive randomization	Based on treatment response The goal is to assign more patients to a promising test treatment
Sample size re-estimation	Based on observed interim data Attention should be paid to bias (e.g. observed interim difference based on small numbers)
Adaptive treatment-switching	In case of evidence of lack of efficacy, disease progression or safety issues
Adaptive hypotesis	Based on observed interim data From single to a composite or multiple hypothesis Between the primary and secondary endpoints

Adaptive design

• Advantages

- Learn and address several hypotheses in order to improve the accuracy of the study and speed up the development of the compound
- Provide a more distinct advantage in the study of novel drugs (not having a clearly understood mechanism of action)

• Disadvantages

- It takes more time to plan as there is the need to involve all stakeholders (e.g. clinicians, biostatistician, drug providers)
- To control type I error rate
- Impact of any adaptation-associated statistical or operational bias on the estimates of treatment effects
- The interpretability of the results

Enrichment design

FDA

Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

- Increase trial efficiency by choosing the 'right patients' for the trial
- Don't do clinical trials in a random sample of the population

  - Make sure people have the disease under study **-> Entry criteria**
  - Have stable disease with stable measurements **-> Lead in periods**
  - Have disease of some defined severity
  - Do not respond too well to placebo **-> Placebo lead in periods**
  - Do not have conditions that would obscure benefit.

ENRICHMENT
used in almost every clinical trial

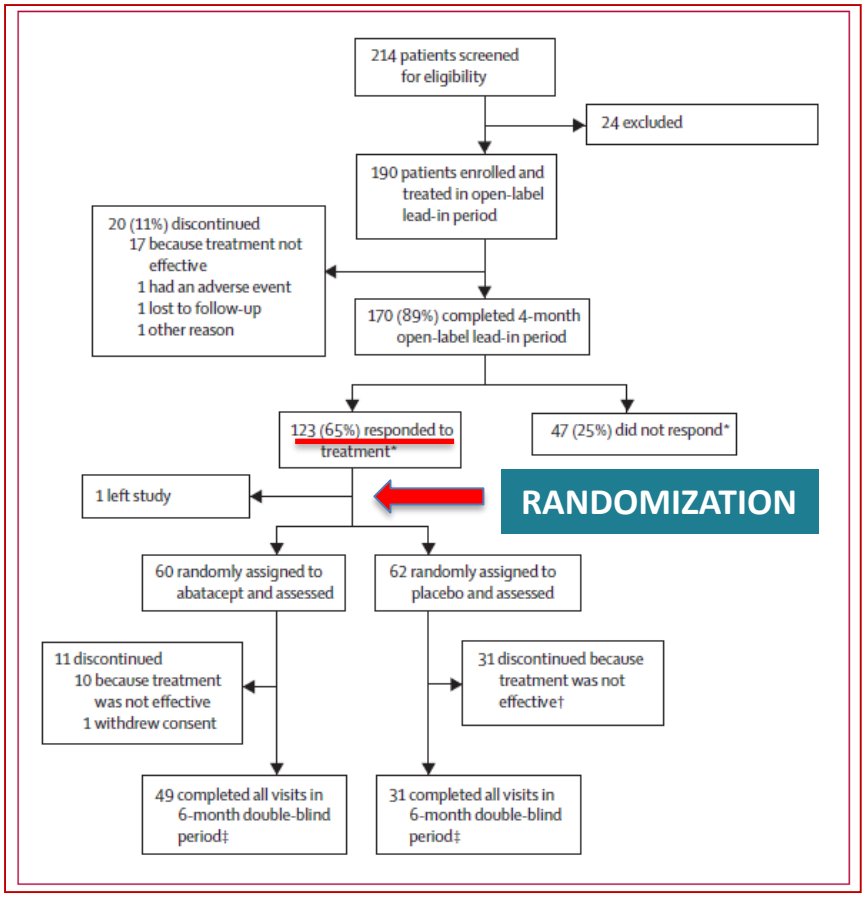
Other steps, not as regularly used, that can be taken **to increase the likelihood that a drug effect can be detected** (if there is one)

Randomized withdrawal design

Patients who show a response to treatment in an open label period are randomized to continued drug treatment or placebo

Suitable to:

- establish long-term effectiveness of drugs in settings in which long-term use of a placebo would not be acceptable (e.g., psychiatric and antihypertensive drug treatments)
- act as an initial trial to show effectiveness when there is an existing population of patients in an open-label treatment setting (e.g. nifedipine)



Enrichment (1)

- It is the prospective use of any patient characteristic - demographic, pathophysiologic, historical, genetic, and others – to select a study population in which detection of a drug effect is more likely than it would be in an unselected population.

- It is intended to increase study power in 3 principal ways, by:
  - ***Decreasing heterogeneity*** (noise): Choosing an appropriate population, i.e. patients who definitely have the disease *(likely compliers, people who will not drop out, no placebo-responders)*
  - ***Prognostic enrichment***: Finding a population with many outcome events, i.e., high risk patients, or patients with relatively severe disease
  - ***Predictive enrichment***: Identifying a population capable (or more capable) of responding to the treatment

Enrichment (2)

The increased study power facilitates ‘proof of principle’ (there is a clinical effect in some population) but, depending on the specific enrichment mechanism used, it can leave open

- the question of **generalizability** of the result and how the drug will work in other populations
- the question of how much data are needed before or after approval in the non selected group

Enrichment (3)

The remedy is to:

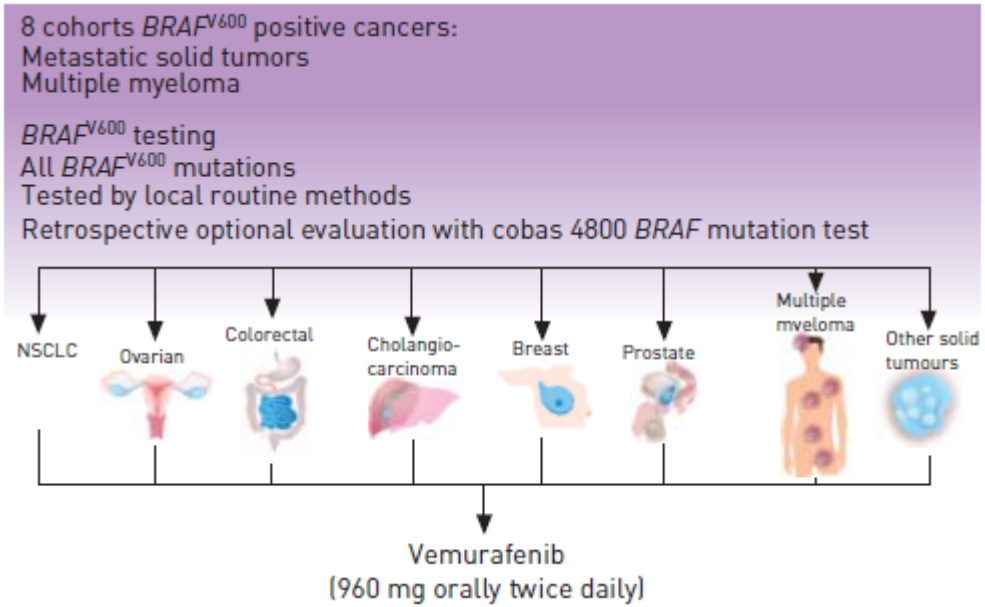
- Use these designs **early**, to show unequivocal drug effect
- Don’t make the enrichment study the **only** study, at least not usually
- Be aware of what you you’ve done and don’t hide it or overstate results

But it is more and more recognized that the selected population is in fact the one where treatment makes the most sense

Basket trials

Single IMP targeting single mutation in different tumour types

A Screening Study to Detect BRAF V600 Mutation-Positive Patients For Enrollment Into Clinical Research Studies of Zelboraf (Vemurafenib), *Clinicaltrial.gov NCT01804140*

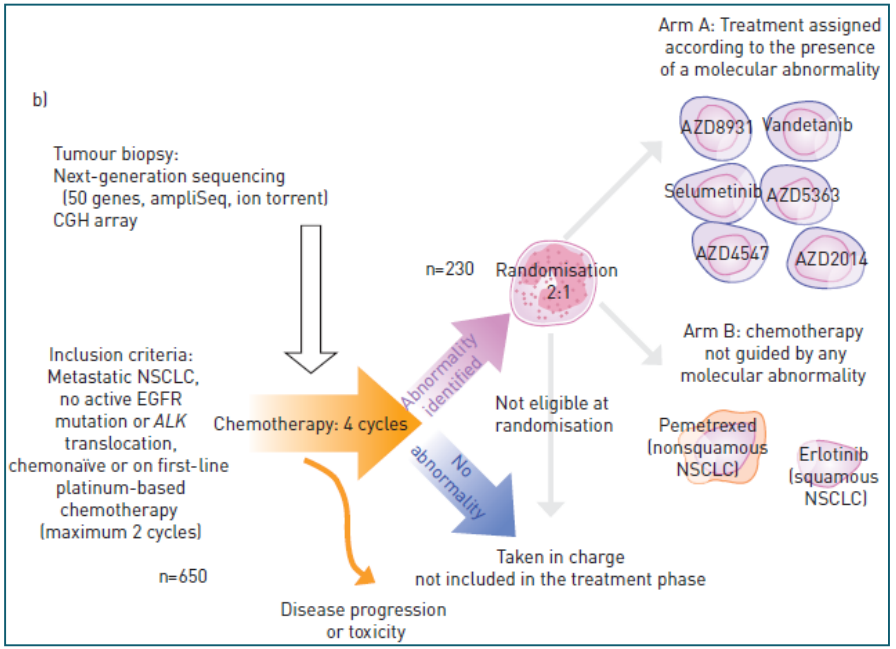


- These trials are often viewed as parallel phase II studies for one drug on the basis of a common denominator that can be molecular alteration.
- They are usually tested locally and often fall into the "trial to learn" category

Umbrella trials

Different IMPs targeting different mutations in the same tumour type

SAFIR02_Lung - Efficacy of Targeted Drugs Guided by Genomic Profils in Metastatic NSCLC Patients, *Clinicaltrial.gov NCT02117167*



- These trials require a strong collaboration to be in place, as consistent molecular profile and harmonisation of the cohorts for each biopsy, assay and medication are needed
- They may fall into the "trial to conclude" category.

Complex trial designs: increased risk factors

Basket trial

Single IMP, different tumours

- Number of different study populations, disease status
- Different types of procedures, study visits per treatment arm
- Different inclusion/exclusion criteria, backgound treatments criteria per treatment arm

Umbrella trial

Different IMPs, single tumour

- Number of IMPs/treatment arms
- Different modes of drug administration
- Different length of study per treatment arm
- Different doses, mechanisms of action, drug class
- Different drug supply chain issues

CTR 536/2014 and complex trial design

Regulatory constraints: application/approval

- Labelling, master protocols, sub-studies

GCP issues

- Complexity increases the risk of non compliance

Statistical challenges

- Power of the studies, multiplicity issues

Safety reporting and surveillance

- Patients switching between treatment arms, causality issues

Key issues and conclusions

- Innovative clinical research models are needed in an era of rapidly changing scientific and methodology environment
- Innovation (new methodological approaches) is a way to improve trial efficiency and quality and to reduce trial costs
- Multi-stakeholder initiative and networks should be envisaged

- Increase the culture of clinical research and trial methodology in physicians, researchers, regulators and all the involved stakeholders
- Increase perceived value of clinical research in the general public