'New perspectives in Clinical Trials'

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VISION

- A clinical trial is a clinical study in which participants are assigned according to a pre-defined therapeutic strategy or plan (protocol) to receive a health-related intervention, such as a medicine, in order to investigate its effects on health outcomes, usually compared to another (or sometimes no) treatment.
- Clinical trials are used to evaluate clinical practices that do not fall within the current practices of a country, or to evaluate a new medicine.
- Clinical trials are used to generate data on the safety and efficacy of the intervention.

- Clinical trials are conducted only after a regulatory authority approval and ethics committee review.
- Clinical trials are often characterised in Phases from I (first-in-human), II (exploratory), III (confirmatory) to IV (post approval).
- Previously, the terms clinical study and clinical trial were used synonymously.

1948: spartiacque per gli studi clinici

Studio del British Medical Research Council (MRC) sulla streptomicina sulla tubercolosi polmonare su 107 pazienti di cui 55 trattati con streptomicina e riposo a letto (Gruppo S) e 52 solo con il riposo a letto (Gruppo C).

Caratteristiche dello studio:
Tubercolosi polmonare acuta progressiva bilaterale
Età compresa fra 15 e 25 anni (in seguito 30)
Randomizzazione nell'assegnazione ai gruppi
Analisi dei risultati dopo 6 mesi

Risultati: Morirono 4 su 55 pazienti del gruppo S e 14 su 52 pazienti del gruppo C. Il risultato è statisticamente significativo e la probabilità che sia dovuto al caso è inferiore a 1 su 100.

J R Soc Med. 2011 Sep; 104(9): 383–386

L'evoluzione nel tempo delle sperimentazioni cliniche

Fino agli anni 30 → Trials non controllati

Anni 30-50 → Trials controllati non randomizzati

Anni 50-80 → Trials controllati randomizzati

Anni 80- → Mega trials, Meta-analisi, Review sistematiche → Evidence Based Medicine

Five steps of EBM in practice

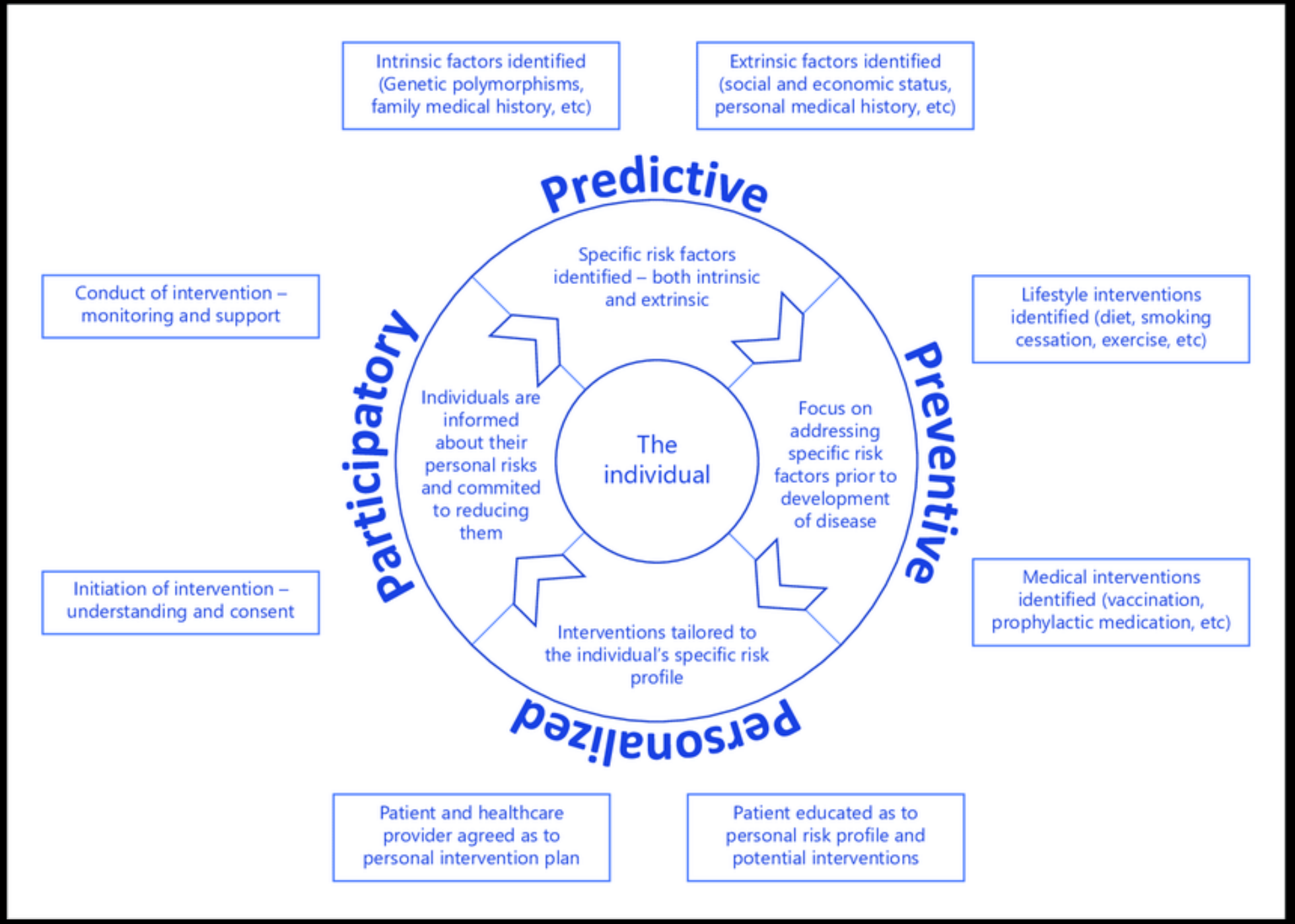
1. Translation of uncertainty to an answerable question; includes critical questioning, study design and levels of evidence[54]
2. Systematic retrieval of the best evidence available[55]
3. Critical appraisal of evidence for internal validity that can be broken down into aspects regarding:[56]
    - Systematic errors as a result of selection bias, information bias and confounding
    - Quantitative aspects of diagnosis and treatment
    - The effect size and aspects regarding its precision
    - Clinical importance of results
    - External validity or generalizability
4. Application of results in practice[57]
5. Evaluation of performance[58]

Cook et al., 1992

Some limitations of evidence based medicine

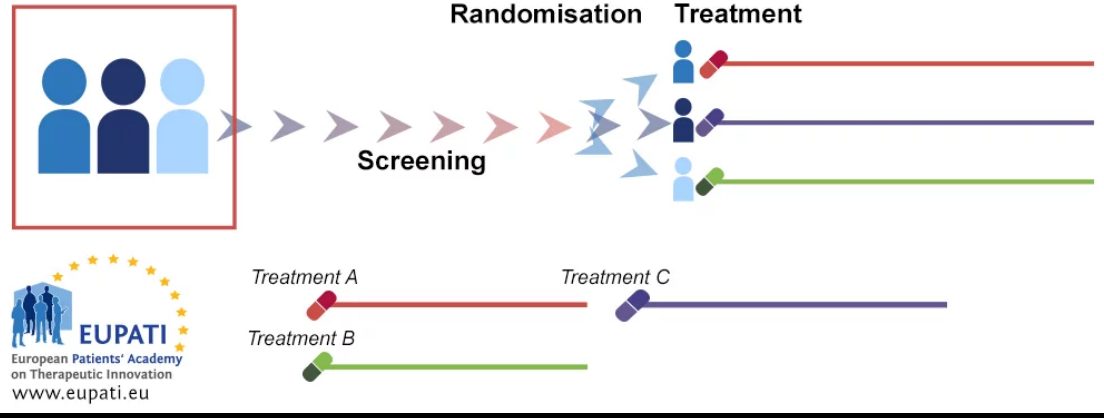
- Many questions do not have answers!
- Evidence from populations - ?relevance to individual
- Trials - not 'real' usage
- Lack of local ownership of recommendations
- Clinical effectiveness vs cost effectiveness

and ... ethical concern
role of medical expertise
patient involvement


Intrinsic factors identified (Genetic polymorphisms, family medical history, etc)
Extrinsic factors identified (social and economic status, personal medical history, etc)
Predictive
Specific risk factors identified – both intrinsic and extrinsic
Conduct of intervention – monitoring and support
Lifestyle interventions identified (diet, smoking cessation, exercise, etc)
Participatory
Individuals are informed about their personal risks and commited to reducing them
The individual
Focus on addressing specific risk factors prior to development of disease
Preventive
Initiation of intervention – understanding and consent
Medical interventions identified (vaccination, prophylactic medication, etc)
Interventions tailored to the individual's specific risk profile
Personalized
Patient and healthcare provider agreed as to personal intervention plan
Patient educated as to personal risk profile and potential interventions

Randomized Clinical Trials (RCT)

Parallel Trial



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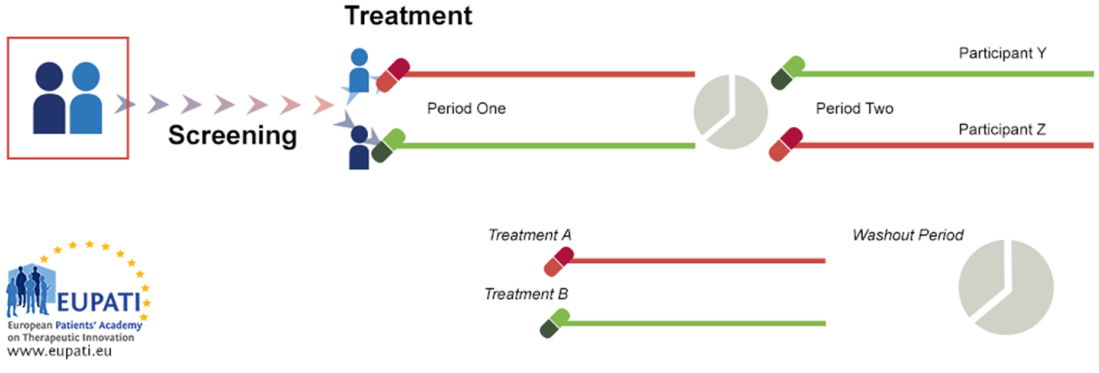
Crossover Trial



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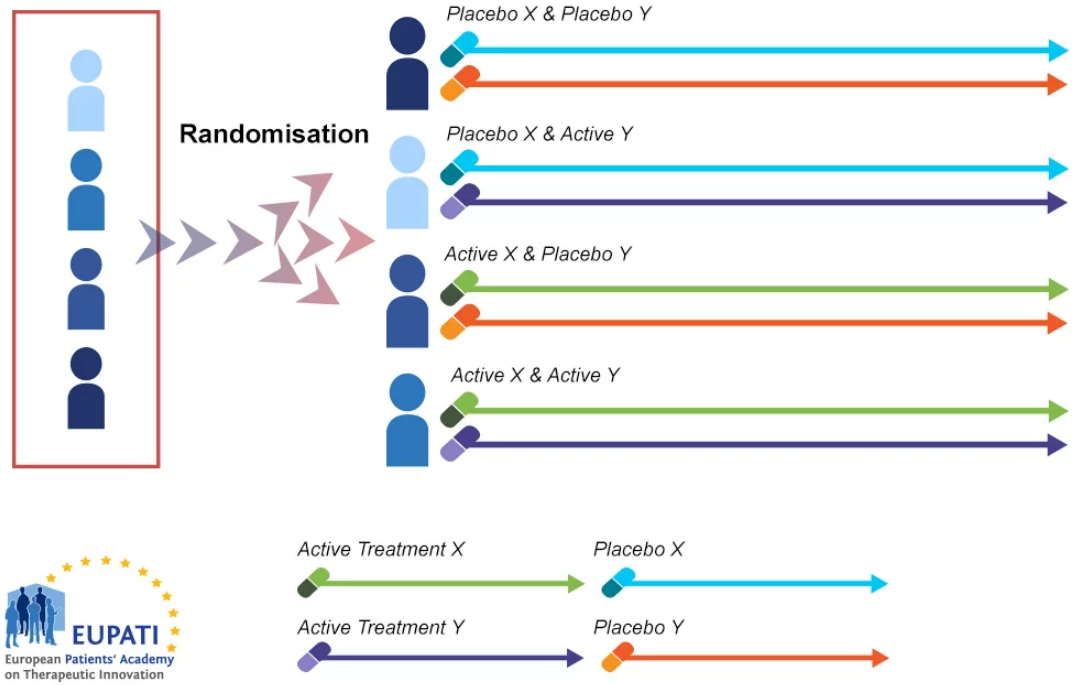
2x2 Factorial design



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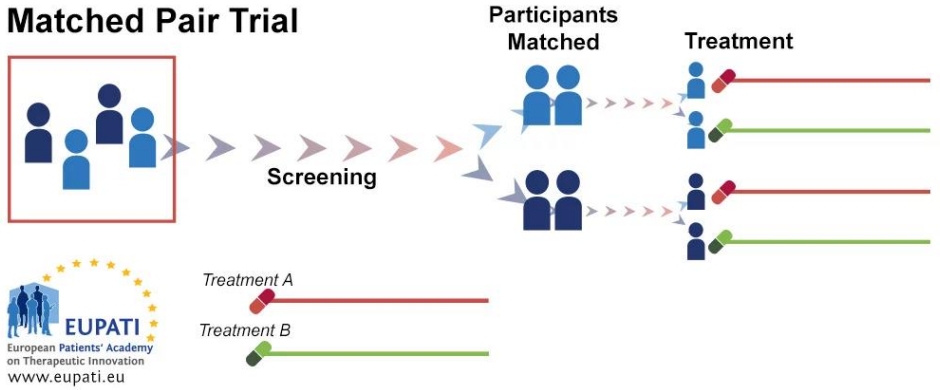
Matched Pair Trial



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Withdrawal Trial

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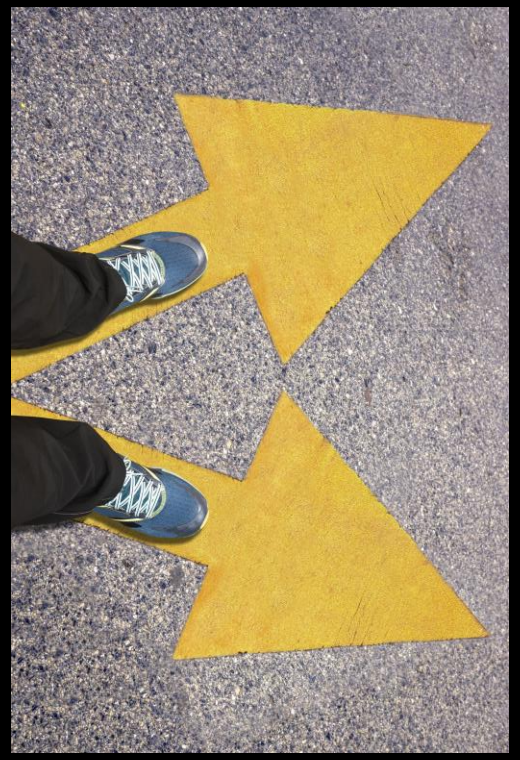


Non-inferiority Trials

Adaptive Design

- In a clinical trial design, there are a number of different types of comparisons that can be included:
  - **Superiority comparison trials** demonstrate that the investigational medicine is better than the control.
  - **Equivalence comparison trials** demonstrate that the endpoint measure is similar (no worse, no better) to the control.
  - **Non-inferiority comparison trials** demonstrate that the investigational medicine is not worse than the control.
  - **Dose-response relationship trials** demonstrate various dose parameters including starting dose and maximum dose.

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*

Challenges in the Design and Interpretation of Noninferiority Trials

Laura Mauri, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

N Engl J Med

Although some new treatments offer greater efficacy, others may promise greater safety or convenience, or less expense, while providing similar efficacy.

Non-inferiority trials are unethical because they disregard patients' interests, Garattini and Bertele', Lancet 2007; 370: 1875–77

- *Pretext for looking for non-inferiority*
- *Looking for non-inferiority or overlooking diff erences?*
- *No limits to the non-inferiority limit*
- *Unreliable messages from questionable methods*
- *Commercial aims, not patients' interests*
- *Enrolling patients in non-inferiority trials betrays their trust*

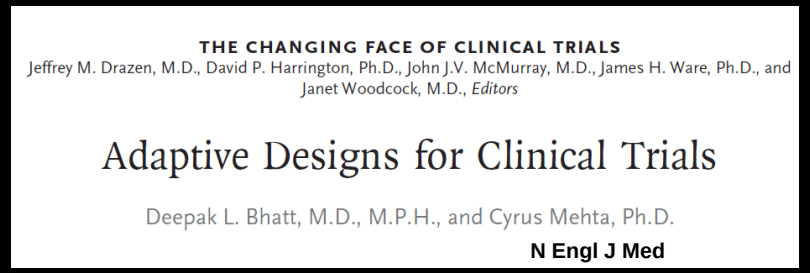
Nunn et al., Lancet 2008; 371: 895

Current treatment of TBC is highly effective, curing 95% or more of patients. However, it requires a minimum of three drugs which have significant side-effects and need to be given for at least 6 months. Shortening treatment duration would improve completion rates and reduce both the time that patients are exposed to potentially toxic drugs and the cost of delivering tuberculosis chemotherapy.
The risks to patients in a properly done non-inferiority trial are no greater than those in a superiority trial.

If non-inferiority designs were banned, there would be no prospect of shortening the duration of chemotherapy for patients with tuberculosis. And that would surely be unethical.

Table 2. Recommendations for the Design, Reporting, and Interpretation of Noninferiority Trials.

CONSORT* recommendations[40]
State hypothesis in terms of noninferiority
Justify choice of noninferiority margins
Describe results with confidence limits for difference or ratio
Food and Drug Administration recommendations[5]
Assess whether active control performed as expected (i.e., determine assay sensitivity)
Be sure noninferiority margin is not larger than the expected difference between active control and placebo
European Medicines Agency recommendations[41]
Make sure the data set for the full analysis, based on the intention-to-treat principle, and the data set for the per-protocol analysis have equal importance, and that their use will lead to similar conclusions for a robust interpretation
Additional recommendations
Compare the noninferiority margin with the expected benefit during design and interpretation
Avoid using composite end points that include discordant components
Perform a sensitivity analysis for missing data (e.g., multiple imputation)[22]



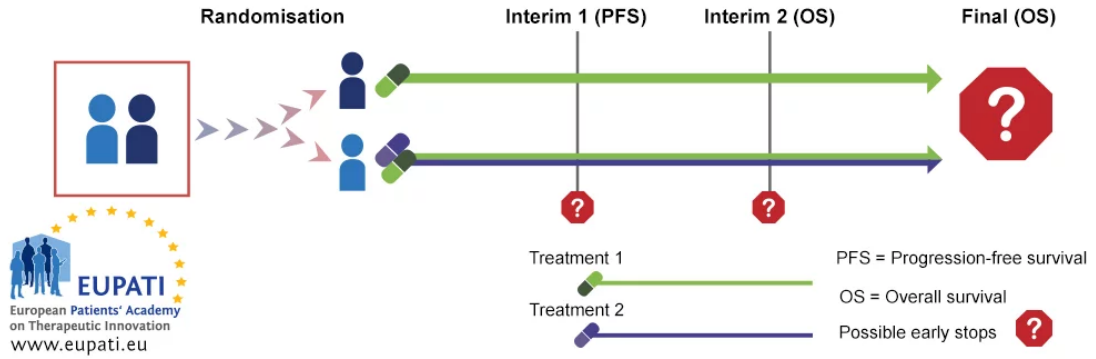
Adaptive designs are relatively flexible clinical trial designs, allowing for modifications during the course of the trial in order to streamline and optimise the process. Analyses of the accumulating study data are performed at pre-planned time points within the trial, can be performed in a fully blinded or unblinded manner. It is important that the process is modified only in such a way that the validity and integrity of the trial are not affected.

Adaptive designs provide an appealing alternative because:

- *They shorten the development process without compromising validity or efficacy*
- *Ineffective treatments can be identified earlier on*
- *They permit a more efficient use of resources.*

Group sequential design

An example trial using group-sequential design



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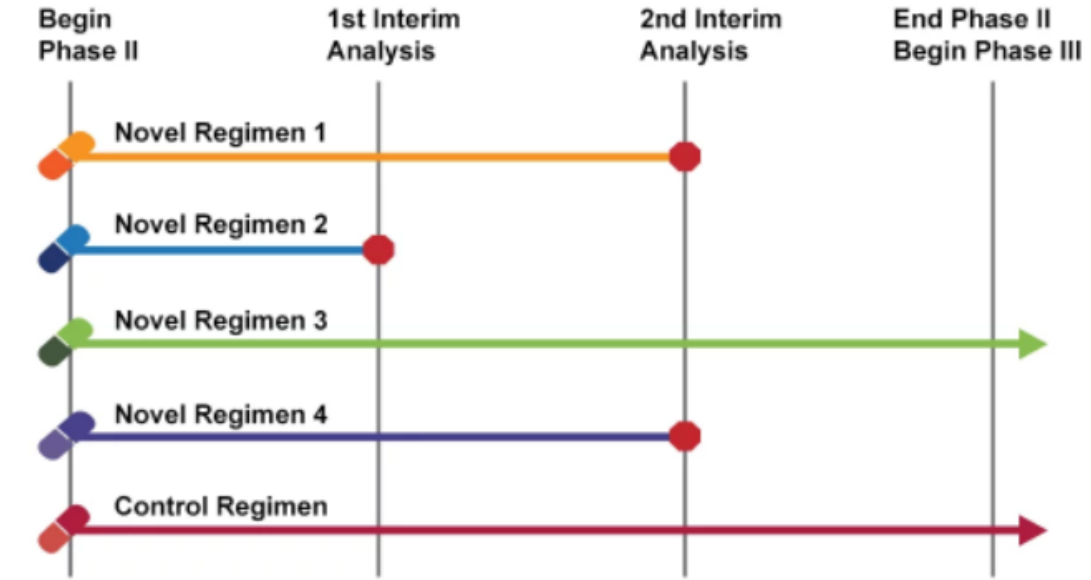
Multi-arm multi-stage (MAMS) design



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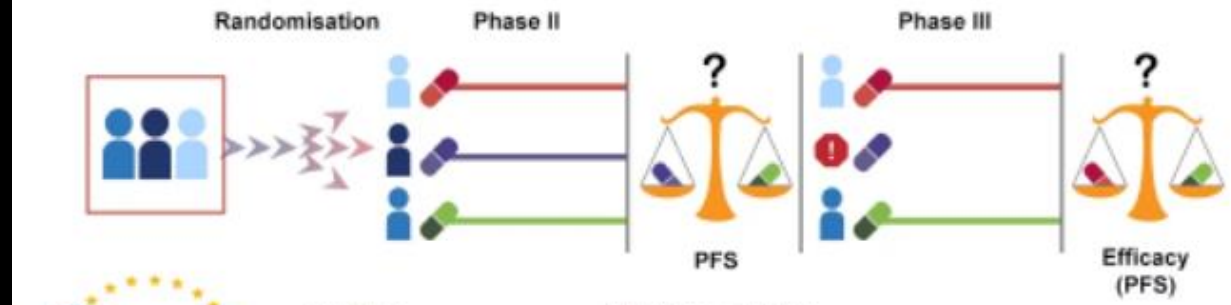
Seamless Phase II/III design



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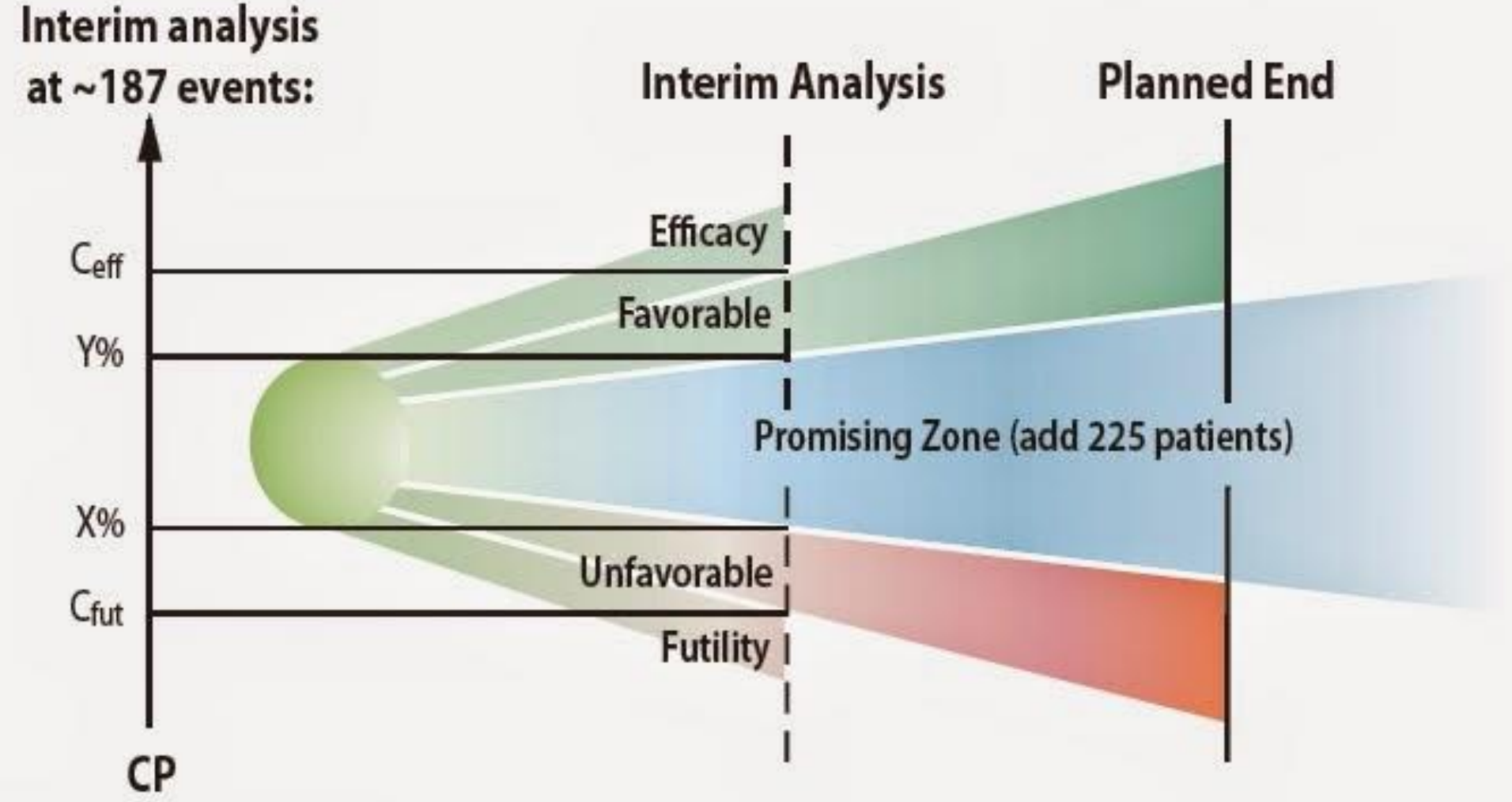


CP = Conditional power
The probability of success (statistical significance) at the end of the trial given current data trend

Interim outcome partitioned into unfavorable, promising, and favorable zones

Informed Consent

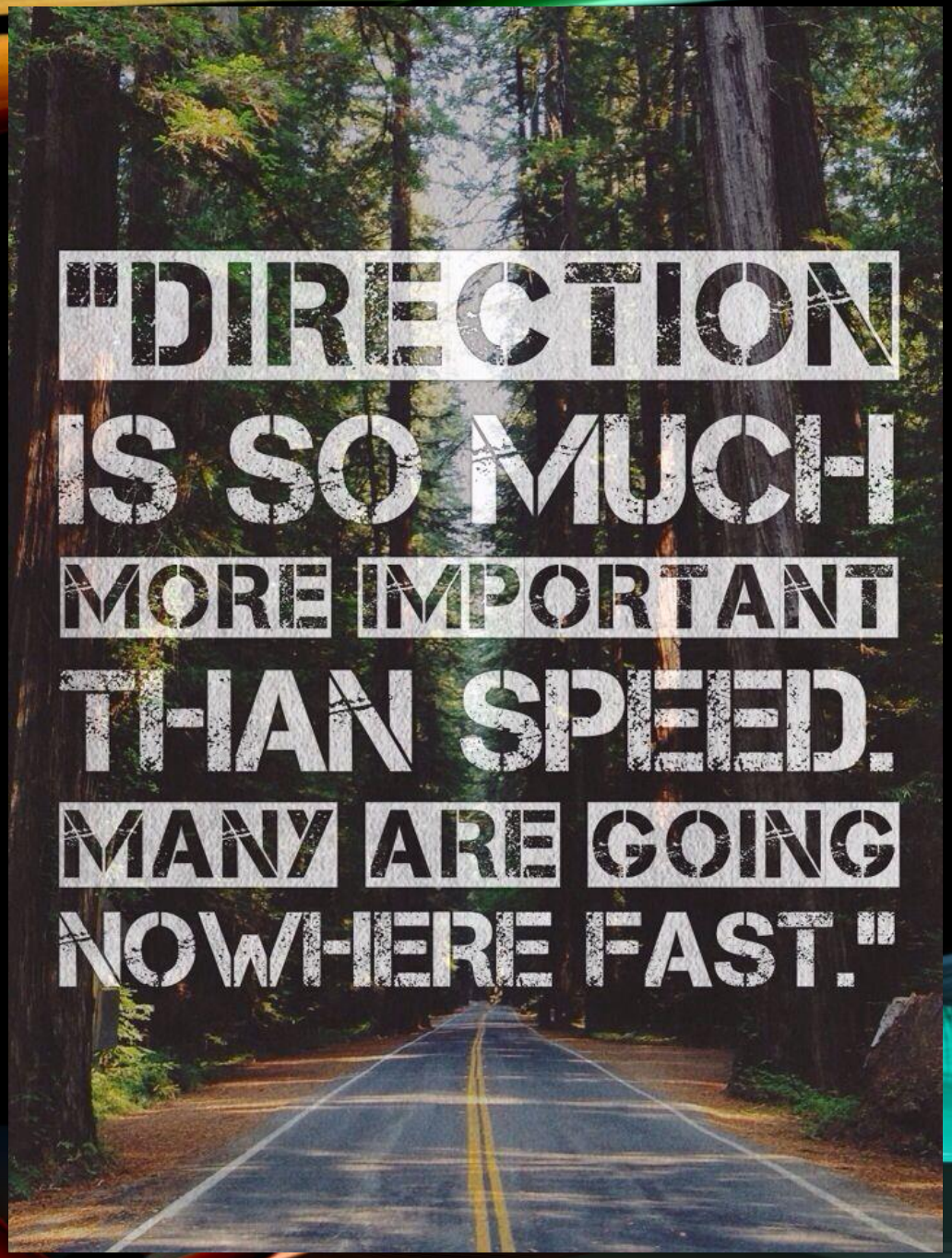
This can pose challenges in trials involving life-threatening illness, because patients can lack a realistic understanding of risk/benefit (therapeutic misestimation) or they can fail to understand the ways that study protocols antagonize treatment objectives (therapeutic misconception).

We are dubious of the suggestion that adaptive allocation studies offer generic ethical advantages. At least in the two-arm setting, they seem to worsen total burden by increasing patient exposure to research procedures and to drugs remain unproven. Telling patients that allocation will be adjusted according to evolving evidence seems to invite therapeutic overestimation.
Adaptive allocation introduces new sorts of validity threats.
So can we say that adaptive allocation is unethical?

Phillips Hey and Kimmelmann. Clin Trials. 2015; 12: 102–106.

More funds are required

Outcome-adaptive trials are more complicated and expensive to plan and coordinate. While some research centers may be able to implement outcome-adaptive allocation as a rule, the requisite funding and stakeholder support cannot be assumed to hold across the research enterprise. Absent this support, outcome-adaptive trials seem more likely to make research less efficient on the whole.


"DIRECTION
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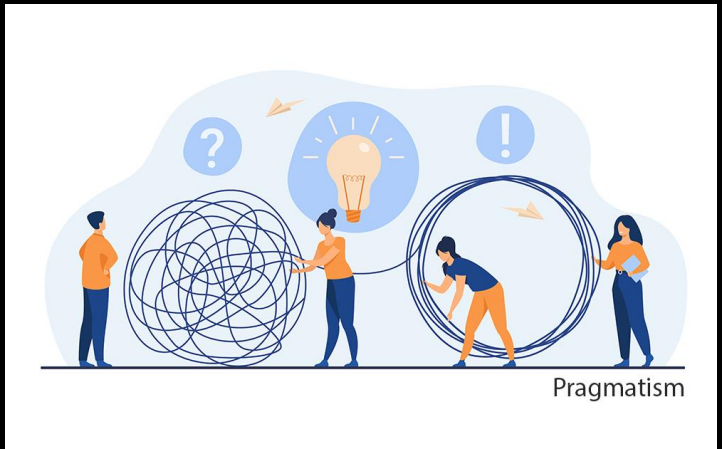
Pragmatic Trials

Ian Ford, Ph.D., and John Norrie, M.Sc.

N Engl J Med 2016;375:454-63.



Pragmatism in clinical trials arose from concerns that many trials did not adequately inform practice because they were optimized to determine efficacy. Because such trials were performed with relatively small samples at sites with experienced investigators and highly selected participants, they could be overestimating benefits and underestimating harm. This led to the belief that more pragmatic trials, designed to show the real-world effectiveness of the intervention in broad patient groups, were required.

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Table 1. Nine Dimensions for Assessing the Level of Pragmatism in a Trial, as Proposed in the Pragmatic–Explanatory Continuum Indicator Summary 2 (PRECIS-2) Tool.*

Dimension	Assessment of Pragmatism
Recruitment of investigators and participants	
Eligibility	To what extent are the participants in the trial similar to patients who would receive this intervention if it was part of usual care?
Recruitment	How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
Setting	How different are the settings of the trial from the usual care setting?
The intervention and its delivery within the trial	
Organization	How different are the resources, provider expertise, and organization of care delivery in the intervention group of the trial from those available in usual care?
Flexibility in delivery	How different is the flexibility in how the intervention is delivered from the flexibility anticipated in usual care?
Flexibility in adherence	How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
The nature of follow-up	
Follow-up	How different is the intensity of measurement and the follow-up of participants in the trial from the typical follow-up in usual care?
The nature, determination, and analysis of outcomes	
Primary outcome	To what extent is the primary outcome of the trial directly relevant to participants?
Primary analysis	To what extent are all data included in the analysis of the primary outcome?

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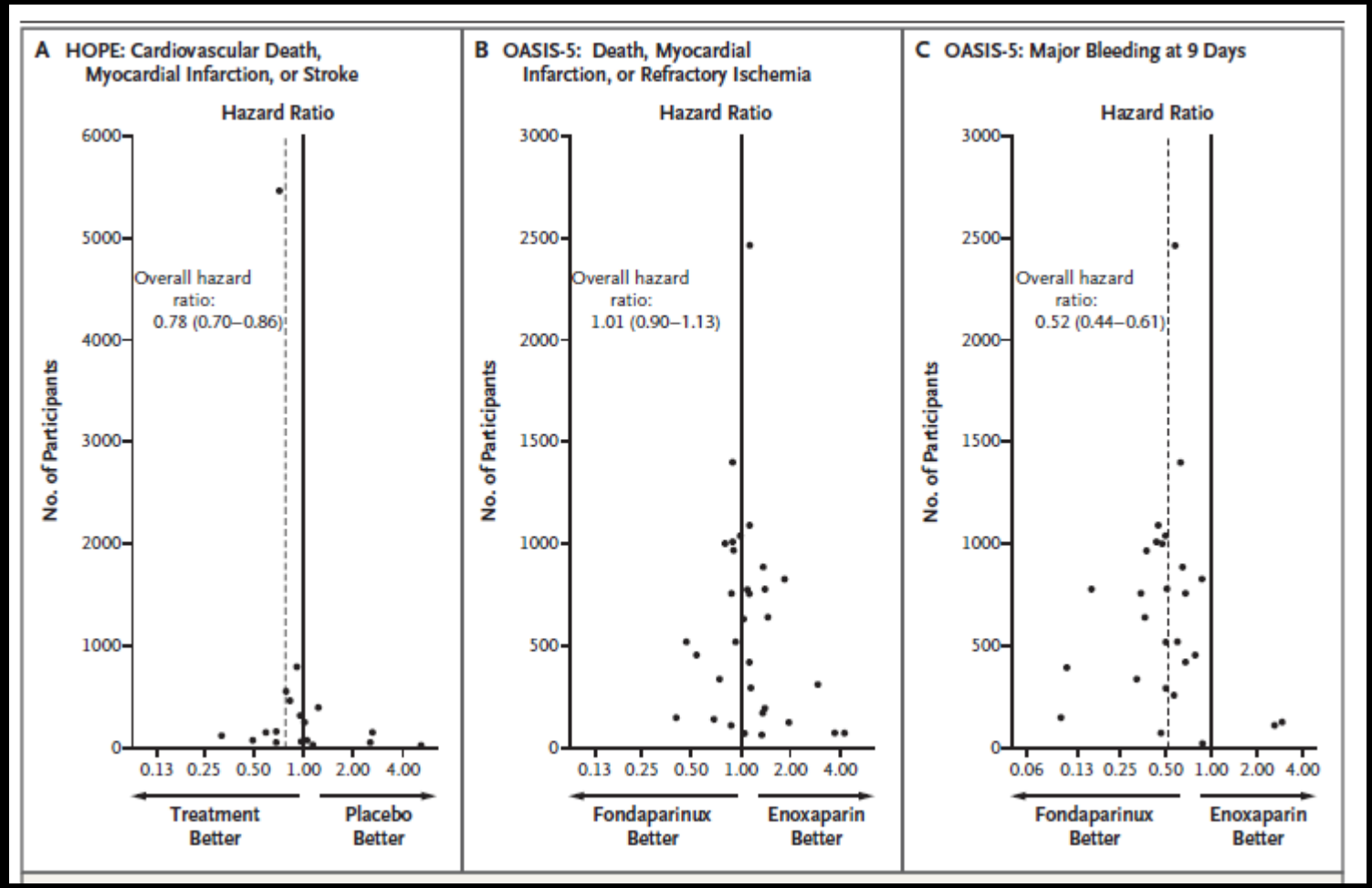
Interpreting Geographic Variations in Results of Randomized, Controlled Trials

Salim Yusuf, M.B., B.S., D.Phil., and Janet Wittes, Ph.D.

N Engl J Med 2016;375:2263-71.



When a randomized, clinical trial shows marked variations in results among countries, one should seek supporting evidence to understand whether the observed results are likely to be real, an artifact of the design analysis or implementation of the trial, or simply due to chance.

Ethical issues in personalized medicine

Many ethical challenges regarding PM have already been reported. In addition to ethical issues concerning the massive data storage and data sharing, these challenges include:

- a possible discrimination by insurance companies and employers
- discrimination in access to PM
- incidental findings in genetic testing
- the lack of health literacy or "genetic literacy" for obtaining informed consent
- the lack of scientific evidence of the efficacy and tolerability of treatments
- the possibility of changing the patient-physician relationship by focusing on data
- and the increasing expectation on patients to contribute with data, time, effort and self-care.

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Informed Consent

Christine Grady, R.N., Ph.D., Steven R. Cummings, M.D., Michael C. Rowbotham, M.D., Michael V. McConnell, M.D., M.S.E.E., Euan A. Ashley, F.R.C.P., D.Phil., and Gagandeep Kang, M.D., Ph.D.

n engl j med 376;9

The changing face of informed consent

Over the past 50 years, the informed consent process has become increasingly regulated and standardized, while the challenges remain persistent and hard to overcome.

Consent forms are increasingly long and complicated, obscuring important details, and are often designed to serve the interests of institutions and sponsors.

Data show that participants often have a limited understanding of study information even when they have signed a consent form.

Technological advances driving changes in research methods and information practices have influenced how we think about informed consent for research, which raises the possibility of new approaches to informed consent and innovative options for obtaining it.

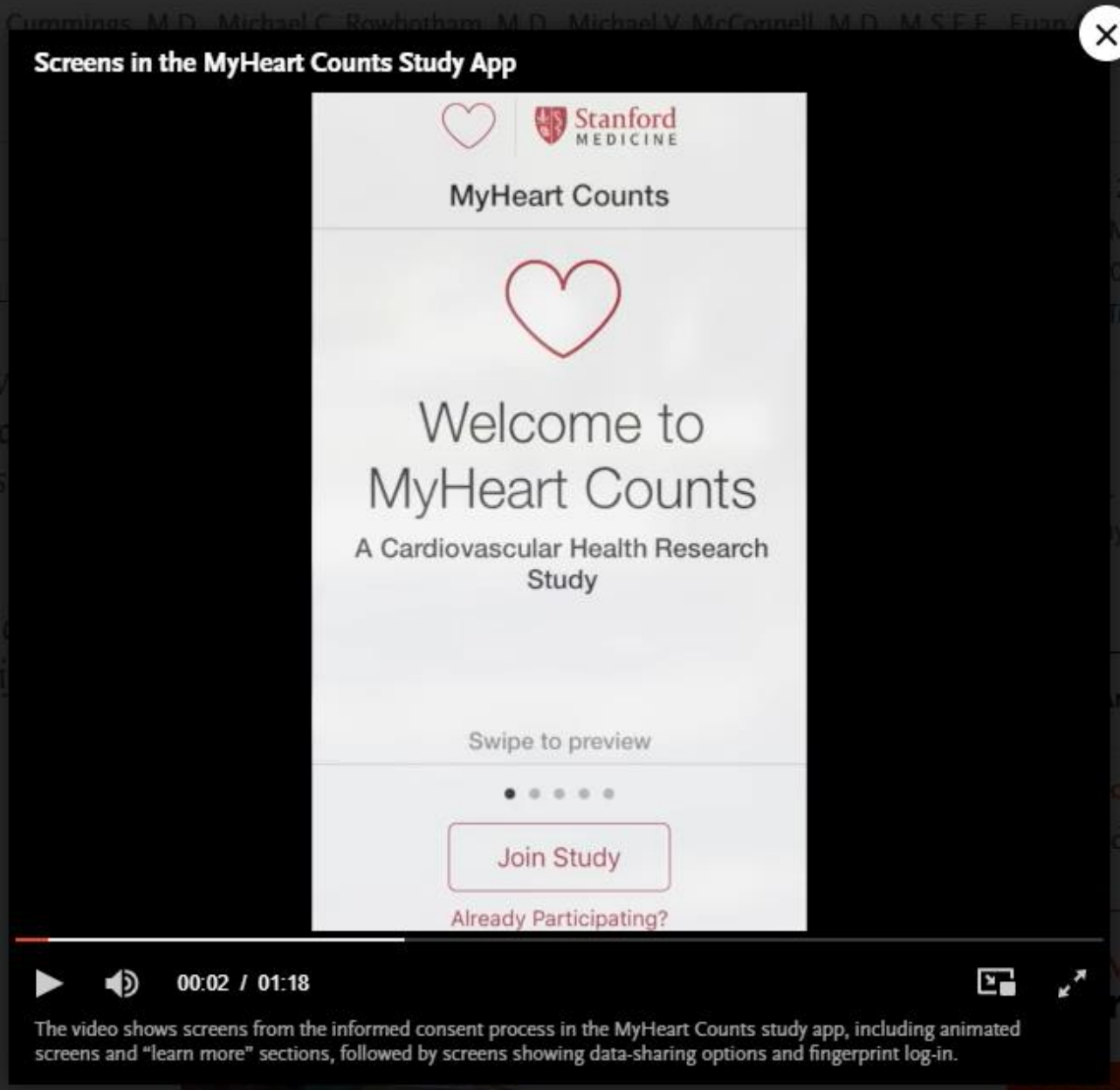
Electronic Informed Consent and Internet-Based Trials

Sufficient information to enable a participant to make an informed decision can be provided electronically, either on-site or remotely.

Informed consent by means of electronic devices (e-consent) often includes multimedia, such as graphics or video, about essential study features that may increase understanding of the study, particularly for people with a low educational level or limited litera

A participant must be given the opportunity to have questions answered during the informed consent process through a telephone call, real-time video, or electronic messaging, and the discussion may be guided by review of a participant's errors

Participants can sign electronically using pass-words known only to the participant or using a fingertip on a mobile device. When e-consent is performed remotely, the identity of the person who is giving the consent can be confirmed in one of several ways, such as digital signature, username and password, or biometrics.



Initial data from the MyHeart Counts study showed both the challenges and the potential of app-based research.

The population that provided consent was predominately young (median age, 36 years) and male (82%), and although the nearly 5000 participants who completed the 6-minute-walk test at the end of 7 days was the largest such cohort reported, it represented only 10% of participants who provided consent.

Table 1. Components and Challenges of Informed Consent with Traditional Paper Forms and Electronic Methods.

Component	Traditional Paper Informed Consent	Electronic and Digital Informed Consent	Challenges and Areas for Research
Disclosure	Information is written, usually on paper Discussion with investigator takes place, usually face to face	Consent can involve electronic information, multimedia information, video graphics, and interactive computer interfaces Investigator can be remote in time or place from participant	All types of disclosure require determining the appropriate content (amount and complexity of information) for disclosure User-friendly disclosure is needed Amount and style of information tailored to electronic platforms need to be determined
Understanding	Investigator and participant discuss information Participant asks questions Investigator assesses understanding, in some cases using questions, structured quizzes, other methods	Interaction can take place during disclosure Questions and assessment of understanding are easily built in Ongoing engagement is enabled Links to additional information can be included	Evidence indicates that people do not read click-through agreements on computers and mobile devices Information should be engaging and user-friendly to promote reading and understanding It may be difficult to assess capacity and understanding Empirical evidence to date indicates that video and multimedia consent strategies have not resulted in consistent advantages or disadvantages with regard to participant understanding[47]
Voluntariness	Investigator asks participant to make a choice in a setting free from coercion and undue influence Research team observes participant's body language and any hesitation	Some electronic systems facilitate participant control Participant can easily sign off or disengage Participant can decline	It may be difficult to assess voluntary choice without the clues of body language and tone It may be difficult to verify the identity of the person consenting Some data collection is passive In some cases, contributing data is a required part of the arrangement
Authorization	Paper consent document is signed Copies of document are kept in records	Options might include clicking agreement or an electronic signature Records of agreement are kept electronically	It may be difficult to verify the identity of the authorizing person

Grady et al., Lancet, 2017

In summary, hot issues to be investigated include:

1) public views about informed consent for the use of big data and electronic consent methods,
2) methods promoting engagement with and comprehension of digital study information,
3) methods of authentication and capacity assessment as part of digital consent, and
4) the extent to which there is selection bias in research in which digital consent technologies are used.

The ethical goals of informed consent and the **importance of considering research context** should guide us as we assimilate technology into research and the informed consent process and develop creative and effective evidence-based practices.

Grady et al., Lancet, 2017


THANK
YOU