ΕΙ 204 ΜΕΘΟΔΟΛΟΓΙΑ ΚΛΙΝΙΚΩΝ ΜΕΛΕΤΩΝ
Δ.Π.Μ.Σ. ΕΞΑΤΟΜΙΚΕΥΜΕΝΗ ΙΑΤΡΙΚΗ του Πανεπιστημίου Πατρών

# Είδη Κλινικών Μελετών Μέρος Β’

Ιωάννης Κατσαρόλης

27 Απριλίου 2024

# Δήλωση διαφάνειας

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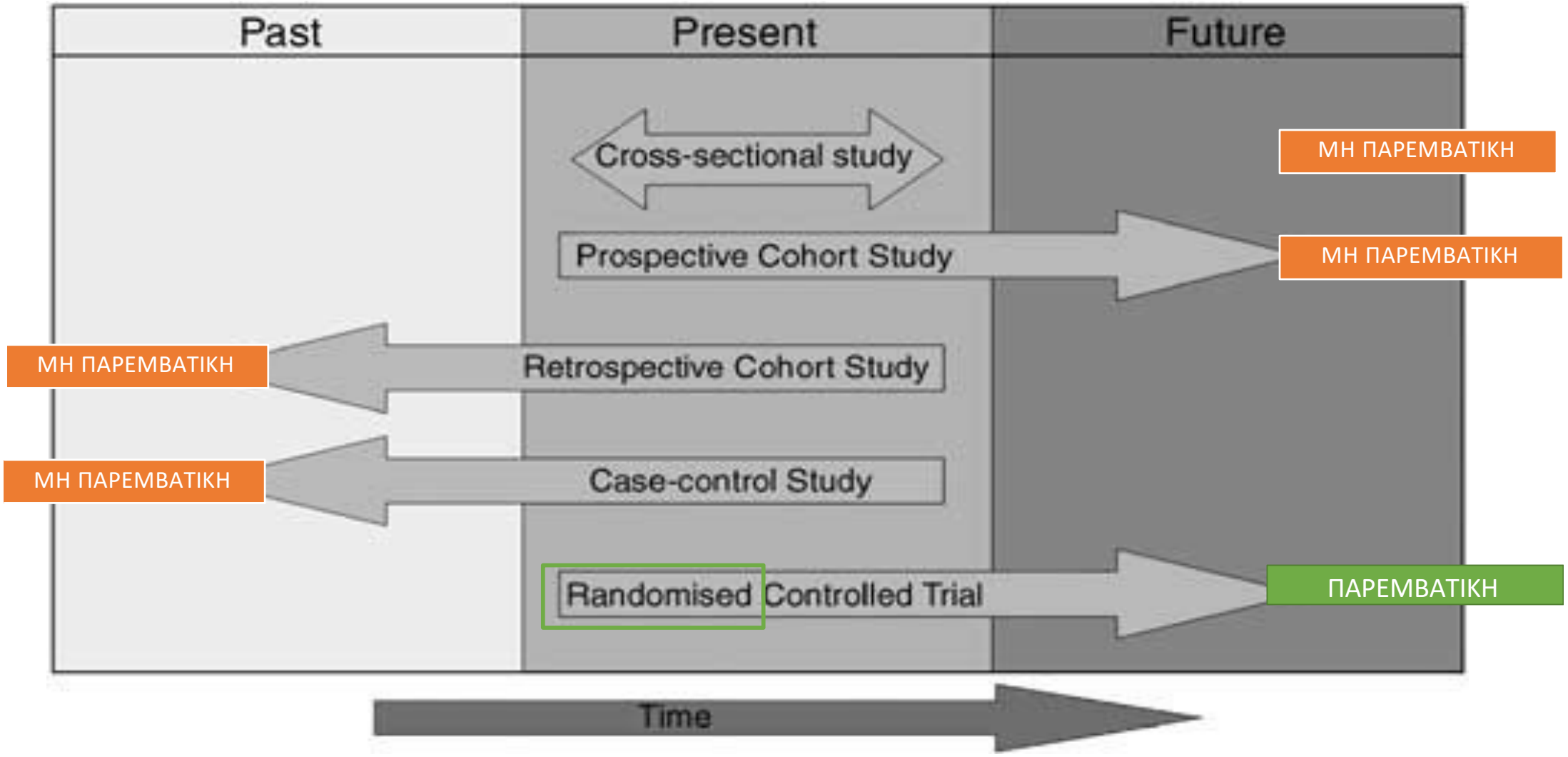
# Μέρος Α’

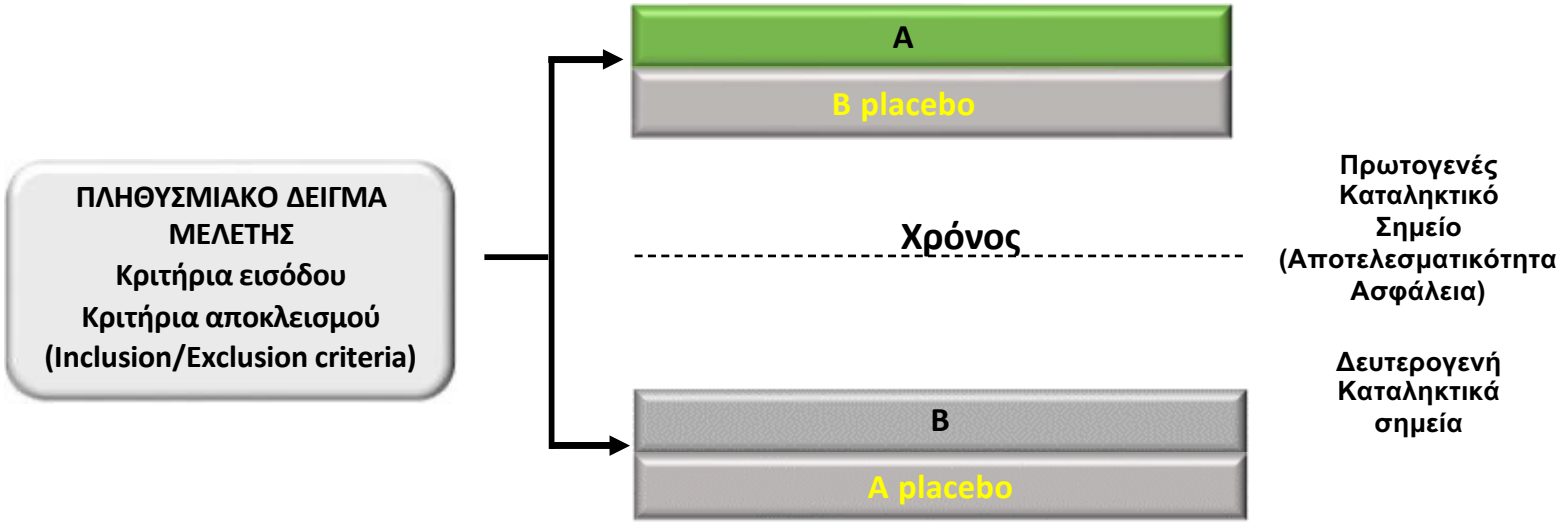
- Βασικές έννοιες και αρχές στην κλινική έρευνα
- Μη παρεμβατικές μελέτες
- Παρεμβατικές μελέτες (Κλινικές δοκιμές)
- Φάσεις κλινικών μελετών


Past
Present
Future
Cross-sectional study
ΜΗ ΠΑΡΕΜΒΑΤΙΚΗ
Prospective Cohort Study
ΜΗ ΠΑΡΕΜΒΑΤΙΚΗ
ΜΗ ΠΑΡΕΜΒΑΤΙΚΗ
Retrospective Cohort Study
ΜΗ ΠΑΡΕΜΒΑΤΙΚΗ
Case-control Study
Randomised Controlled Trial
ΠΑΡΕΜΒΑΤΙΚΗ
Time

## Randomised controlled trials (RCTs) are considered the gold standard to demonstrate efficacy in the context of marketing authorisations and reimbursement decisions on drugs.

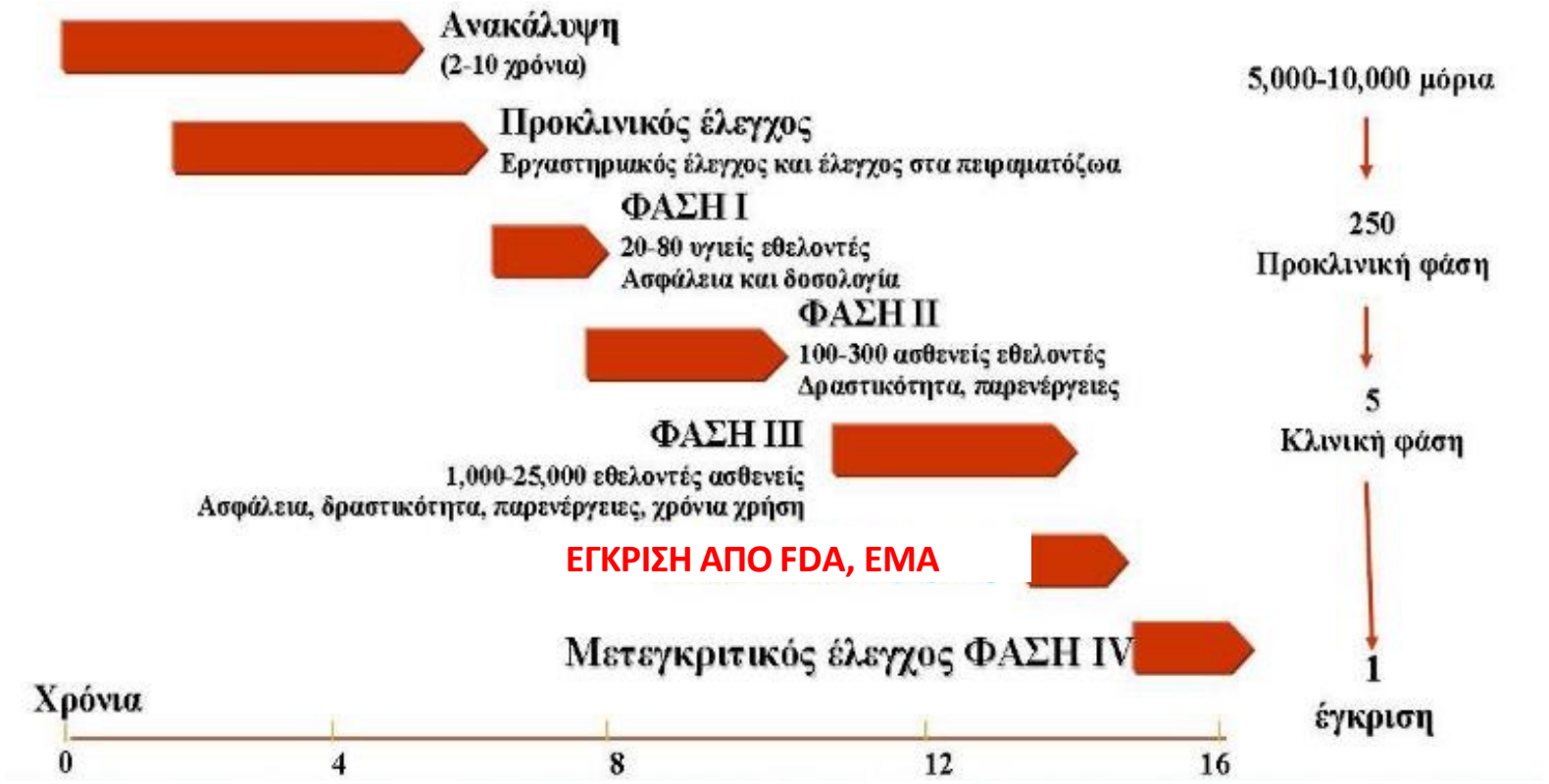
- Ideally, there is the wish to obtain an **unbiased estimate of the effect** of the treatment being investigated compared to placebo or to another active compound.
- The goal of obtaining an unbiased estimate of the size of effect is true in studies in small populations as well as large trials for common diseases.
- In developing any treatment, a comparative randomised trial will usually be preferable but may not always be possible.


# Randomized, double-blind, double-dummy, active-Controlled, multi-centered Trial




RCTs Τυχαιοποιημένη κλινική δοκιμή με ενεργό φάρμακο στην ομάδα ελέγχου

# Η διαδικασία ανάπτυξης ενός νέου φαρμάκου διαρκεί πολλά χρόνια




Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry Profile 2007 (Washington, DC: PhRMA, March 2007)
FDA= Food and Drug Administration, EMA= European Medicines Agency

# RCTs have well known limitations

## Πιθανά μειονεκτήματα των RCTs

1. Είναι τα αποτελέσματα γενικεύσιμα;
   - **Είναι αντιπροσωπευτικό το δείγμα; volunteer effect**
2. Συμμετοχή ασθενών και αναγκαίος αριθμός ασθενών
3. Είναι αποδεκτή η τυχαιοποίηση;Acceptability of Randomization Process
   - **Από τους επαγγελματίες της υγείας;**
   - **Από τους ασθενείς;**
4. Διοικητικές διαδικασίες, γραφειοκρατία, κόστος
5. Hawthorne effect

# There are situations where a RCT may *not* be feasible or ethical

e.g.

- for a new drug with very strong biological rationale in a biomarker-selected population of patients
- for new drug demonstrating an unprecedented objective response rate in a setting of high unmet need with no effective therapies
- for an already approved molecularly targeted agent when being tested in a rare tumour histology expressing the appropriate biomarker
- in orphan diseases and areas of high unmet need, where subjects are scarce, or no effective standard of care is available
  - paediatric clinical studies are often required to fulfil a Paediatric Investigation Plan agreement with Health Authorities, but may present recruitment difficulties, especially when alternative treatments already exist
  - therapeutic areas such as chronic kidney disease, where natural history of the disease and standard treatment options have remained stable for several years with an accumulating body of data from control arms of failed clinical development programmes which could be considered predictive of control responses in future clinical trials.

# Μέρος Β’

- Η «επόμενη ημέρα» των κλινικών μελετών – καινοτόμες προσεγγίσεις στην κλινική έρευνα
- Προσεγγίζοντας την εξατομικευμένη ιατρική μέσω της κλινικής έρευνας

# Conventional fixed trial designs

**No plan for any modifications to major design components (eg, sample size, allocation ratio, and number of interventions) throughout the trial**

- data are accumulated over time, and some clinical trials might take years to complete.
- no learning during the trial from the accumulating trial interim data because the
- interim data are not analyzed throughout the trial
- Investigators usually make assumptions about the population, interventions, outcomes, and other trial parameters on the basis of information that is available at the planning stage and continue these assumptions throughout the trial until the last participant has completed their follow-up.

around 80% of non-COVID-19 trials Stopped/Interrupted,

What about labs, communication, conferences, supply chains, resources, academic grants, researchers?

World Report

# COVID-19 and readjusting clinical trials

The COVID-19 pandemic has disrupted clinical trials worldwide, with long-lasting effects on medical science. Aaron van Dorn reports.

**disruption and fast, effective readjustment to address a new challenge**

www.thelancet.com Vol 396 August 22, 2020

inical Trial Design Draft ☐ Final ✱

efpia
European Federation of Pharmaceutical Industries and Associations


# Innovation in Clinical Trial Design: A review of The Clinical Trial Design Landscape

A white paper by the EFPIA Clinical Trial Design Taskforce

on behalf of the EFPIA Clinical Research Expert Group

**Innovation in Clinical Trial Design: A review of The Clinical Trial Design Landscape (A white paper by the EFPIA Clinical Trial Design Taskforce on behalf of the EFPIA Clinical Research Expert Group)**
https://www.efpia.eu/media/547507/efpia-position-paper-innovation-in-clinical-trial-design-white-paper.pdf (7th March 2020)

# Why use novel and innovative clinical trial designs throughout all phases of drug development?

- Clinical trials form an essential part of a drug development program for a new medicine.
  - burden for patients participating in clinical trials
  - time and number of patients required to complete all the phases of drug development
  - the high risks and costs of failure at each phase
- The aim is to **accelerate** patient access to new medicines and **improve** the efficiency and the success rate of clinical trials.

# Categories of innovative and novel clinical trial designs

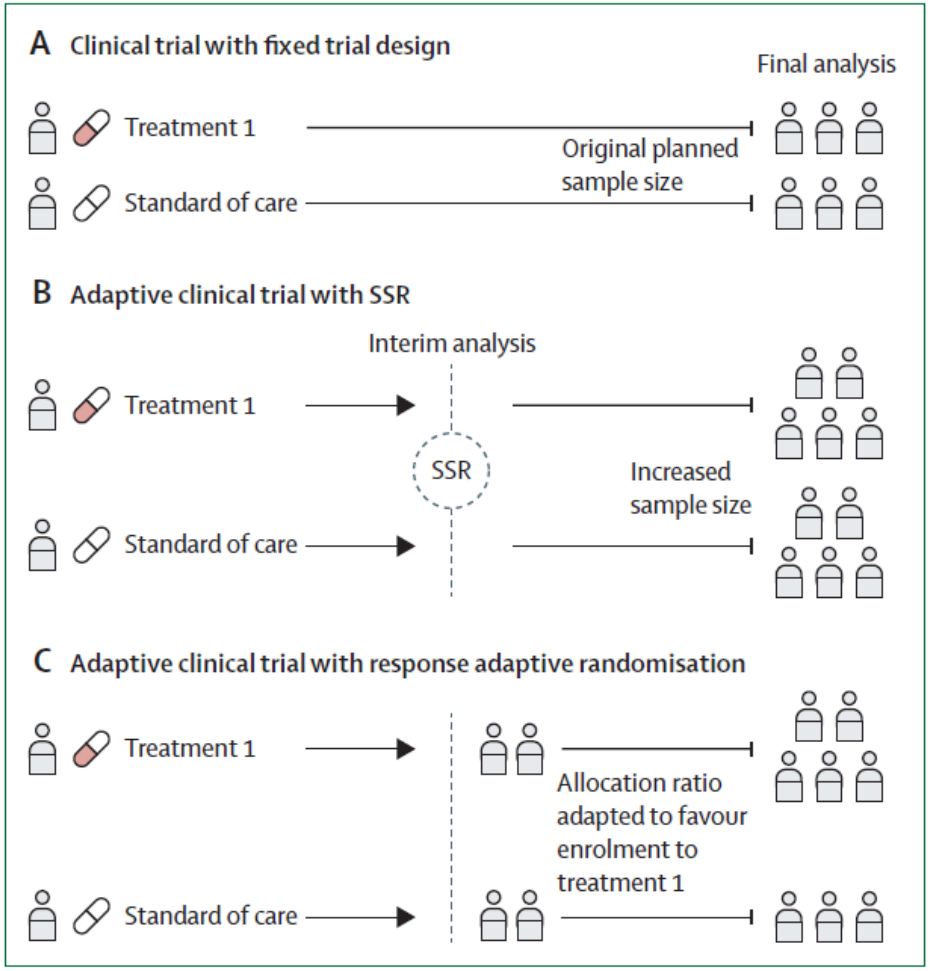
- Enrichment designs
- Adaptive designs
- Master protocols
- Use of historical controls in clinical trials

Data-driven approach

An adaptive trial design, an extension of conventional fixed trial designs, is a type of trial design that allows for prespecified modifications (or adaptations) to the trial design during the trial, including plans for interim evaluations and decision rules

- **Group sequential design** is a type of design that allows for early stopping with stopping rules, usually based on a frequentist statistical metric in test statistics (typically p value boundaries)
  - If the interim data assessment shows crossing of stopping boundaries, then the trial might stop under a group sequential design.
  - With more frequent observations, inflation of type I error rates can occur (multiplicity), especially without statistical adjustments.
- **Sample size reassessment** is another type of adaptive trial design that allows for an increase in sample size based on interim data.
  - Sample size reassessment was developed to mitigate risks for false-negative findings.

**The purpose is to make clinical trials more flexible, efficient and fast.**




SSR=sample size reassessment

# Adaptive designs

These trials can

- Improve how doses are selected in early phase studies
- allow ineffective doses to be dropped in later phase studies
- reduce the time between phases of drug development with seamless designs for example phase 2/3 designs.
- More recently, complex adaptive designs have emerged where the probability of which treatment group to assign the next patient depends on the responses of previous patients enrolled in the trial using adaptive randomisation schemes.

# Types of Adaptation

- Stopping Early for Futility
- Early stopping for efficacy
- Sample Size Re-assessment
- Arm dropping
- Response Adaptive Randomisation (RAR)
- Seamless designs

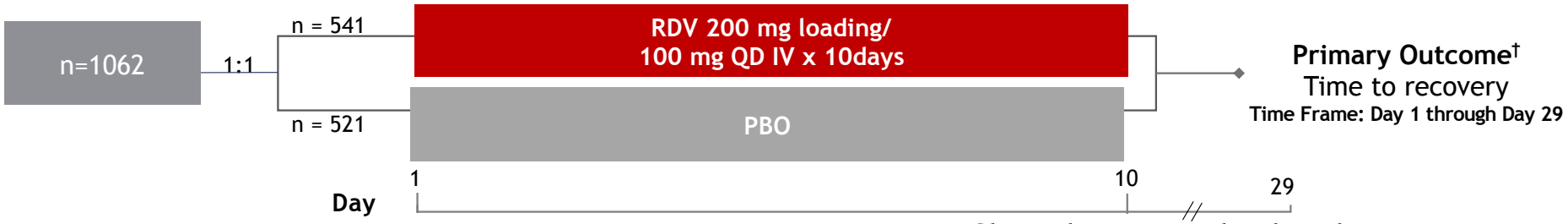
# Developments that are not specific to adaptive designs but are particularly relevant to them

- Clinical Trial Simulation
- Dose Response Modelling
- Bayesian Statistics
- Endpoint adaptation
- Utility Function
- Disease Modelling
- Improved Endpoints

NCT04280705 (NIAID Sponsored Research)

# ACTT-1 Study Design: Adaptive COVID-19 Treatment Trial

## Stage 1 of phase 3 adaptive, randomized, double-blind, PBO-controlled, multicenter global trial[1,2]




### Key Inclusion Criteria

- ≥18 years old hospitalized
- +SARS-CoV-2 by PCR
- Illness* and ≥ 1 of the following
  - Infiltrates by imaging or
  - Clinical assessment** and $SpO_2$ ≤94% on room air or
  - Requiring supplemental $O_2$ or
  - Requiring mechanical ventilation

### Key Exclusion Criteria

- AST or ALT > 5x ULN
- eGFR < 30 ml/min or dialysis
- Pregnancy or breast feeding

### Clinical status ordinal scale

1: Not hospitalized, no limitations of activities
2: Not hospitalized, limitation of activities and/or home oxygen requirements
3: Hospitalized, on room air and no longer requiring ongoing medical care (hospitalization for infection control reasons)
4: Hospitalized, on room air but requiring ongoing medical care
5: Hospitalized, Low flow
6: Hospitalized, on high flow/ Non-invasive ventilation (NIV)
7: Hospitalized, on invasive mechanical ventilation (IMV)/extracorporeal membrane oxygenation (ECMO)
8: Death

ACTT, Adaptive COVID-19 Treatment Trial
* Illness of any duration
** Evidence of rales/crackles on exam
† Primary outcome was changed in response to evolving information, external to the trial, indicating that COVID-19 may have a more protracted course than previously anticipated

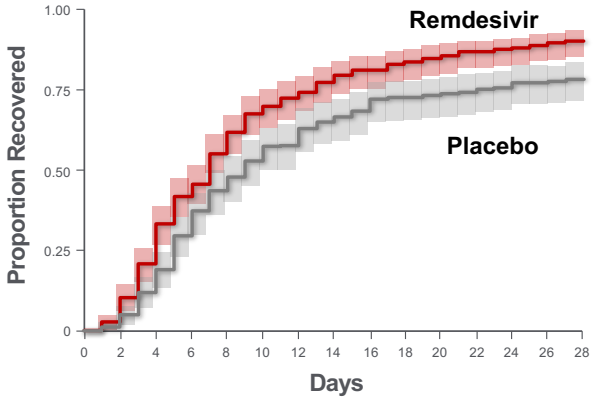

1. Beigel JH, et al. *N Eng J Med*. 2020;383:1813-1826. https://doi.org/10.1056/NEJMoa2007764
2. ClinicalTrials.gov. Identifier: NCT04280705. https://clinicaltrials.gov/ct2/show/NCT04280705

ACTT-1 NCT04280705 (NIAID Sponsored Research)

# ACTT-1: Kaplan-Meier Estimates of Recoveries

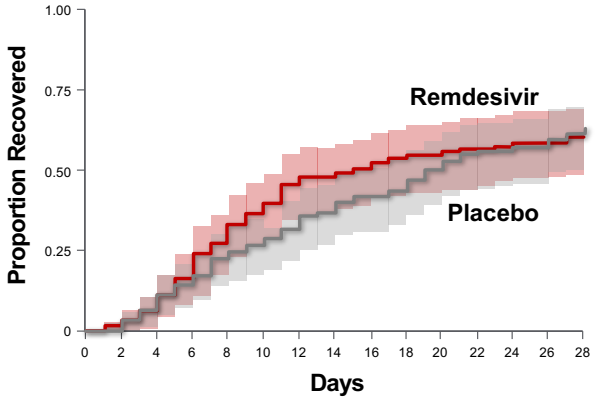
**Less Severe Disease** → **More Severe Disease**

### Patients Receiving Low-flow Oxygen



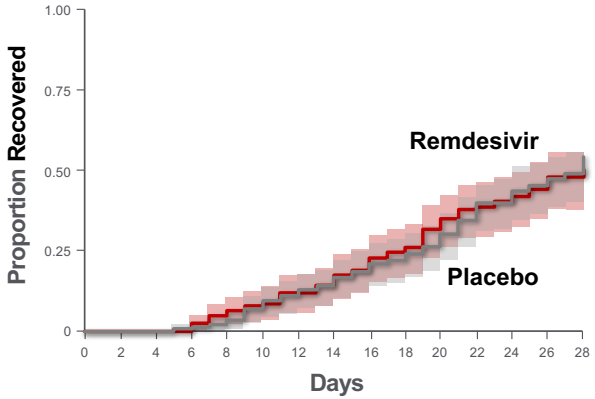

| No. at Risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Remdesivir | 232 | 223 | 181 | 132 | 101 | 73 | 62 | 51 | 42 | 38 | 34 | 29 | 28 | 24 | 13 |
| Placebo | 203 | 199 | 175 | 140 | 111 | 93 | 83 | 69 | 62 | 54 | 53 | 51 | 48 | 44 | 28 |

### Patients Receiving High-flow Oxygen or Noninvasive Mechanical Ventilation




| No. at Risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Remdesivir | 95 | 91 | 86 | 75 | 65 | 57 | 48 | 46 | 44 | 41 | 40 | 38 | 37 | 36 | 27 |
| Placebo | 98 | 98 | 92 | 84 | 76 | 72 | 67 | 62 | 57 | 55 | 49 | 44 | 43 | 41 | 27 |

### Patients Receiving Mechanical Ventilation or ECMO




| No. at Risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Remdesivir | 131 | 131 | 129 | 129 | 122 | 118 | 113 | 110 | 103 | 96 | 87 | 79 | 76 | 69 | 42 |
| Placebo | 154 | 153 | 152 | 151 | 149 | 142 | 136 | 130 | 121 | 116 | 110 | 98 | 89 | 79 | 48 |

**The benefit of remdesivir was most apparent in patients in less severe disease stages.**

ACTT, Adaptive COVID-19 Treatment Trial; ECMO, extracorporeal membrane oxygenation.
Beigel JH, et al. *N Eng J Med*. 2020;383:1813-1826. https://doi.org/10.1056/NEJMoa2007764.

NCT04401579 (NIAID Sponsored Research) NCT04330690

# ACTT-2 Study Design: RDV + Baricitinib (BARI) vs RDV

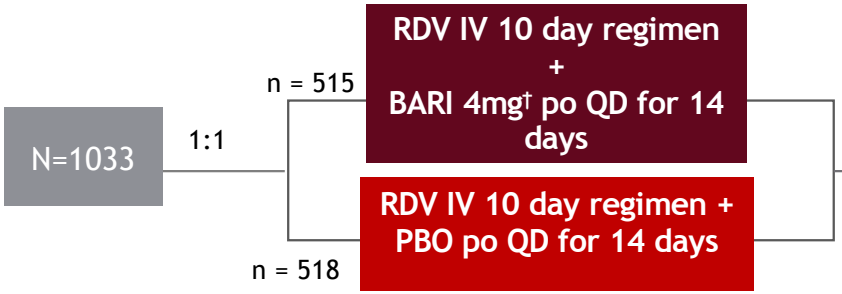
## Adaptive Phase 3 randomized, double-blind, PBO- controlled, multicenter global trial[1, 3]

**Key Inclusion Criteria***

- Hospitalized
- ≥18 years old
- +SARS-CoV-2 by PCR
- Illness and ≥ 1 of the following
  - Infiltrates by imaging or
  - $SpO_2$ ≤94% on room air or
  - Requiring supplemental $O_2$ or
  - Requiring mechanical ventilation or ECMO

**Key Exclusion Criteria***

- AST or ALT > 5x ULN
- eGFR < 30 or renal replacement therapy
- Pregnancy or breast feeding
- History of venous thromboembolism
- Various exclusions related to risks of immune-suppression and use of other immune modulating agents




**Primary Outcome**
Time to recovery‡
[ Time Frame: Day 1 through Day 29 ]

### Clinical status ordinal scale

1: Not hospitalized, no limitations of activities
2: Not hospitalized, limitation of activities and/or home oxygen requirements
3: Hospitalized, room air and no longer requiring ongoing medical care (hospitalization for infection control reasons)
4: Hospitalized, room air but requiring ongoing medical care
5: Hospitalized, Low flow
6: Hospitalized, high flow/ Non-invasive ventilation (NIV)
7: Hospitalized, invasive mechanical ventilation (IMV)/extracorporeal membrane oxygenation (ECMO)
8: Death

**Update: November 19, 2020[4]**

- BARI has been authorized by FDA for emergency use (EUA) to be used in combination with RDV to treat COVID-19 in hospitalized adults and pediatric patients ≥2 years of age requiring supplemental oxygen, invasive mechanical ventilation, or ECMO

ACTT, Adaptive COVID-19 Treatment trial
*List does not reflect full Inclusion/Exclusion criteria from protocol. For more details of the trial, please go to clinicaltrials.gov
† For those with eGFR <60ml/min, BARI 2mg PO QD was administered
‡ Recovery Defined as first day, during the 28 days after enrollment on which patient is categorized 1, 2, or 3 of the ordinal scale

1. NIAID protocol 20-0006.
2. ClinicalTrials.gov.
Identifier: NCT04401579. https://clinicaltrials.gov/ct2/show/NCT04401579
3. Kalil et al. N Eng J Med. 2020; DOI: 10.1056/NEJMoa2031994
4. Baricitinib. US EUA Factsheet. Eli Lily and Company; 2020

NCT04492475 (NIAID Sponsored Research)

# ACTT-3 Study Design: RDV + Interferon β-1a vs RDV

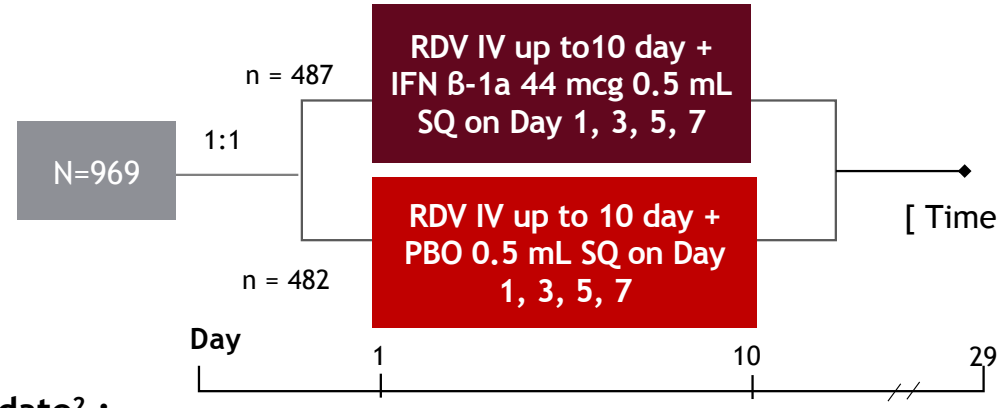
## Adaptive Phase 3 randomized, double-blind, PBO-controlled, multicenter global trial[1]

**Key Inclusion Criteria***

- Hospitalized
- ≥18 years old
- +SARS-CoV-2 by PCR
- Illness and ≥ 1 of the following
  - Infiltrates by imaging or
  - $SpO_2$ ≤94% on room air or
  - Requiring supplemental $O_2$

**Key Exclusion Criteria***

- AST or ALT > 5x ULN
- eGFR < 30 mL/min
- Pregnancy or breast feeding
- WBC <1500 cells/mcL
- PLT <50,000 mcL
- History of chronic liver disease




**Primary Outcome**
Time to recovery
[ Time Frame: Day 1 through Day 29 ]

### Study Update[2] :

- Time to recovery was 5 days in both groups (RR: 0.99 [95% CI 0.87-1.13]; p=0.88)
- Mortality at day 28 was 5% (95% CI 3-7%) in the RDV + Interferon β-1a group vs 3% (95% CI 2-6) in the RDV + PBO group (HR: 1.33 [95% CI 0.69- 2.55]; p=0.39)
- Patients on RDV + Interferon β-1a were likely to have more adverse events compared to those on RDV + PBO
  - Not on High flow $O_2$ at baseline with at least 1 AEs: 7 % (33/442) vs 3% (15/435)
  - On High flow $O_2$ at baseline with AEs: 69% (24/35) vs 60% (21/35) and SAEs: 39% (13/33) vs 24% (8/33)

**RDV + Interferon β-1a was not superior to RDV alone among hospitalized patients with COVID-19**

*List does not reflect full Inclusion/Exclusion criteria from protocol. For more details of the trial, please go to clinicaltrials.gov
RR= rate ratio; HR= Hazard ratio; AEs= Adverse events; SAEs= Serious adverse events


1. ClinicalTrials.gov. Identifier: NCT04492475. https://clinicaltrials.gov/ct2/show/NCT04492475
2. Kalil, et al. Lancets Respir Med. 2021 Dec 2021 Dec;9(12):1365-1376. doi: 10.1016/S2213-2600(21)00384-2

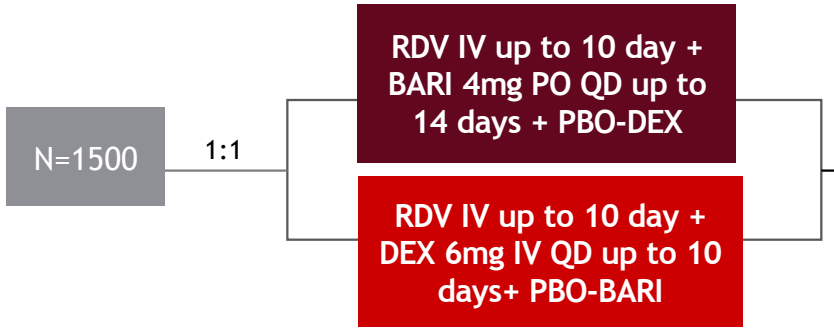
NCT04640168 (NIAID Sponsored Research)

# ACTT-4 Study Design:
## RDV+ Baricitinib (BARI) vs RDV + Dexamethasone (DEX)

**Adaptive Phase 3 randomized, double-blind, PBO-controlled, multicenter global trial[1,2]**

**Key Inclusion Criteria***
- Hospitalized with symptoms suggestive of COVID-19
- ≥18 years old
- +SARS-CoV-2 by PCR
- Illness of any duration
- Within 7 days prior to randomization requiring new use of supplemental $O_2$, low or high flow O2 or non-invasive Mechanical ventilation

**Key Exclusion Criteria***
- Enrollment in ACTT-3 or ACTT-4
- Invasive mechanical ventilation at randomization
- ANC <1000 cells/μL
- Absolute lymphocyte count <200 cells/μL
- Pregnancy or breast feeding




**Primary Outcome**
The proportion of subjects not meeting criteria for one of the following two ordinal scale categories at any time: 8) Death; 7) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
[ Time Frame: Day 1 through Day 29 ]

- **Primary Objective:** To evaluate the clinical efficacy of BARI + RDV vs DEX + RDV as assessed by the mechanical ventilation free survival by Day 29
- **Study Update April 15, 2021[2]:**
  - NIAID closes enrollment at N >1000 because the study met pre-defined futility criteria suggesting that neither treatments were likely significantly better than the other
  - There were no safety issues with either treatment

ACTT, Adaptive COVID-19 Treatment Trial; RECOVERY, Randomized Evaluation of COVID-19 Therapy; SoC, Standard of Care

*List does not reflect full Inclusion/Exclusion criteria from protocol. For more details of the trial, please go to clinicaltrials.gov

1. ClinicalTrials.gov. Identifier: NCT04640168. https://clinicaltrials.gov/ct2/show/NCT04640168
2. NIAID, April 2021.NIH Closes Enrollment in Trial Comparing COVID-19 Treatment Regimens [online] Available at: < https://www.nih.gov/news-events/news-releases/nih-closes-enrollment-trial-comparing-covid-19-treatment-regimens >

- Traditional approach = relatively broad patient population e.g. patients with mild/moderate/severe disease/condition X/Y/Z etc.
  - What if there is an unsuccessful outcome?
  - Or if the treatment difference is much smaller than anticipated?
  - Interrogation of the data may reveal some patients responded to study drug and others did not

- Are those responders different in some way
- Can they be prospectively identified (e.g. with a specific phenotype or biomarker etc.)
- If a trial was restricted only to that specific subpopulation, would the probability of a successful outcome be increased?

## *Enrichment*

Strategy implemented after an unsuccessful trial or preferably it is done based upon a thorough understanding of the disease state and the pharmacology of a drug to drive successful outcomes from initial studies in man through to approval.

# *enrichment design*

The prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one in fact is present) is more likely than it would be in an unselected population

↓ heterogeneity

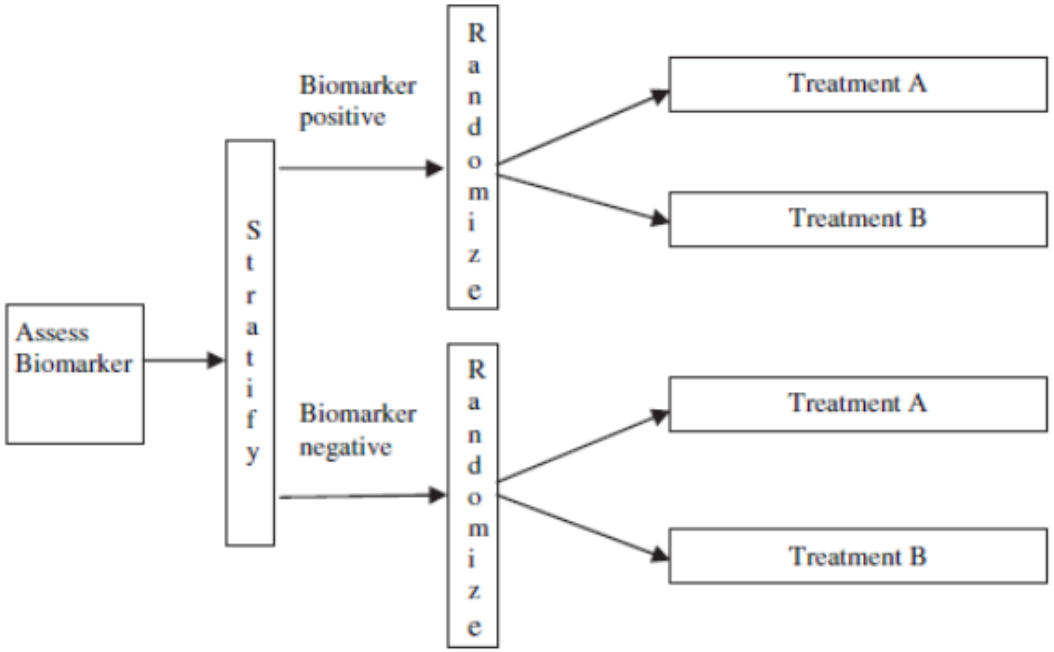
↑ prognostic capacity — patients most likely to relapse or to have specific events of interest

↑ predictive capacity — recruit only those patients most likely to respond to a drug

**Enrichment designs are intended to increase the efficiency of drug development and support precision medicine by tailoring treatments to those patients who will benefit based on clinical, laboratory, genomic, and proteomic factors.**

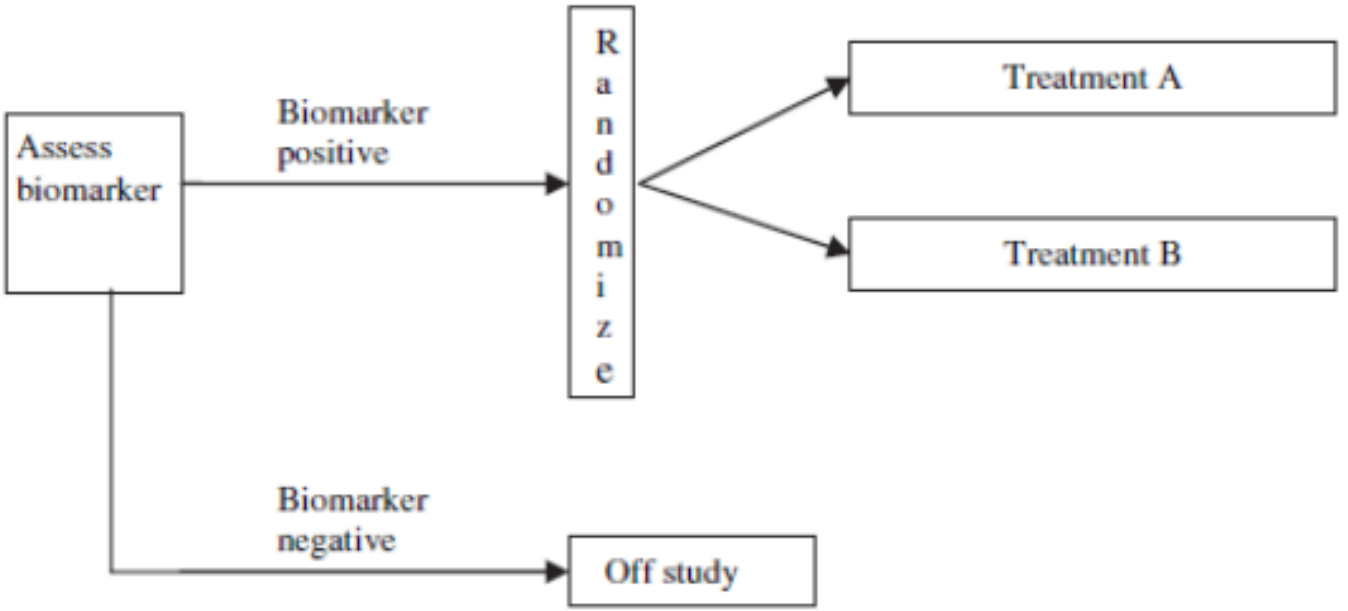
All patients are randomly assigned regardless of biomarker status with the random assignment and analysis plan stratified by the biomarker status.

- Biomarker-stratified design



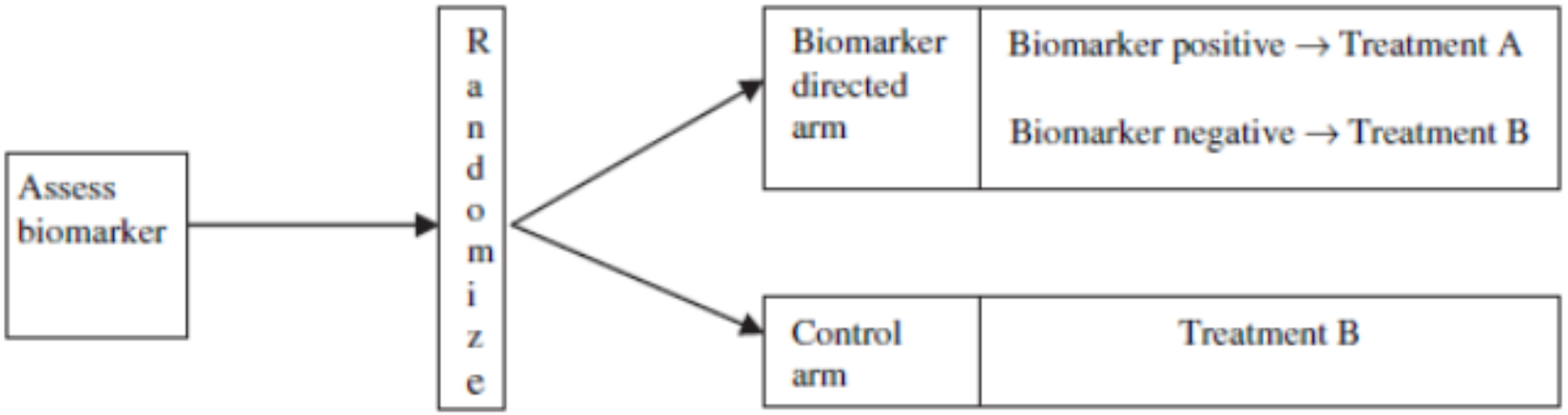
The biomarker is evaluated on all patients, but random assignment is restricted to patients with specific biomarker values

- Enrichment design



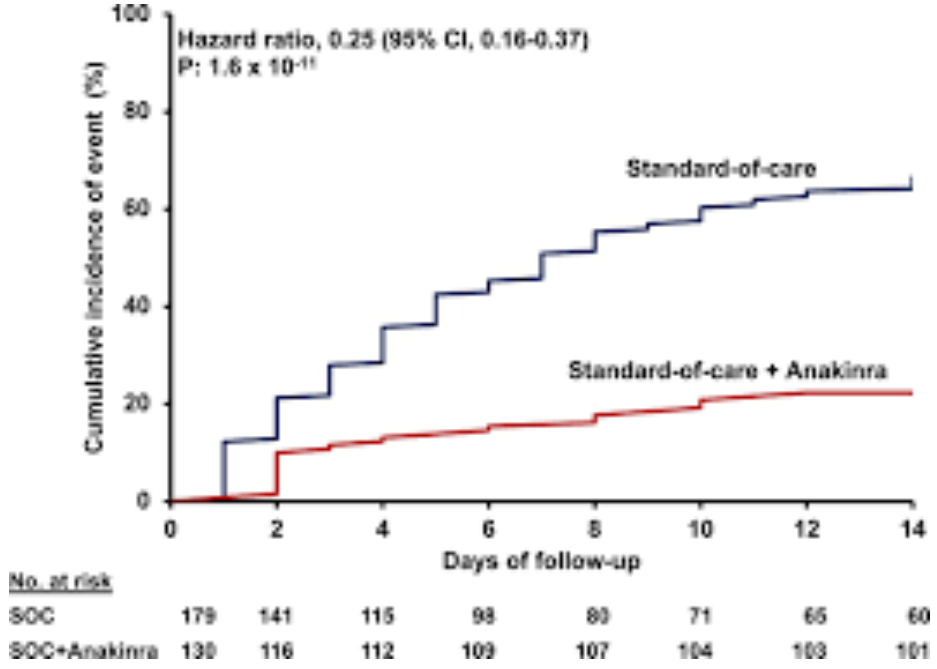
Patients are randomly assigned to an experimental treatment arm that uses the biomarker to direct therapy or to a control arm that does not.

- Biomarker-strategy design



# suPAR as a biomarker

Σε ασθενείς με πνευμονία που λαμβάνουν συμπληρωματικό οξυγόνο υψηλής παροχής και σοβαρό κίνδυνο για αναπνευστική ανεπάρκεια, όπως καθορίζεται από τα επίπεδα ορού της πρωτεΐνης soluble urokinase plasminogen activator receptor (suPAR) ≥ 6 ng/ml μπορεί να χρησιμοποιηθεί anakinra (EODY 2022)




ARTICLES
https://doi.org/10.1038/s41591-021-01499-z
nature medicine
Check for updates

OPEN

## Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial

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# Master protocols

- Umbrella trial → new treatments in the same diseases
- Basket trial → new treatment in a number of related diseases
- Platform trial → multiple therapies in a single disease in a perpetual and open-ended manner

**Complex in terms of their design, how trials are operationalised and how trials are analysed**:

- the set of treatments to be studied in a trial can change during the trial
- the patient populations to be included in a trial can change over time, and
- the data to be collected could evolve after a trial has started.

In a traditional clinical trial design these aspects are fixed at the start of a trial, platform trials are complex.

- Master protocols refer to a single overarching protocol that has been developed to evaluate multiple hypotheses, with the general goal of improving efficiency and establishing uniformity through standardization of procedures in the development and evaluation of interventions.

# Master Protocols

- The use of biomarkers to identify small genetic sub-populations within a disease has resulted in increasing limited numbers of patients being eligible for a specific treatment regimen.
- This has led to the need for trial designs which encompass several treatment options depending on the genetic subtype of patient entering the trial.
- Such master protocols are particularly useful in the field of oncology, where using biomarkers to identify those patients likely to respond to a therapy is now standard practice.
- Master protocols can also be useful in other therapeutic areas where there are several treatment options to be tested or where a given disease can be differentiated in multiple sub-categories.
  - Recent examples of the uptake of these designs outside oncology include clinical trials for Alzheimer's Disease and infective diseases

# Master protocols = overarching protocols designed to answer multiple questions

Multiple benefits:

- Allow to **quickly** test hypotheses and answer scientific questions
- Evaluate and compare treatments and combinations thereof, **maximizing trial opportunities** for patients
- Access to **complex disease areas and/or rare indications** (small populations)
- **Collaborative** set-up, allows for better **efficiency**
- **Faster time to activation** of additional study arms to investigate new sub-populations or study drugs
- **Faster clinical development** and **patient access** to transformative drugs

NCT04593940 (NIAID Sponsored Research)

# ACTIV-1 IM Master Protocol

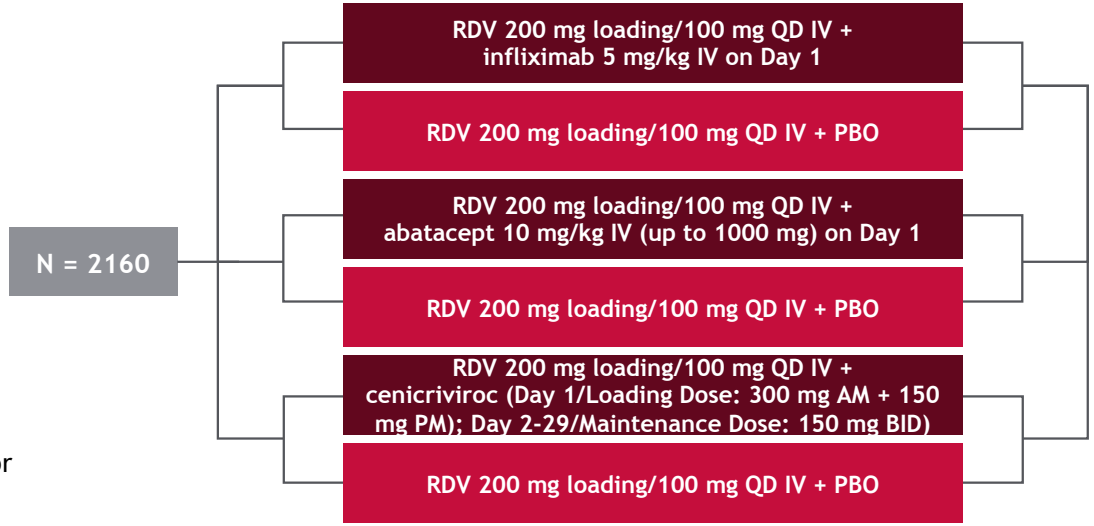
## Adaptive Phase 3, randomized, triple-blind, PBO-controlled trial to evaluate efficacy and safety of immune modulators in hospitalized adults with moderate to severe COVID-19[1,2]

**Key Inclusion Criteria[1]***

- Hospitalized
- + COVID-19 test within 14 days prior to enrollment
- Ongoing illness of any duration, and ≥1 of the following:
  - Radiographic infiltrates (CXR, CT scan, etc.)
  - $SpO_2$ ≤94% on room air
  - Requiring supplemental oxygen
  - Requiring mechanical ventilation or ECMO

**Key Exclusion Criteria[1]***

- ALT or AST >5x ULN
- eGFR <30 mL/min (including hemodialysis or hemofiltration)
- ANC <1000 cells/μL
- Absolute lymphocyte count <200 cells/μL
- Pregnancy or breastfeeding
- Anticipated discharge or transfer to another hospital within 72 hours
- Received cytotoxic or biologic treatments
- Suspected or active TB, bacterial, fungal, or viral infection
- Severe hepatic impairment or heart failure




**Primary Endpoint[2]**
Time to recovery by Day 29

**Objective[1]:**

- Evaluate each agent with respect to speed of recovery, mortality, illness severity, and hospital resource utilization. Comparisons of the agents among themselves is not a research objective

ACTIV, Accelerating COVID-19 Therapeutics Interventions and Vaccines
*List does not reflect full Inclusion/Exclusion criteria from protocol. For more details of the trial, please refer to the protocol
1. ClinicalTrials.gov. Identifier NCT04593940. https://clinicaltrials.gov/ct2/show/NCT04593940
2. ACTIV-1 IM protocol.

NCT04315948

# WHO-INSERM* DisCoVeRy Study

## An EU Sub-study for WHO SOLIDARITY

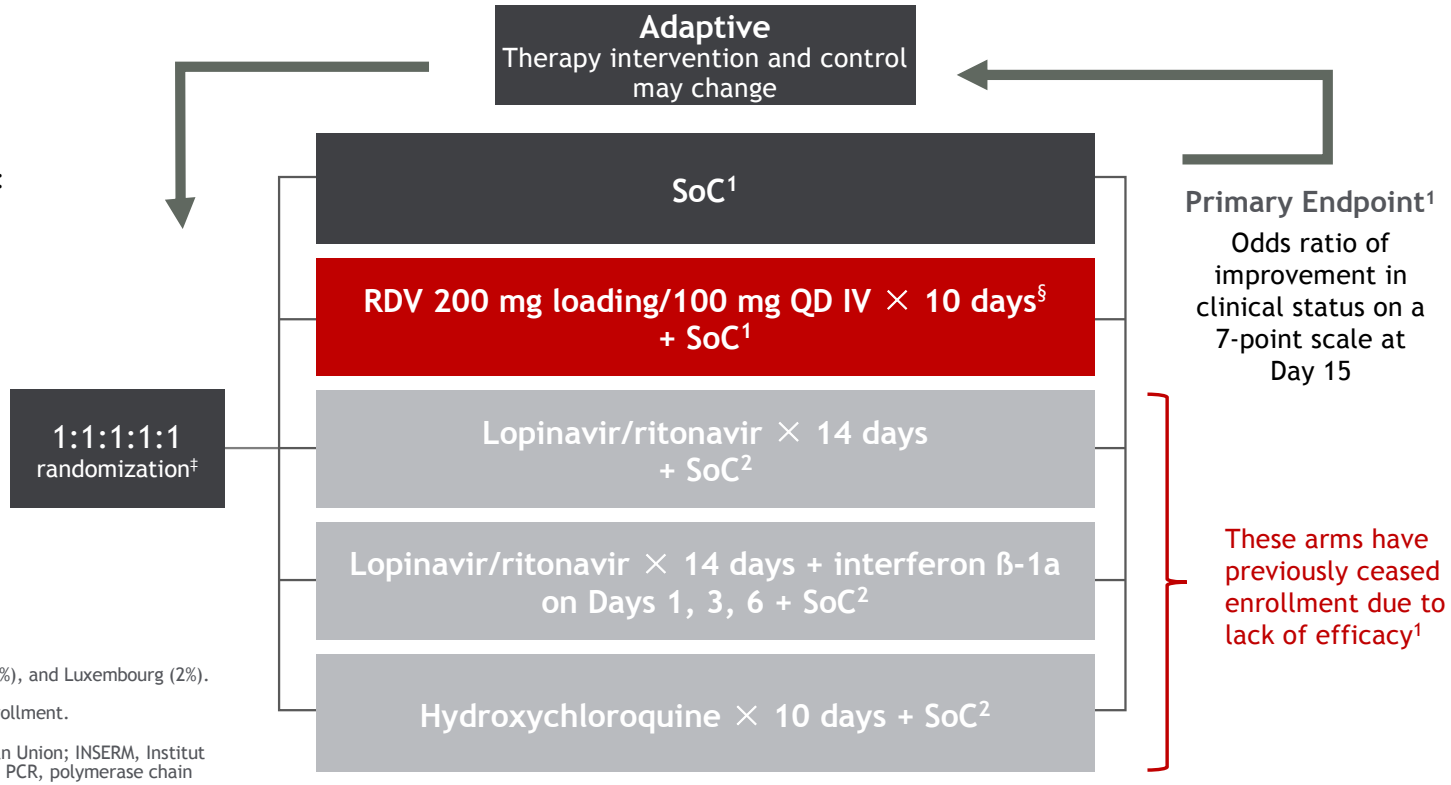
### Phase 3, open-label, multi-center, adaptive, randomized study of the safety and efficacy of treatments of COVID-19 in hospitalized patients[1]

**Key Inclusion Criteria[1]**

- ≥18 years old hospitalized
- +SARS-CoV-2 by PCR <9 days prior to randomization
- Illness of any duration and ≥1 of the following:
  - Clinical assessment† and $SpO_2$ ≤94% on room air, OR
  - Requiring supplemental $O_2$ and/or mechanical ventilation

**Key Exclusion Criteria[1]**

- AST or ALT level >5 × ULN
- Stage 4 CKD or dialysis
- Pregnancy or breast feeding
- Use of any experimental treatment for COVID-19 in the past 29 days



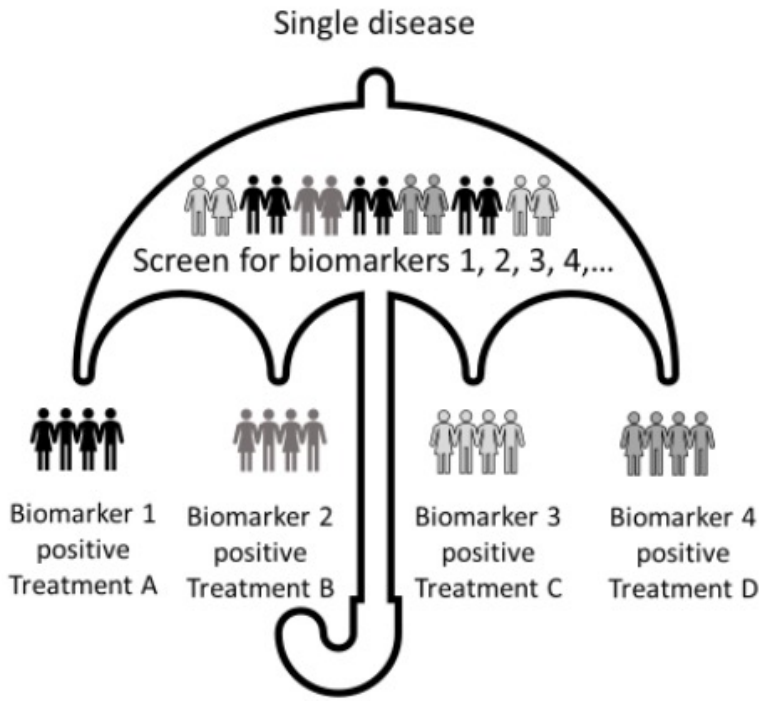

* Participating countries: France (84%), Belgium (6%), Portugal (4%), Austria (4%), and Luxembourg (2%).
†Evidence of rales/crackles on exam.
‡Randomization was stratified by European region and severity of illness at enrollment.
§Or continued until discharge (after at least 5 days).
CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; EU, European Union; INSERM, Institut National de la Santé Et de la Recherche Médicale; IV, intravenous; $O_2$, oxygen; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; $SpO_2$, oxygen saturation; SoC, standard of care; ULN, upper limit of normal; WHO, World Health Organization.


1. Ader F, et al. Lancet ID. 2022 Feb;22(2):209-221
2. Ader F, et al. *BMJ Open*. 2020;10(9):e041437. https://doi.org/10.1136/bmjopen-2020-041437.

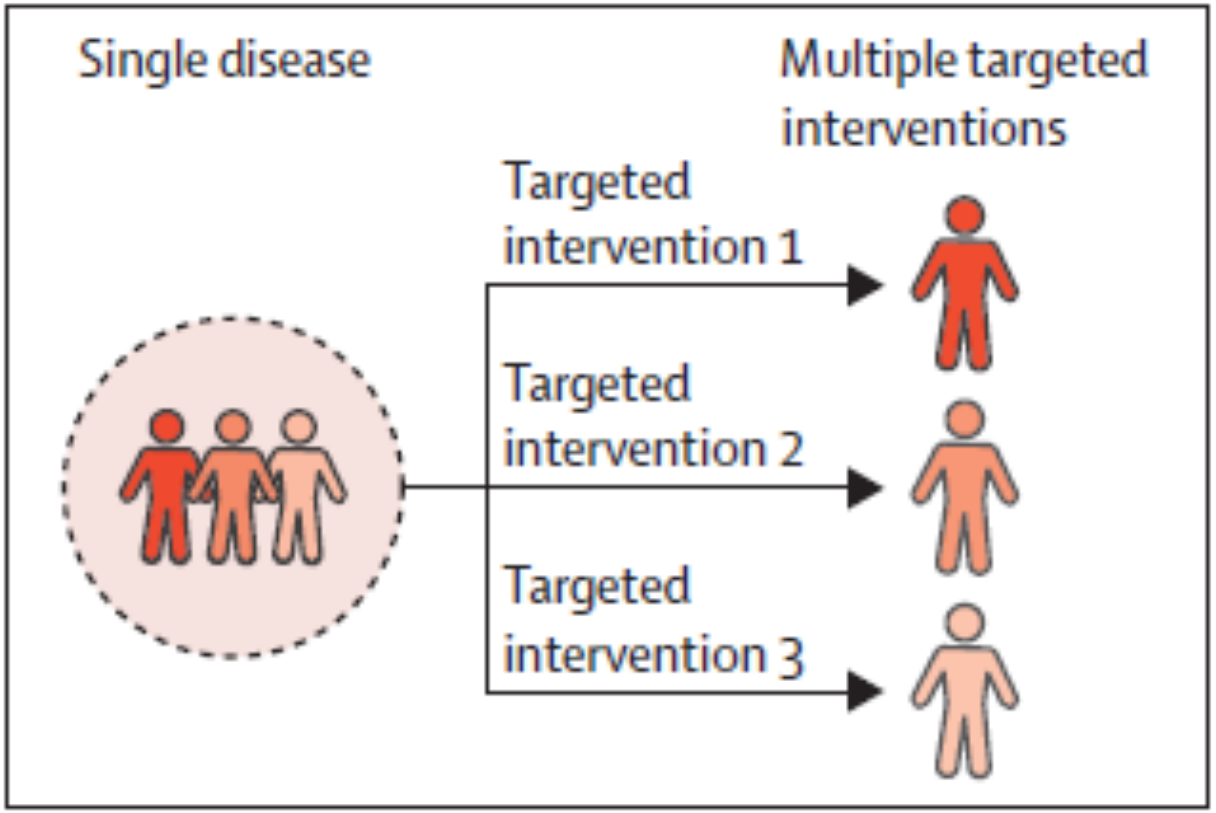
**Platform, basket, and umbrella trials are often organised and planned with a modular protocol structure, with the master protocol containing all generic elements of the trial and intervention appendices that are specific to each active intervention.**

- With the use of a modular format, adding a new intervention or discontinuing a current intervention can become more operationally seamless because the main study master protocol does not need to be updated every time a new intervention is added or discontinued in platform trials.
- In basket and umbrella trials, common screening mechanisms with standardized laboratory procedures are used in different institutions and across different geographical settings under one single master protocol. This standardization in operating procedures can help to provide harmonization of clinical trial research efforts across different geographical settings in the global health field.

# Umbrella Trials

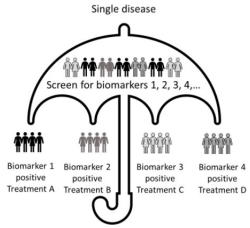


# Umbrella trial



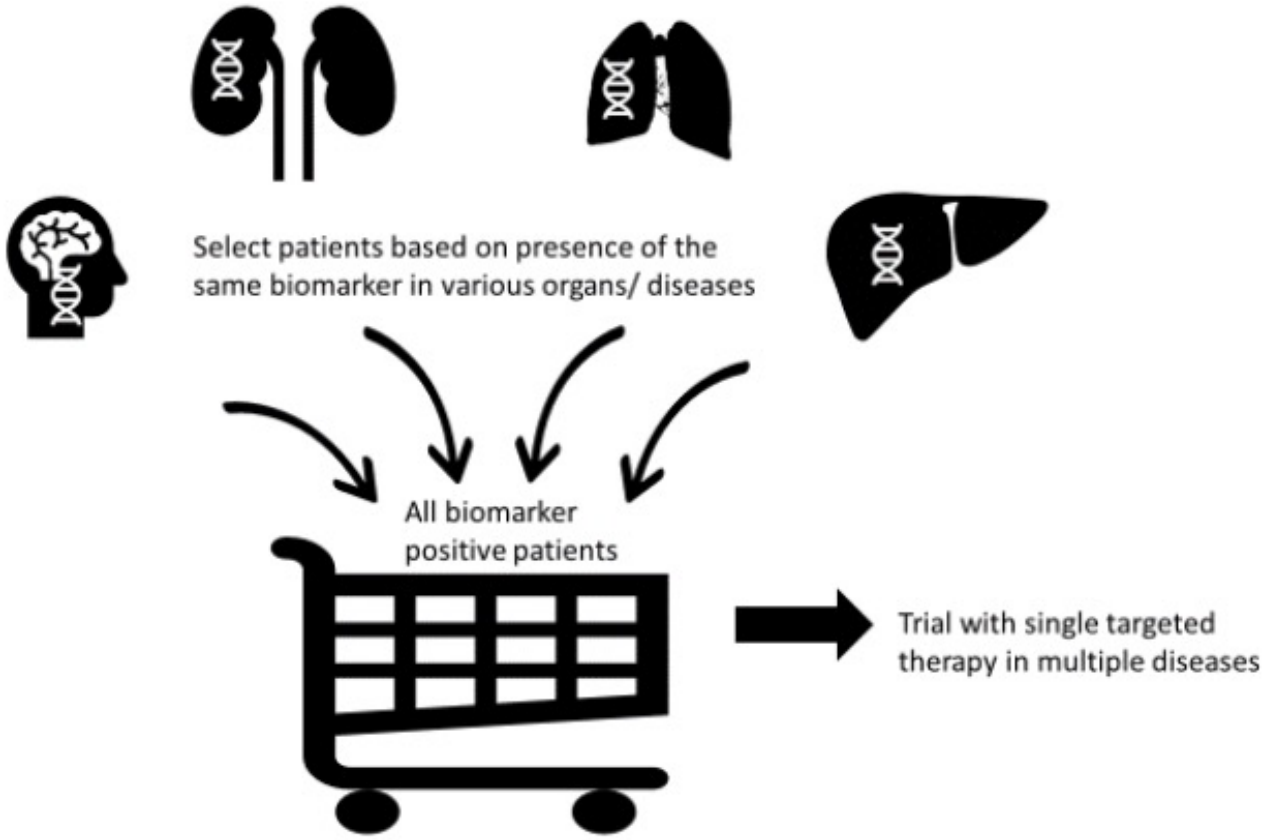

multiple therapies for a single disease that is stratified into different groups on the basis of molecular alterations or other risk factors.

# Umbrella Trials

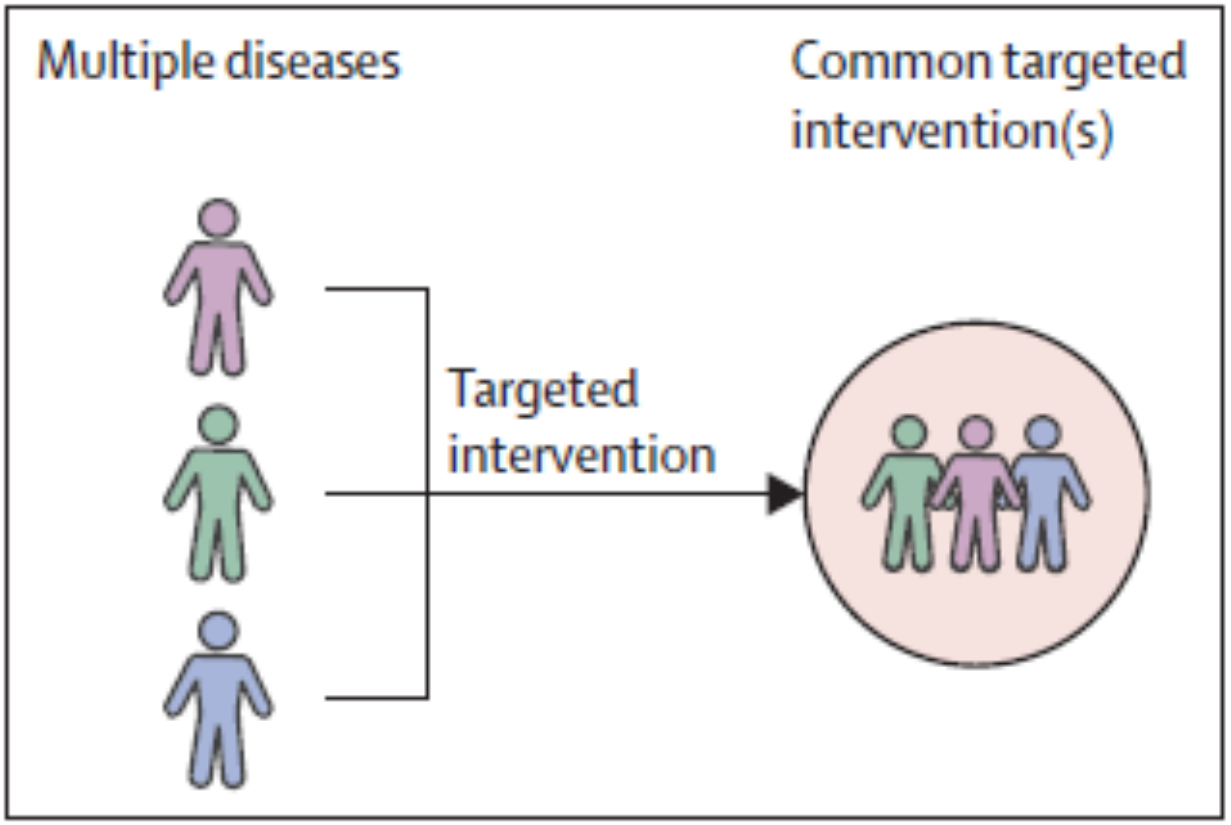



| BENEFITS | LIMITATIONS |
|---|---|
| • A single control arm can be used with a standard comparator treatment for the disease being investigated<br>• Clustering different biomarkers under a single trial will help to reduce the screen failure rate, avoid multiple screening of patients, and increase the likelihood of a patient being eligible to participate in a study<br>• Enables a direct comparison of several treatment options for a disease<br>• Due to the multi-pronged approach, umbrella trials can accelerate the speed of development, save costs and support rapid approval of new drugs (however, regulatory acceptance varies in the different regions).<br>• Operational efficiencies due to familiar trial procedures for the different arms. | • There are statistical challenges for introducing new treatment arms after a study has started regarding potential introduction of bias compared to treatments and control in place at the start of the trial<br>• Treatment assignment/stratification is often based on molecular biomarkers so centralized screening tests are required for multiple biomarkers, as locally performed genotyping can lead to less reproducible results<br>• Each new diagnostic biomarker needs to be validated and will be subject to a regulatory approval pathway<br>• Standard of care for a disease may change during the course of lengthy trials as new treatments become available, potentially requiring changes to the control arm treatment, which could have implications for statistical inferences (see also section on use of historical controls and changes in standard of care) |

# Basket Trials

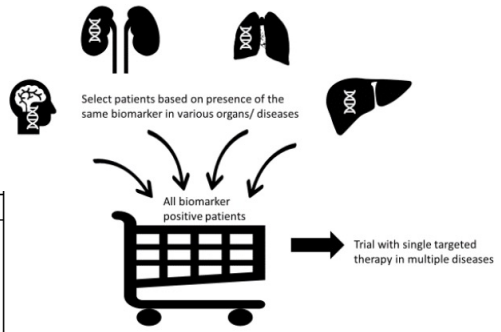


# Basket trial




a targeted therapy is evaluated for multiple diseases that share common molecular alterations or other risk factors.

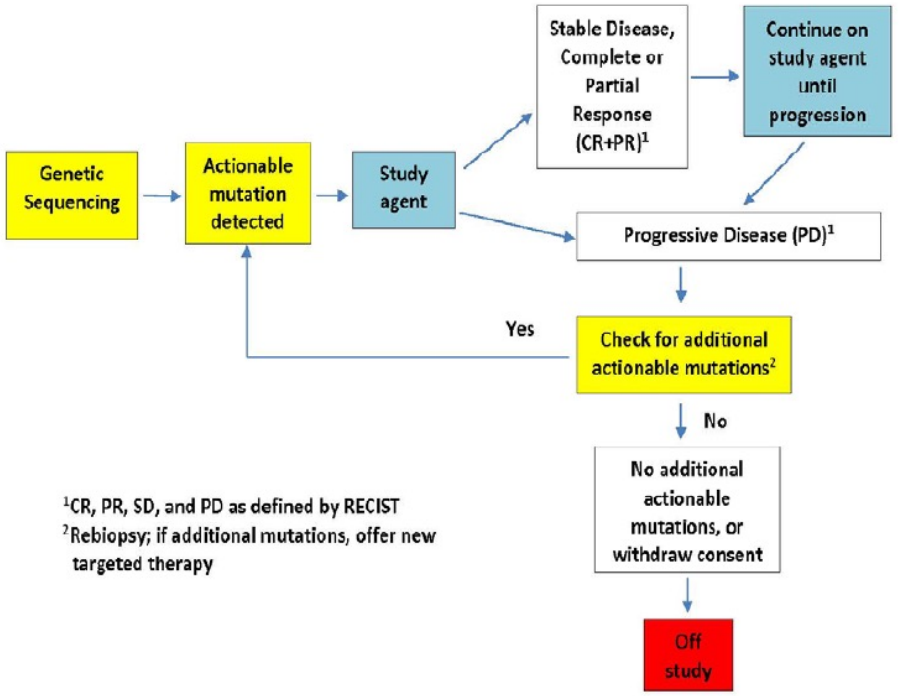
# Basket Trials




| BENEFITS | LIMITATIONS |
|---|---|
| • Quick identification of several possible therapeutic indications<br>• Quick termination possible for those arms where patients are showing low responses<br>• Possible to investigate several rare diseases where patients' numbers are limited and collect more safety data than with individual trials<br>• Exposure in multiple contexts can provide additional understanding of mechanism of sensitivity and resistance of target<br>• Each trial requires the development / approval of only a single biomarker assay and this can often be tested locally at the sites<br>• These trials can reach statistical power with fewer subjects in less time. If the treatment has already been approved for one disease, this design can rapidly verify if efficacy converts to other indications.<br>• Use of basket designs in areas where certain phenotypes are found across disease populations (e.g. patients with different types of pain) can increase the probability of technical success for a drug with a specific mechanism of action.<br>• Basket trials take less time than performing individual trials per indication, which can accelerate the speed of development, save costs and support rapid approval of new therapies. | • Dose and/ or safety of the drug may be different in the various indications<br>• Potential issue of heterogeneity being introduced by the basket design<br>• Challenges from a technical perspective in using the same trial endpoints across different diseases sharing the same biomarker.<br>• Different types of standard of care and comparator treatments may be established for the various diseases, requiring multiple control arms to assess benefit of therapy<br>• Some arms within a basket trial may have small sample sizes and be difficult to evaluate. High treatment efficacy is a prerequisite to correctly determine the trial arms which should be continued or discontinued and avoid a selection bias based on chance findings in a few patients<br>• Many patients must be tested to find the few who fit the disease profile targeted by the treatment. It is frustrating for patients who agree to be screened when they are told they are not eligible to be treated because their disease profile does not match the drug target.<br>• Complexity of basket trials can lead to very lengthy protocols (> 500 pages) which present problems for ECs and investigators<br>• Basket trials require several individual patient information leaflets and different informed consent forms for the various indications<br>• Suitable principle investigators and facilities are required at each trial site to cover each of the indications in a basket trial, which is often difficult to realize |

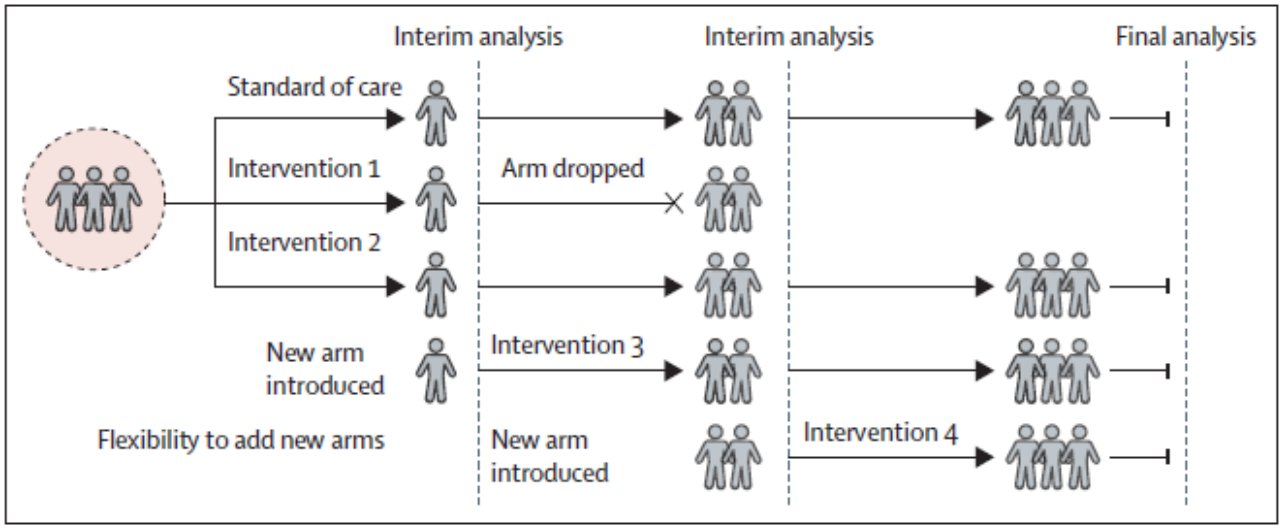
# Platform trials

A major concern of Health Authorities and Ethics Committees with platform trials is that, in theory, additional arms to explore new treatment options can be added indefinitely and potentially result in “never-ending” trials. So, it is important that in the master protocol and any sub-protocols the end of the clinical trial is defined, including how it will comply with legal obligations on reporting and trial transparency.




* RECIST = response evaluation criteria in solid tumors.

# Platform trial




flexibility of dropping ineffective interventions and adding new interventions during the trial, while evaluating several interventions against a common control.

RECOVERY

RESPIRATORY SUPPORT

**INCLUSION CRITERIA**

✓Adults ≥ 18 years

✓2. Hospital inpatient with suspected or proven COVID-19

✓$FiO_2$ ≥0.4 **and** $SpO_2$ ≤94%

✓Plan for escalation to intubation if needed

**EXCLUSION CRITERIA**

X Planned intubation and mechanical ventilation imminent within 1 hour

X Known or clinically apparent pregnancy

X Any absolute contraindication to CPAP or HFNO

X Decision not to intubate due to ceiling of treatment or withdrawal of TREATMENT anticipated

X Equipment for both CPAP and HFNO not available

**If you have any questions:**

**Ask:** Your local Principal Investigator
**Visit:** www.warwick.ac.uk/recovery-rs
**Email:** RECOVERY-RS@warwick.ac.uk
**If urgent call:** *<Insert trial Tel Number>*

WARWICK

NIHR | National Institute for Health Research


RECOVERY

Randomised Evaluation of COVID-19 Therapy

# HAVE YOU BEEN ADMITTED TO HOSPITAL WITH SUSPECTED OR CONFIRMED COVID-19?

## Are you interested in research?

We still have so much to learn about effective treatments for COVID-19.

Oxford University is running the **RECOVERY** Trial which will enable reliable assessment of the effects of multiple different treatments on major outcomes among people with suspected or confirmed COVID-19.

Some of the treatments will be drugs used for other conditions, other new drugs may become available during the trial.

All patients participating in the trial will receive usual standard of care.

## We need your help

If you are interested in joining the **RECOVERY** Trial, please ask your medical team for information about the trial.

UNIVERSITY OF OXFORD

RECOVERY Poster

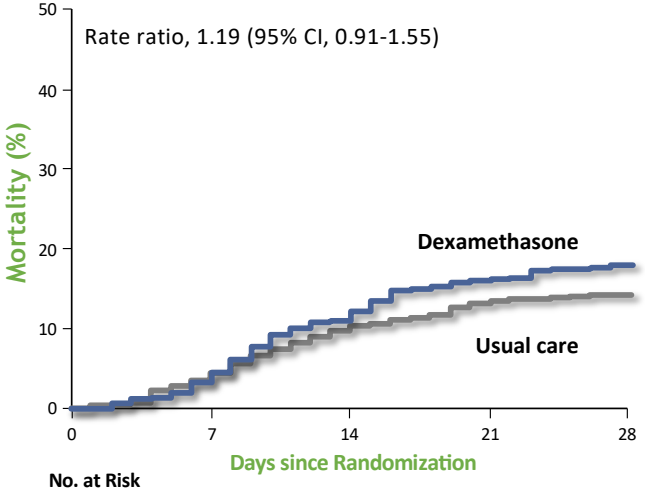
V3.0 11-Nov-2020

NCT04381936

# RECOVERY: Dexamethasone reduced mortality in patients on oxygen or with invasive ventilation but not in less severe disease

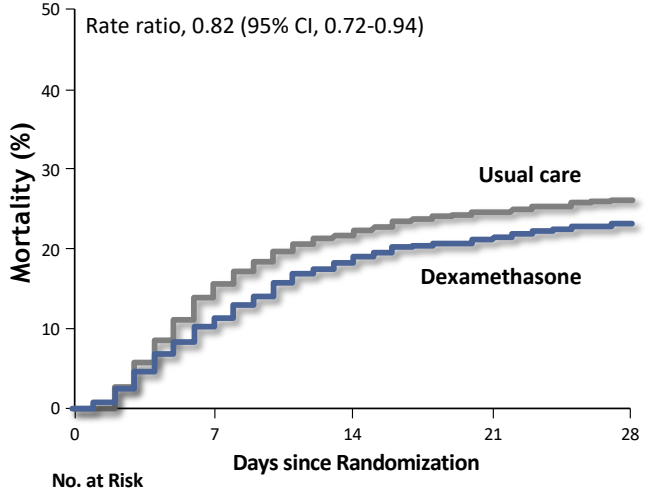
Less Severe Disease → More Severe Disease

## No Oxygen Received (N=1535)



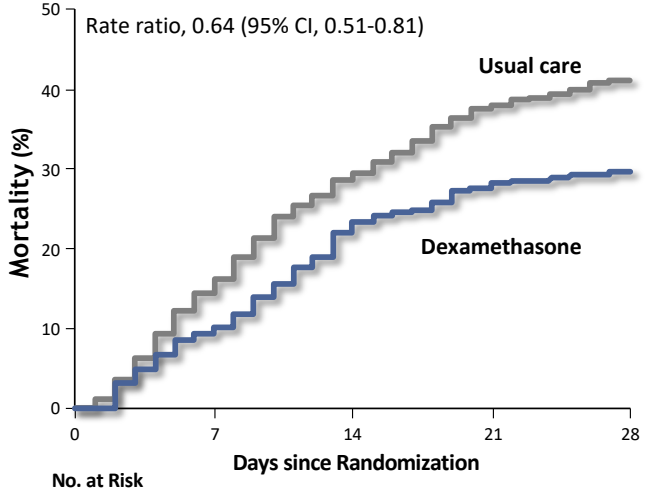

| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Usual care | 1034 | 987 | 928 | 897 | 889 |
| Dexamethasone | 501 | 477 | 440 | 420 | 411 |

## Oxygen Only (N=3883)




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Usual care | 2604 | 2195 | 2018 | 1950 | 1916 |
| Dexamethasone | 1279 | 1135 | 1036 | 1096 | 981 |

## Invasive Mechanical Ventilation (N=1007)




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Usual care | 683 | 572 | 481 | 424 | 400 |
| Dexamethasone | 324 | 290 | 248 | 232 | 228 |

**Reduction in 28-day mortality with dexamethasone for patients with more severe disease**
**Earlier administration results in an increased mortality trend**

CI, confidence interval.

RECOVERY Collaborative Group. *N Engl J Med*. 2021; 384:693-704. https://doi.org/10.1056/NEJMoa2021436

# Explosion in recent years on the availability of data
# → Access to existing data sources, Big Data and real-world data

## using historical control data

where patient recruitment can be difficult, for example in **rare disease populations** with limited number of patients, or in **more common disease areas** where patient recruitment is increasingly difficult due to logistical and patient burden issues

## advantages

- ability to run a clinical trial (that may previously have been considered impractical) effectively and efficiently thereby reducing patient burden as well as time and resources needed for the study

## challenges

- whether the historical control data available contain the specific information of interest
- which historical control is most appropriate
- what are the potential biases and limitations of the historical controls in terms of their clinical characteristics and treatment strategies that were previously available relative to how current patients are being treated
- which patients are eligible for a treatment.

# Benefits and limitations of Clinical Trials Designs

| BENEFITS | LIMITATIONS |
|---|---|
| **Randomised Clinical Trials** | |
| • Randomisation ensures reasonable similarity of the test and control groups and protects against various imbalances and biases that could lead to erroneous conclusions<br>• Randomisation is ethical when there is equipoise | • RCTs are expensive and lengthy. Need alternative designs to speed up drug development to address recruitment challenges and minimise patient burden<br>• Equipoise is a useful principle, but it can break down when conventional care offers little benefit and mortality is extremely high, or where there are no currently available treatment options. |
| **Single arm studies** | |
| • Require fewer resources<br>• Take less time to complete<br>• Appropriate in refractory populations<br>• Easily understood by the target patient population | • Defined study population frequently not comparable to historic controls<br>• If response rate is marginal it may not reflect true clinical benefit<br>• Poor characterization of safety |
| **Augmented RCT using historical controls to supplement or partially replace concurrent controls** | |
| • Increased availability of high quality, curated, and trusted clinical data, e.g. through data-sharing initiatives (e.g. TransCelerate Placebo Standard of Care database, Project Data Sphere)<br>• Statistical methods for establishing causal treatment effects using non-randomised data are available, although typically require stronger assumptions than inference based on an RCT<br>• Potential for long run Type I error to be lower when using historical borrowing (Viele et al 2018)<br>• May be more appealing to participants who want a higher probability of being assigned to the experimental arm. | • If standard of care has improved over time, this tends to induce positive bias in favour of active treatment if using historical controls<br>• Challenge of assessing relevance of historical data, and risk of bias/type 1 error inflation if historical and current controls are not comparable |

# Personalised medicine allows treating patients based on their individual demographic, genomic or biological characteristics for tailoring the ‘right treatment for the right person at the right time’.

- characterization of individuals’ phenotypes and genotypes (eg, molecular profiling, medical imaging, lifestyle data)

And / Or

- tailoring the right therapeutic strategy for the right person at the right time
- determine the predisposition to disease
- deliver timely and targeted prevention

# Study designs for clinical trials applied to personalized medicine: a scoping review

Superchi C, Brion Bouvier F, Gerardi C, et al

BMJ Open 2022;12:e052926

**“most common design is the enrichment design, whereby only biomarker-positive patients are randomly assigned to the targeted or control arm”**

- the use of enrichment designs is recommended only when the biomarker is a perfect predictor of the response in order not to deny biomarker-negative patients a treatment they would have otherwise benefited from.
- Prospective validation of the candidate biomarker is therefore strongly recommended before applying these trials designs.

BMJ Open 2022;12:e052926

# Clinical trials have long been a premier method of testing and validating new drugs and therapies.

- New drug approval is predicated on successful trials into the safety and efficacy of new treatments.
- Trials can involve hundreds of different sites around the world, all with different conditions and facing different effects and government regulations on what is permissible.
- number of people involved in a clinical trial (for many patients who have turned to clinical trials as a last resort )
- researchers who formulate the protocol for the trial and work to secure funding (either from governments, foundations, pharmaceutical or device manufacturers, or a combination of the above)
- clinical caregivers and nurses who work with patients at clinical trial sites
- postgraduate researchers
- postdoctoral fellows
- research scientists
- others  who work on the analysis of data generated by the trial, some of whom may or may not interact with patients, but all of whom are essential to the final result.

# Some future considerations

- **direct patient input into study designs**
  - likely become **the new normal** (?)
  - growing use of **patient-facing digital technologies** = new ways to engage with patients + change the types of endpoints and ways in which data are collected in clinical trials.
  - what procedures and how many procedures patients feel they can **tolerate** = incorporating this feedback into study protocols reduces the number of procedures to those essential and could prevent and/or reduce dropouts and the extent of missing data to assess study outcomes.
  - understand reasons for **recruitment challenges** = may support use of historical control data to reduce number of patients exposed to placebo in new trials
  - **informed consent** forms = user friendly with a trend for patients to provide their consent electronically.
  - need for patients to **attend sites** for assessments = data collection remotely with technology - increasing retention of patients in clinical trials.

New digital technologies for data capture and sharing of both clinical trial and real-world data, combined with growing use of AI and machine learning tools to extract patterns from these data, offer the potential to build and continuously update predictive models of disease natural history or patient outcomes under existing treatment options. Such models could be used to generate synthetic control arm information to supplement or replace concurrent controls in RCTs

# Κύριες βιβλιογραφικές πηγές


- Innovation in Clinical Trial Design: A review of The Clinical Trial Design Landscape (A white paper by the EFPIA Clinical Trial Design Taskforce on behalf of the EFPIA Clinical Research Expert Group) (7th March 2020) https://www.efpia.eu/media/547507/efpia-position-paper-innovation-in-clinical-trial-design-white-paper.pdf
- Clinical Trials in Global Health. The Lancet Global Health (Published: April 15, 2021) https://www.thelancet.com/series/clinical-trials-global-health