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L'ecosistema delle Linee Guida: le innovazioni metodologiche necessarie nella generazione delle evidenze

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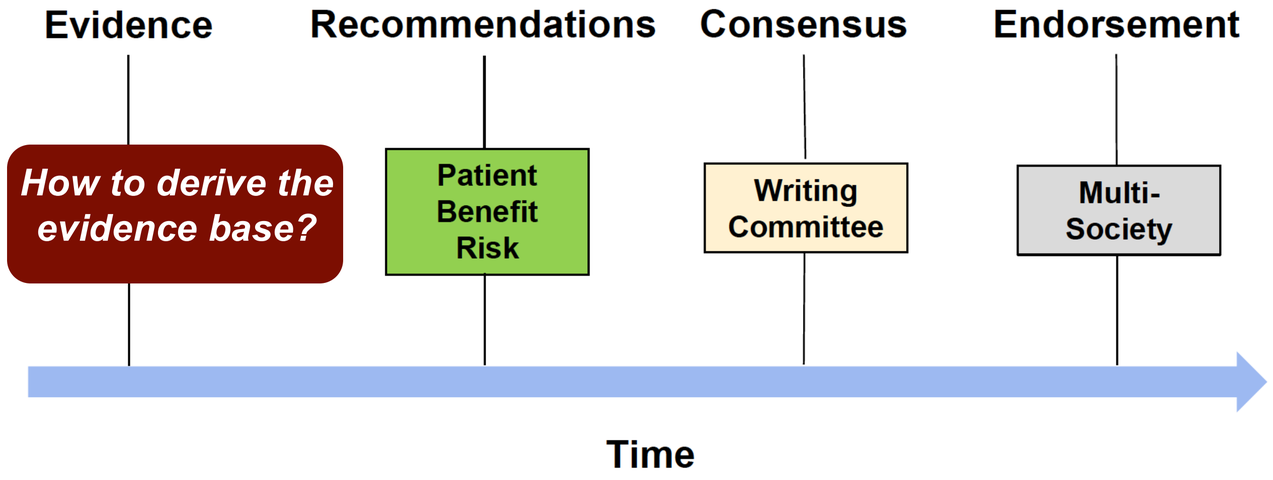
GUIDELINES METHODOLOGY



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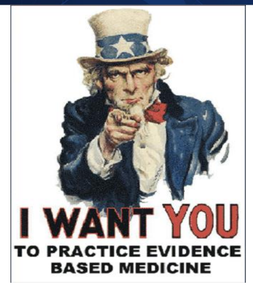

RCTs or megatrials have been put forward by the "evidence-based-medicine movement" as the criterion reference source of evidence, superior to any other method for measuring the effectiveness or effect size of medical interventions

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RCTs: the criterion reference source of evidence

- (Should) Answer relevant clinical questions
- Protocols maximally semplified
- Clear design, predefined sample size, with expected duration, and with essential dataset
- RCT is the uncontested "gold standard" for establishing causation between a therapy and outcomes for a compelling reason: it is the only study design that can guarantee that control and intervention subjects are similar in all the known and unknown attributes that influence outcomes
- In general, RCTs define the "average" overall benefit. When well conducted, RCTs have internal validity, and a therapy that is found to have a net biological benefit is considered efficacious

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RCTs: Limitations

- Large studies for small objectives, which mainly interest those who pay them, with rigid designs
- Mostly funded by companies and managed by CRO with slowly and cumbersome realization.
- Trials conducted in populations that are not always representative (*Diversity*)
- Mostly composite endpoints with subsidiary driving components
- Neutral operators, not involved in the cultural process that a trial should instead activate
- Ancillary investigations to answer pathophysiological questions are limited by costs, time and the scarce interest of the sponsors.

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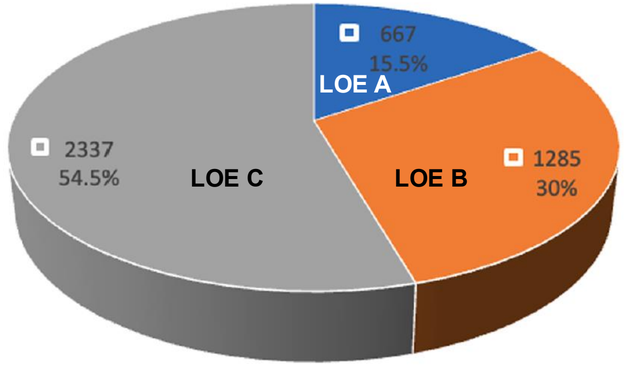
The scale of scientific evidence behind the current ESC clinical guidelines

ESC guidelines by 2022

- **37 different clinical CV topics**
- **4289 recommendations**



Tantawy M et al. IJC Heart & Vasculature 2023; 45:101175

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Clinical Trial Ecosystem Under Stress

Risk averse environment: patients and hospitals

Weak clinical study infrastructure

- Contracting
- Inexperienced sponsors, sites, and investigators

Financial challenges

- High cost of studies
- Reimbursement delays or non-coverage

Delays in study initiation

- Regulatory requirements
- IRB approval

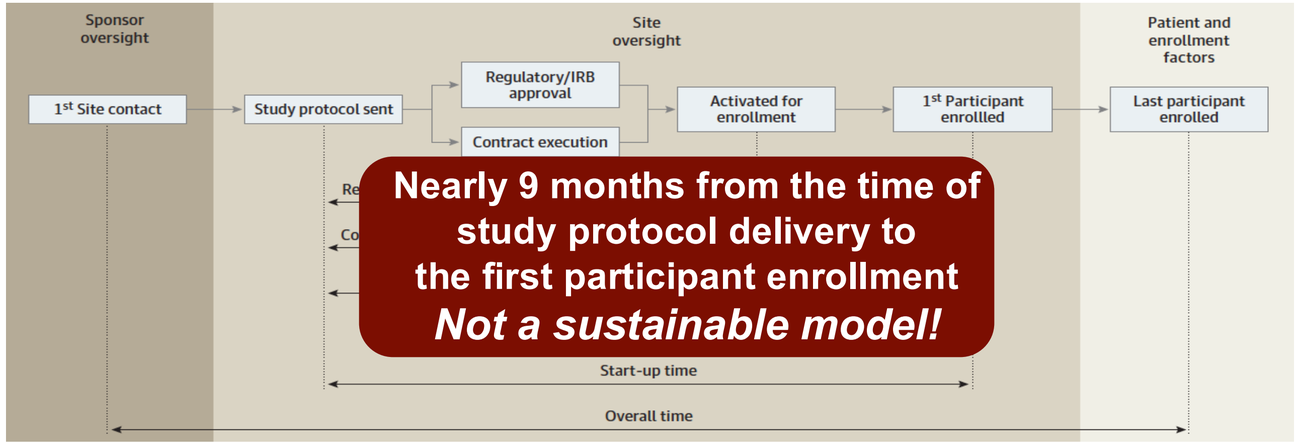
Enrollment challenges

- Restrictive selection criteria
- Competing studies

Excessive time needed to complete studies

Site Performance During the Start-up of Large Cardiovascular Clinical Trials
Reconfiguring the CV Clinical Trial Enterprise

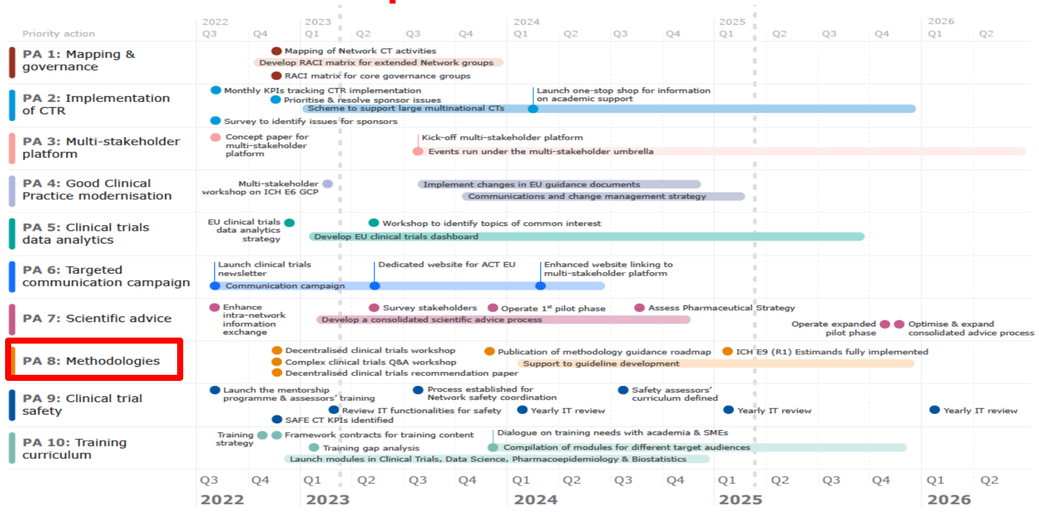
Time Intervals for Various Trial Milestones



Goyal A et al. JAMA Netw Open. 2021; 4:e2117963

HMA Heads of Medicines Agencies
European Commission
EMA EUROPEAN MEDICINES AGENCY

EC-HMA-EMA initiative Accelerating Clinical Trials in the EU Workplan 2022-2026



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Novel Methods of Evidence Generation

Clinical research is reorienting!

- **Diversity**
- **Real World Evidence (RWE)**
- **Precision medicine (Master Protocols)**

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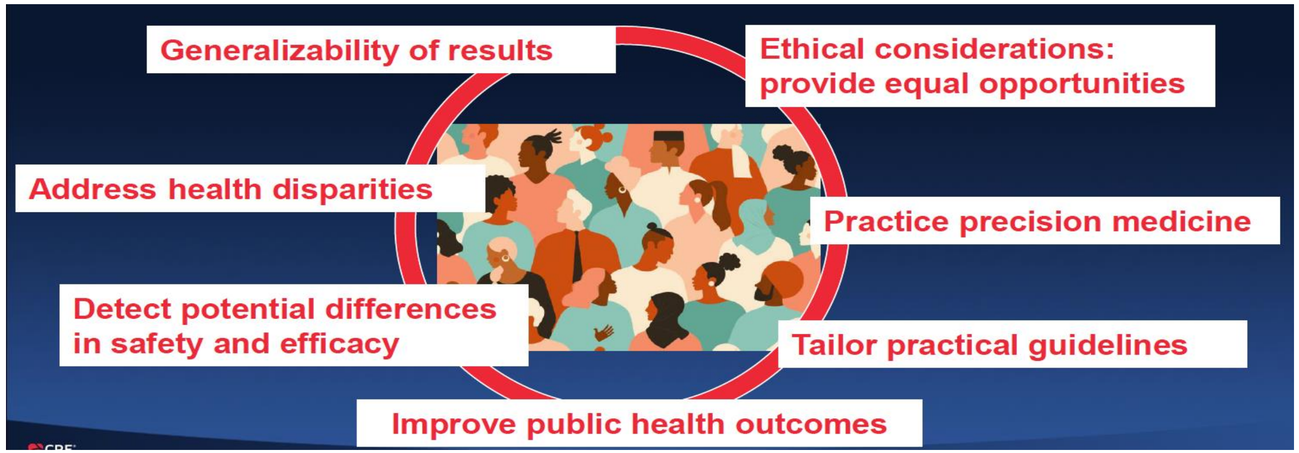
Diversity in RCTs -Why does it matter?



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Overcoming Lack of Diversity in Clinical Trials

FDA Initiatives

- **Race-only (African American Heart Failure Trial)**
- **Sex-only (WIN-DES) trials**
- **Promoting diversity and inclusion in clinical trials**

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Novel Methods of Evidence Generation

- Diversity
- **Real World Evidence (RWE)**
- Precision medicine (Master Protocols)

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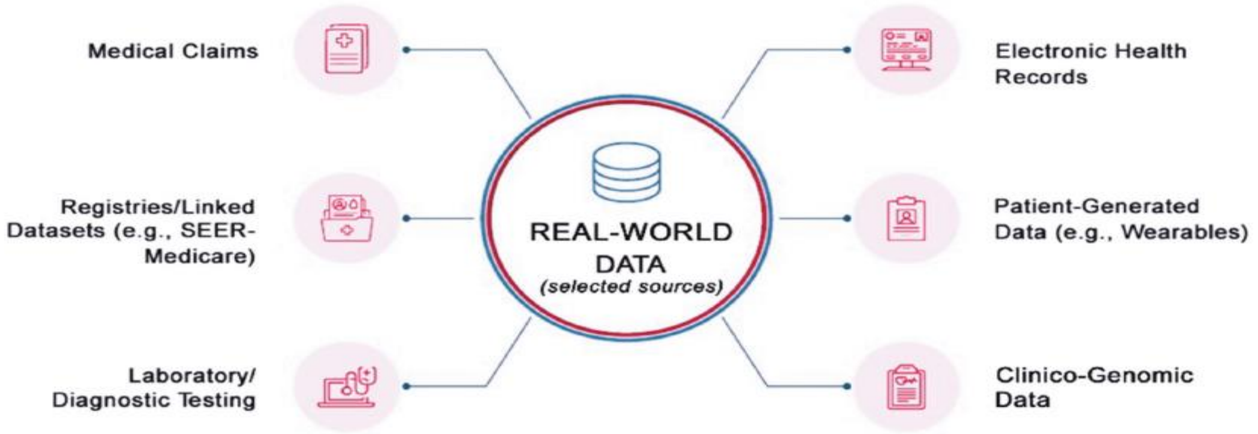
Real world data source



Zhao X et al. Clin Transl Sci. 2022;15:2293–2302

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Using and analyzing RWD

- Pragmatic (Digital, Virtual Trials)
- Target Trial Emulation
- Applications of ML and AI techniques

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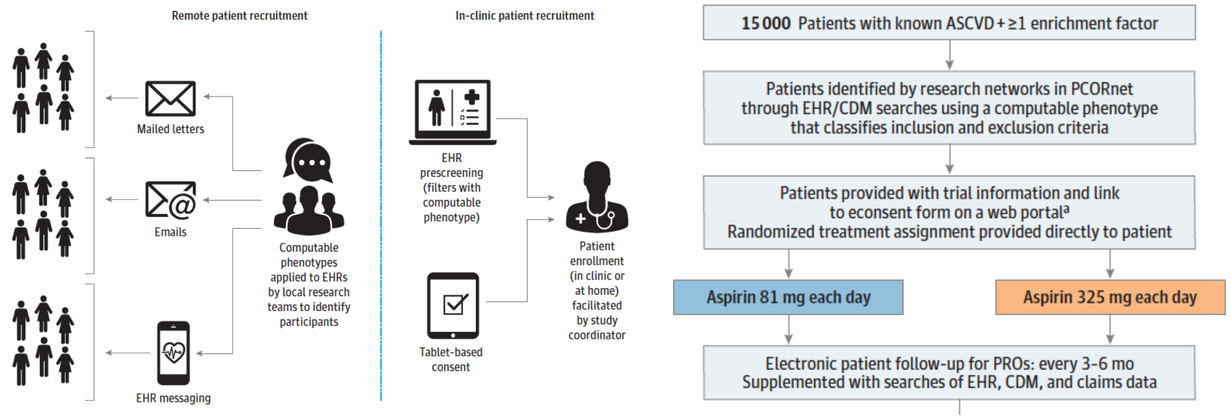
What is a Pragmatic Clinical Trial?

"the generation of real-world evidence without the limitations associated with observational studies, or the time, expense, and lack of generalizability that are barriers to conducting conventional randomized clinical trials" **US National Academy of Medicine**

1. **PCTs should aim to answer a 'practical care' need.**
2. **PCTs should target conditions affecting several patients, have the potential to improve quality of care, and demonstrate benefit over a short period (1 to 3 years).**
3. **The research question should be a service or a treatment added to usual care, possibly delivered as part of it.**

Pragmatic means a digital trial that uses digital technology to improve recruitment, data collection, and analysis."

The Aspirin Dosing: a Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) Study Design



Jones WS et al. N Engl J Med 2021;384:1981-90

The HEARTLINE Trial of the Apple Watch to Detect Atrial Fibrillation in Participants >65: Entering the Era of the Virtual / Giga Trial

A randomized trial of up to 180,000 patients to test whether the new Apple watch (with a built-in single lead EKG) can detect new onset atrial fibrillation in participants >65

Does this reduce the risk of all cause death, stoke, MI and CV hospitalization?

This virtual trial will cost 1% of what it costs to do a traditional RCT

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Target Trial Emulation

Target trial emulation is the application of trial design and analysis principles from (target) randomized trials to the analysis of observational data drawing valid causal inferences about an intervention from RWD.

Hernán MA, Robins JM.. Am J Epidemiol. 2016;183:758–64.

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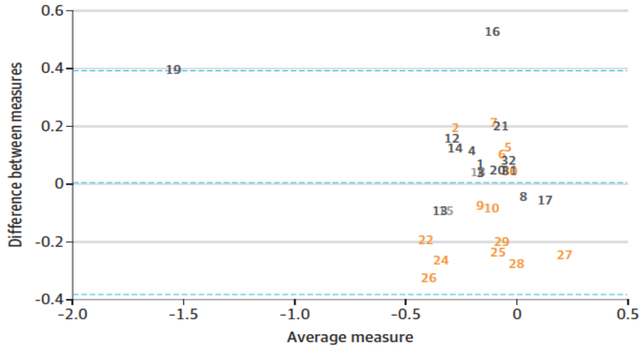
Emulation of RCTs With Nonrandomized Database Analyses Results of 32 Clinical Trials



- The overall observed agreement between the RCT and the database emulation results was a Pearson correlation of 0.82
- In a post hoc analysis limited to 16 RCTs with closer emulation of trial design and measurements, concordance was higher (Pearson r, 0.93; 95%CI, 0.79-0.97; 94% meeting statistical significance)

Wang SV et al. JAMA 2023; 329:1376-1385

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Using and analyzing RWD

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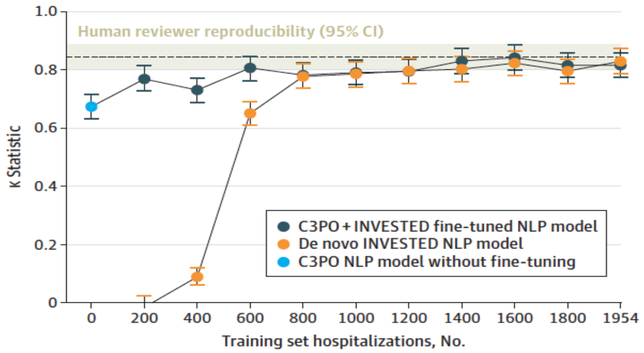
Application of ML/AI based on various aspects of drug/device development

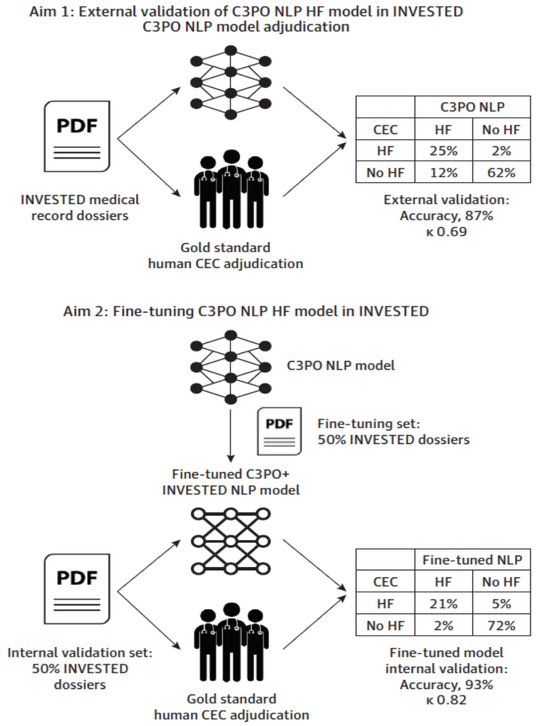
		Traditional Statistical Methods	ML	DL/AI
Clinical Trials Data Analysis	Ph1 – 4 Trials Focused on Inference or Estimation of Trt Effect	✓		
	Ph 0 Trials	✓	✓	
	Small – Medium Dimensional Data for Evidence Generation & Translational Research	✓	✓	
	High-dimensional Translational Data Focused on Prediction		✓	
Translational Research or Drug Discovery Data Analysis	Small – Medium Dimensional Data	✓	✓	
	High-dimensional data		✓	✓
Development of Systems	Systems with human-like reasoning to optimize drug development process (e.g., in manufacturing or trial operations)			✓

The AAPS Journal 2022; 24: 19

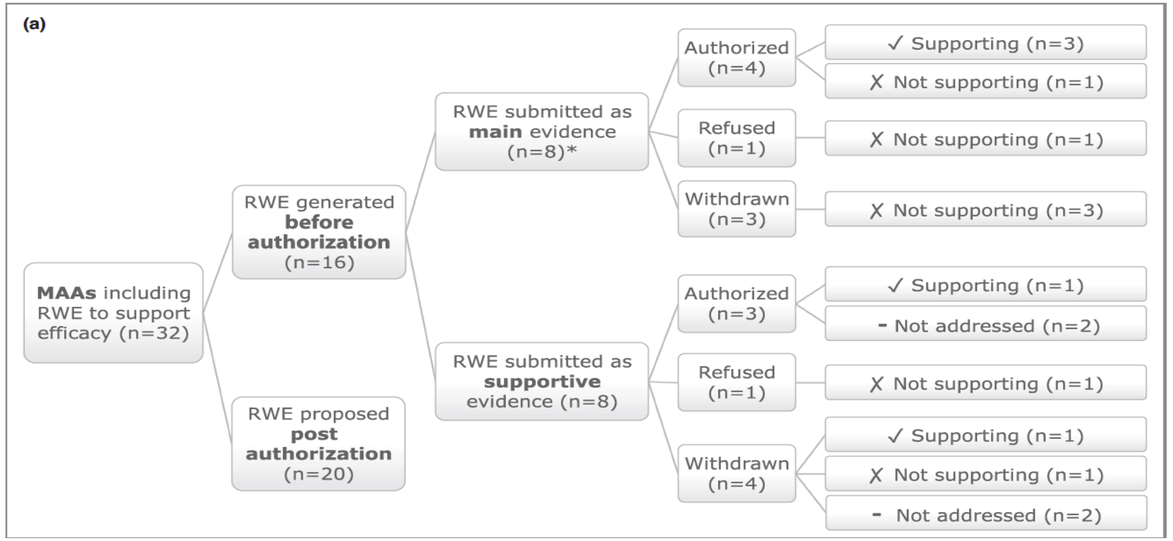
Natural Language Processing for Adjudication of Heart Failure in a Multicenter Clinical Trial



JAMA Cardiology November 11, 2023



Contribution of RWE in EMA's Regulatory Decision Making



Backer A et al. Clinical Pharmacology & Therapeutics 2023; 113

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Novel Methods of Evidence Generation

- Diversity
- Real World Evidence (RWE)
- **Precision medicine (Master Protocols)**

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Methodological Innovation in Clinical Reasearch

Important clinical questions go unanswered

↓

“Precision medicine” trials to evaluate targeted therapies

↓

“Mechanism based trials” in which eligibility is based on criteria other than traditional disease definitions

↓

The common denominator is the need to answer more questions more efficiently and in less time

↓

A methodologic innovation responsive to this need is Master Protocols

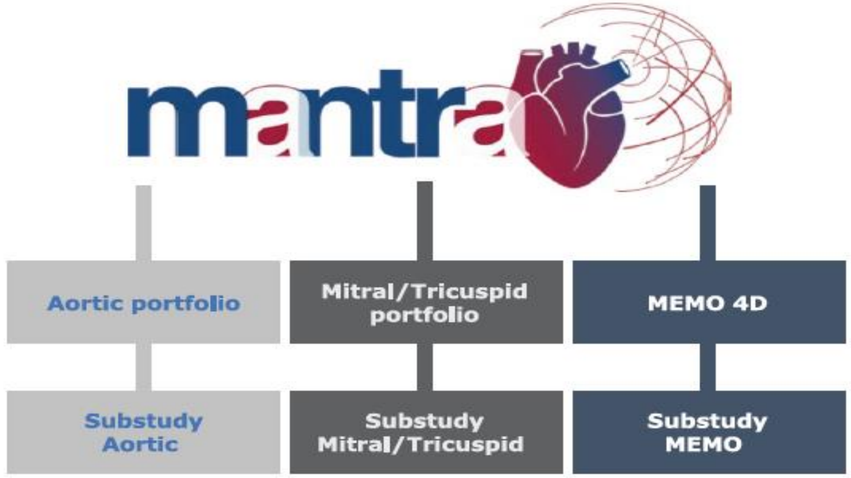
Types of Master Protocols

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Examples of Master Protocols in Cancer

Trial	Description	Design	Drug or Drugs	Disease and Target	Study Population	End Points
B2225[6]	Basket trial to determine cancers responsive to imatinib	Phase 2, multicenter, open-label, noncomparative trial	Single: imatinib (400 or 800 mg per day)	40 cancers (solid tumors and hematologic cancers) with activation of imatinib target kinases	186 patients ≥15 yr of age	Tumor response (SWOG criteria and investigator's assessment)
BRAF V600[7]	Basket trial to evaluate the efficacy of vemurafenib in nonmelanoma cancers	Early phase 2, multicenter, open-label, noncomparative, adaptive trial using Simon's two-stage design	Vemurafenib monotherapy or (in some patients with colorectal cancer) vemurafenib plus cetuximab	Multiple nonmelanoma cancers with *BRAF* V600 mutations; eight tumor-specific cohorts plus an "all others" cohort	122 adults (≥18 yr of age)	Response rate (assessed by investigators according to RECIST or IMWG criteria) at wk 8
NCI-Match[8]	Umbrella trial to determine whether treating cancers according to molecular abnormalities is effective	Exploratory, multicenter, noncomparative trial	Multiple: 30 treatments (as of May 2016), both FDA-approved and investigational, that target gene abnormalities	Advanced solid tumor, lymphoma, or myeloma; DNA sequencing for actionable mutations	35 adults planned per substudy; pediatric study to begin in 2017	Tumor response (primary) and progression-free survival
BATTLE-1[9]	Umbrella trial to evaluate targeted therapies in chemotherapy-refractory NSCLC	Phase 2, single-center, comparative, adaptive randomization trial	Multiple: three monotherapies (erlotinib, vandetanib, and sorafenib) and one combination (erlotinib plus bexarotene)	Advanced NSCLC; targets included *EGFR* mutation, *KRAS*/*BRAF* mutation, VEGF expression, and RXRs/CyclinD1 expression	255 adults in whom ≥1 chemotherapy regimen had failed	Complete or partial response or stable disease according to RECIST criteria at wk 8 (primary), progression-free survival, overall survival, and toxicity
I-SPY 2[10-12]	Adaptive platform trial to identify treatment regimens for locally advanced breast cancer in the context of neoadjuvant therapy on the basis of biomarker signatures	Phase 2, multicenter, comparative, adaptive randomization trial	Multiple: standard chemotherapy and five new drugs (initially) as add-on to chemotherapy; 12 treatments tested to date, with latest (pertuzumab) added October 2016	Early, high-risk breast cancer; three biomarkers (hormone-receptor status, HER2 status, and MammaPrint risk score) define eight genetic subgroups	1920 women (estimated) with invasive tumor ≥2.5 cm in diameter	Pathological complete response
Lung-MAP[13-15]	Master protocol to evaluate biomarker-matched therapies in rare squamous-cell subsets of NSCLC	Phase 2–3 comparative trial	Multiple: four investigational drugs plus one therapy for no-match control group (initially); three investigational drugs remain	Squamous-cell NSCLC; multiple targets (four molecular targets initially; three remain)	100–170 patients planned for phase 2 (40 are now enrolled); 300–400 planned for phase 3	Objective response rate, progression-free survival, and overall survival

Umbrella structure for the MANTRA study, encompassing heart valve disease



Meuris et al. Journal of Cardiothoracic Surgery 2023; 18:110

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Mobilizing the clinical trial ecosystem

- The strength of the RCT appears unquestionable when measuring small to moderate treatment effects in large populations.
- Developing better treatments for patients and advancing the future of health care will involve reexamining current approaches to clinical research and adopting more agile, innovative solutions.
- New therapeutic modalities and new approaches to evidence generation may promote the acceptability of non-randomized data in regulatory decision making.
- The digitalization of the health system is expected to expand in the future and clinical trials will benefit from machine learning and artificial intelligence.

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History could change…even for us Italians

- **Each citizen will have their own EHR, the new EHR 2 (FSE2), with the law no. 25 of 28 March 2022. The systematic, orderly and complete collection of health data of every citizen can and must radically change the National Health System.**
- **According to the PNRR the new Health System must be fully operational by 2026**
- **AGENAS is responsible for managing the IT structure of the entire ECO system**
- **The data, if complete and interoperable, with the support of artificial intelligence as digital, will be excellent material for scientific health research, not just epidemiological ones.**