International Federation of Associations
of Pharmaceutical Physicians &
Pharmaceutical Medicine

«Βασική & Κλινική Έρευνα στην ανάπτυξη φαρμάκων και προηγμένων θεραπειών : Πως αντιλαμβάνονται και εκπληρώνουν οι επιστήμονες των βιοιατρικών επιστημών τον ρόλο τους στην σύγχρονη διεπιστημονική αυτή διαδικασία»

«ΠΜΣ ΕΚΠΑ: Λοιμωξιολογία»

Γ εξάμηνο-Παρασκευή 15-12-2023

Dr. Βαρβάρα Μπαρούτσου,EMAUD,GFMD

Εσωτερικός Παθολόγος

IFAPP President

Περίγραμμα

1	• Εισαγωγή στην Φαρμακευτική Ιατρική • Τάσεις στην Κλινική Έρευνα & Ανάπτυξη
2	• COVID-19 • Επίδραση στην ανάπτυξη εμβολίων και μοντέλων έρευνας
3	• Ρυθμιστικό πλαίσιο για τις Κλινικές Δοκιμές στην ΕΕ
4	• Συμπεράσματα

Μέρος 1

Φαρμακευτική Ιατρική & Τάσεις στην Κλινική Έρευνα

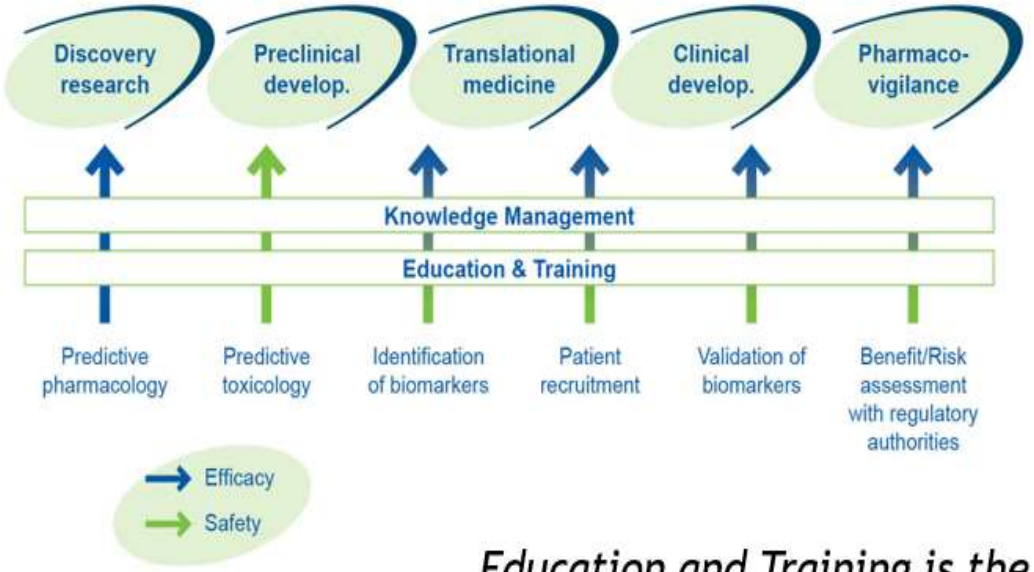
Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians -UK

- Pharmaceutical Medicine is the medical scientific discipline concerned with the **discovery, development, evaluation, registration, monitoring and medical aspects of marketing of medicines** for the **benefit of patients and the health of the community.**
- At core of the discipline is the clinical testing of medicines, translation of pharmaceutical drug research into new medicines, **safety and well-being** of research participants in clinical trials, and understanding the safety profile of medicines and their **benefit-risk balance.**
- In addition to expertise in the science of drug development pharmaceutical physicians need a thorough understanding of **pharmacoeconomics,** medical aspects of the marketing of medicines, business administration and the social impact of healthcare on patients and public health.
- Pharmaceutical physicians work in the **pharmaceutical industry, drug regulatory authorities and contract research organisations**, but have a close affinity with their medical colleagues **in primary and secondary health care and at universities.**

Source/reference: Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the United Kingdom (https://www.fpm.org.uk/)

Research Scientific Postgraduate Education and continuous learning –

Pharmaceutical Medicine Specialty: UK, Ireland, Belgium



IFAPP Pharmaceutical Medicine

Education and Training is the foundation for the entire value chain

Ευρωπαϊκός Οργανισμός PharmaTrain

- https://www.pharmatrain.eu/

PharmaTrain
MASTERING MEDICINES DEVELOPMENT

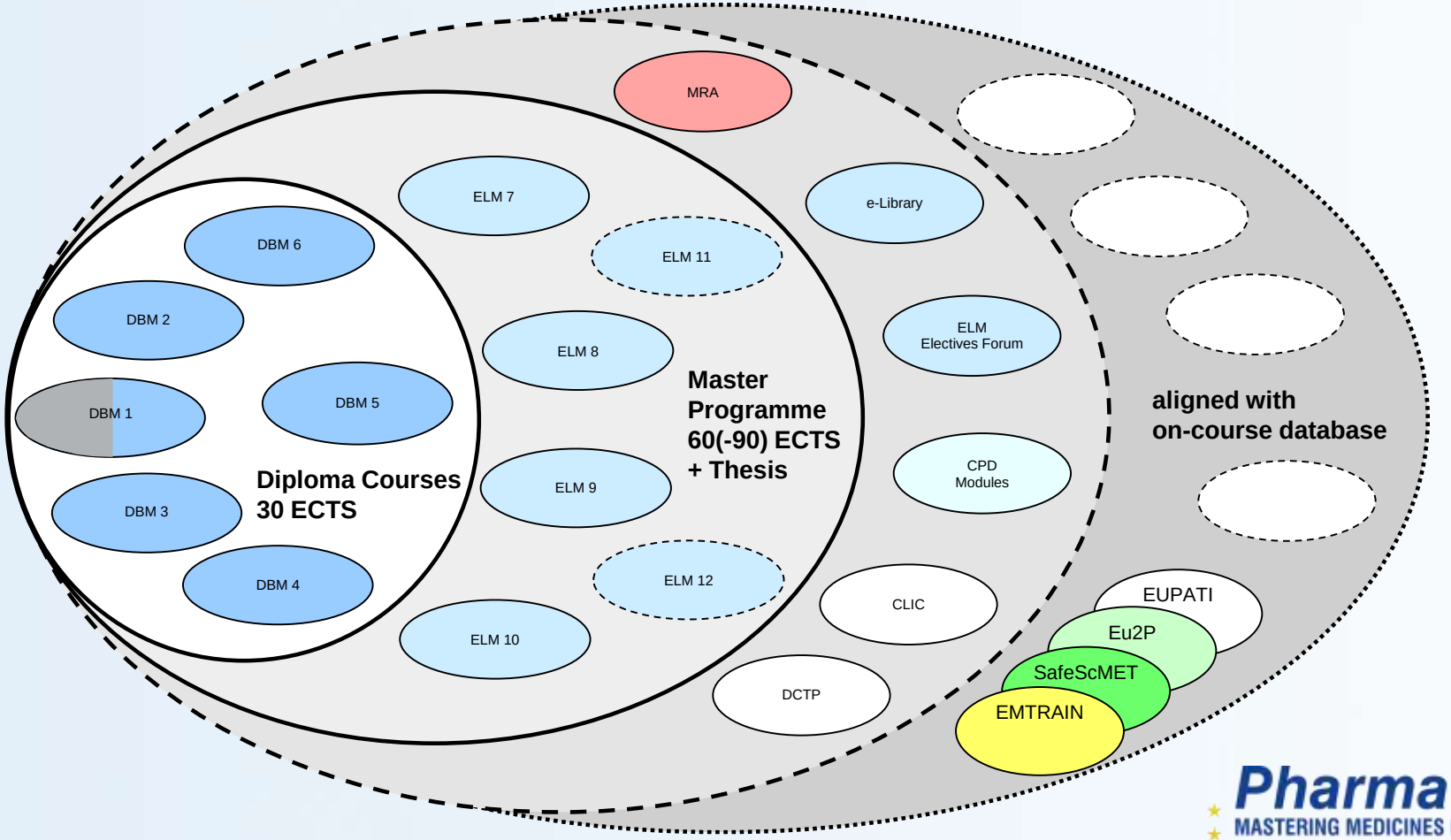
IFAPP Webinar: 27 October, 2022

Objectives and Achievements of the IFAPP - PharmaTrain Collaboration

IFAPP and PharmaTrain – A successful collaboration on quality in education in pharmaceutical medicine

PharmaTrain Modular Product Portfolio

More than 200 Modules from European and Global Partners build the integrated programmes and can be used à la carte:



Diploma Basic course

Introductory course

Drug discovery & development planning

Non-clinical testing, pharmaceutical & early clinical development

Exploratory & confirmatory clinical development

Clinical trials

Regulatory affairs, drug safety & pharmacovigilance

Healthcare marketplace & Economics of healthcare

PharmaTrain
MASTERING MEDICINES DEVELOPMENT

Elective Modules

ELM 1	Medicines Regulation
ELM 2	Generic & Biosimilar Medicinal Products
ELM 3	Project Management in Medicines Development
ELM 4	Biomarkers and Surrogate Endpoints
ELM 5	Medicines Development for Rare Diseases
ELM 6	Medicines Development in Children
ELM 7	Medicines Development in a Geriatric Population
ELM 8	Practical Approach to Ethical & Legal Aspects of CTs
ELM 9	Systematic Review and Meta-Analysis
ELM 10	Pregnancy and Medications
ELM 11	Principles & Practices of Medical Device Development
ELM 12	Drug Discovery Pharmacology
ELM 13	Model-Based Medicines Development
ELM 14	Statistics and Data Management
ELM 15	Advanced Pharmacokinetics
ELM 16	Pricing & Reimbursement Strategies
ELM 17	Health Economics
ELM 18	Drug Safety: Pharmacoepidemiology, Pharmacovigilance and Risk management
ELM 19	Biological and Advanced Therapies
ELM 20	Clinical Development Strategy & Trial Management for Medicines for Vulnerable Populations
ELM 21	Modern Development of Oncological Treatments
ELM 22	Risk Management in Clinical Trials
ELM 23	Medical Statistics and Data Management
ELM 24	Clinical Research Methodology
ELM 25	Advanced Pharmacokinetics (with Biostatistics)
ELM 26	Pharmacoeconomics and Medical Information

PharmaTrain Quality Criteria for Courses

A formalised and transparent QA/QC policy

1 University accreditation OR a suitable system for approving, monitoring and reviewing the training offered

2 A system for ensuring quality of teaching staff

3 Regular review of the QA/QC processes

A set of documented criteria for individual modules, courses or course programmes

4 Defined and transparent admission criteria

5 A predefined set of teaching objectives, leading to defined learning outcomes

6 Adequate facilities, infrastructure, leadership and competences

7 Assessment of the trainees' achievement according to the learning outcomes

8 A system for collecting, assessing and addressing feedback

9 Adaequate reference materials

PharmaTrain MASTERING MEDICINES DEVELOPMENT

PharmaTrain Centre Assessment Process

Recognition request by the centre
Preparation of documents and questionnaires

Nomination of 3 assessors
Preparation of the assessment visit

Assessment on-site or virtual
(1-2 assessors)

Assessment report with recommendation
Approval by the Executive Board PTF

PharmaTrain
MASTERING MEDICINES DEVELOPMENT
CENTRE RECOGNITION

PharmaTrain
MASTERING MEDICINES DEVELOPMENT
CENTRE OF EXCELLENCE

PharmaTrain
MASTERING MEDICINES DEVELOPMENT

PharmaTrain Recognition

PharmaTrain Centers of Excellence

University-based courses in pharmaceutical medicine fulfilling the PharmaTrain Centre of Excellence Recognition requirements

PharmaTrain Centers

Diploma and master programmes as well as large training organisations covering topics of the PharmaTrain Syllabus and fulfilling the PharmaTrain Centre Recognition requirements

PharmaTrain Courses

Individual “short” courses of at least 8 hours duration covering a PharmaTrain Syllabus topic and fulfilling the PharmaTrain Course Recognition requirements

PharmaTrain
MASTERING MEDICINES DEVELOPMENT

PharmaTrain Federation's and IFAPP's Global Role

Creation of a global quality environment in pharmaceutical medicine and clinical research through

- Training of different stakeholders in medicines development
  - ✓ Physicians' specialisation in pharmaceutical medicine
  - ✓ MD/Non-MD "Specialist in pharmaceutical medicine"
  - ✓ "University Professional in Clinical Trial Practices"
  - ✓ Responsibility-adapted training of investigators
- Growing the course quality recognition environment "PharmaTrain Course Recognition"
- Enabling the competence of professionals working in pharmaceutical medicine / medicines development

PharmaTrain
MASTERING MEDICINES DEVELOPMENT

Επαγγελματική σταδιοδρομία στην Κλινική Έρευνα

Life Science Career Tips | Tips for PhD students & Postdocs

Why Clinical Research is a Hot Career Choice For 2021 and Beyond

Last updated Oct 19, 2020 — 0

Imagine waking up to the news that the vaccine you relentlessly worked upon has saved millions of lives across the globe! Clinical research is one of the noblest fields that attempt to improve the quality of life! It involves translating basic and advanced research involving human subjects into novel treatments and therapies. Indeed, with medical and pharmaceutical companies growing at a fast pace, there is a huge demand for proficient clinical research professionals. Let us look at what clinical research has to offer us in the near future!

https://www.enago.com/academy/clinical-research-hot-career-2021-beyond/?utm_source=emailer&utm_medium=email&utm_campaign=news_061020

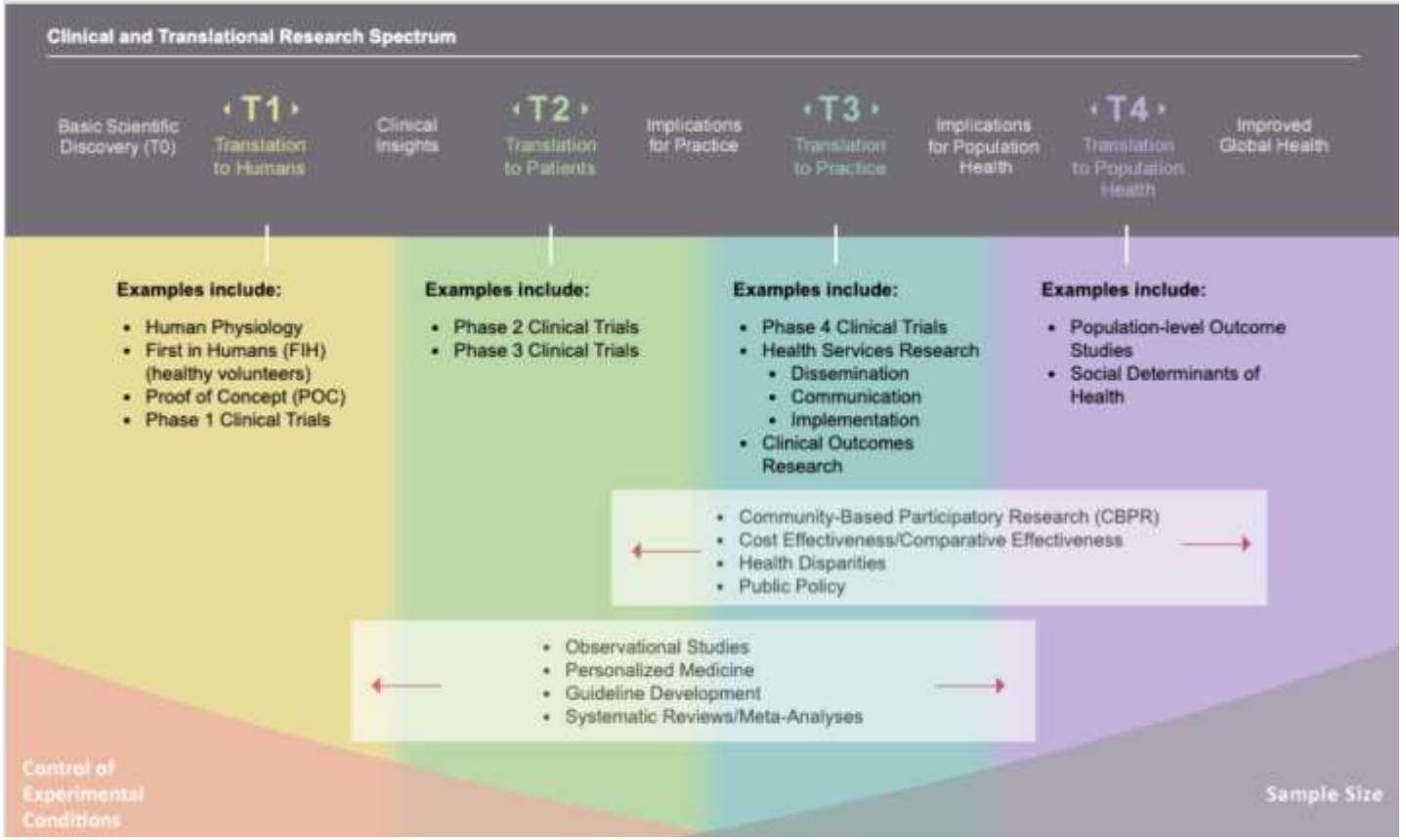
NIH Core competencies for Clinical Research

CLIC Center for Leading Innovation & Collaboration — *Amplifying research impact*

- Core competencies for Clinical and Translational Research
- Special Interest Competencies which include competencies for:
  - Pediatric Translational Research
  - Special Considerations for T1 Research
  - Academia-Industry Drug Development
  - Medical Device Innovation & Technology Transfer

https://clic-ctsa.org/education/competencies

Clinical and translational research is characterized by a spectrum of activities where critical insights are passed between research modalities so that biomedical discoveries can lead to tangible improvements in human health.

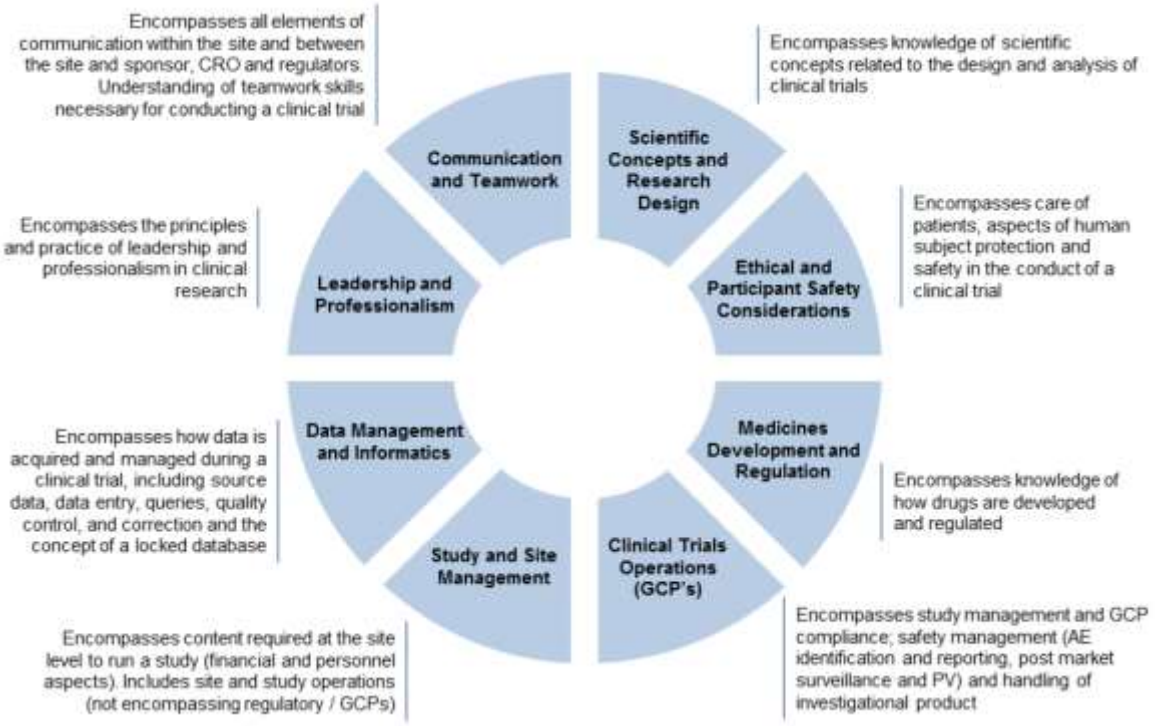


Translational Medicine pathfinder is based on material contained in the following three journal references.

- Sung NS, Crowley WF Jr, Genel M, Salber P, Sandy L, Sherwood LM, et al. Central challenges facing the national clinical research enterprise. JAMA. 2003 Mar 12;289(10):1278-87. PubMed ID: 12633190
- Westfall JM, Mold J, Fagnan L. Practice-based research – "Blue Highways" on the NIH roadmap. JAMA. 2007 Jan 24;297(4):403-6. PubMed ID: 17244837
- Szilagyi PG. Translational research and pediatrics. Acad Pediatr. 2009 Mar-Apr;9(2):71-80. PubMed ID: 19329097

Η Βασική κατάρτιση των κλινικών ερευνητών 6/2014

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD



https://mrctcenter.org/clinical-trial-competency/

Ατομική αντίληψη ερευνητικών ικανοτήτων ανά τομέα

TABLE 1: Self-Perceived Level of Competence in JTF Domains by Role

Domains	Competence/Role (mean value)					
	DM (n = 47)	RA (n = 90)	CRC/CRN (n = 559)	CRA (n = 177)	RM/PM (n = 357)	PI/CoPI (n = 354)
Scientific Concepts and Research Design	0.3	0.3	0.3	0.4	0.4	0.8
Ethical and Participant Safety Considerations	0.4	0.7	0.7	0.7	0.7	0.8
Medicines Development and Regulation	0.3	0.5	0.4	0.5	0.5	0.5
Clinical Trials Operations	0.4	0.6	0.6	0.8	0.7	0.8
Study and Site Management	0.3	0.4	0.5	0.6	0.7	0.7
Data Management and Informatics	0.7	0.4	0.6	0.7	0.6	0.7
Leadership and Professionalism	0.4	0.5	0.6	0.6	0.7	0.8
Communication and Teamwork	0.5	0.5	0.6	0.6	0.6	0.8

Note: ANOVA $p<0.0001$ between roles across all domains at 5% significance. Shaded area ≥ 0.6, "competent."

Εμπειρία Βιοεπιστημόνων Χορηγών

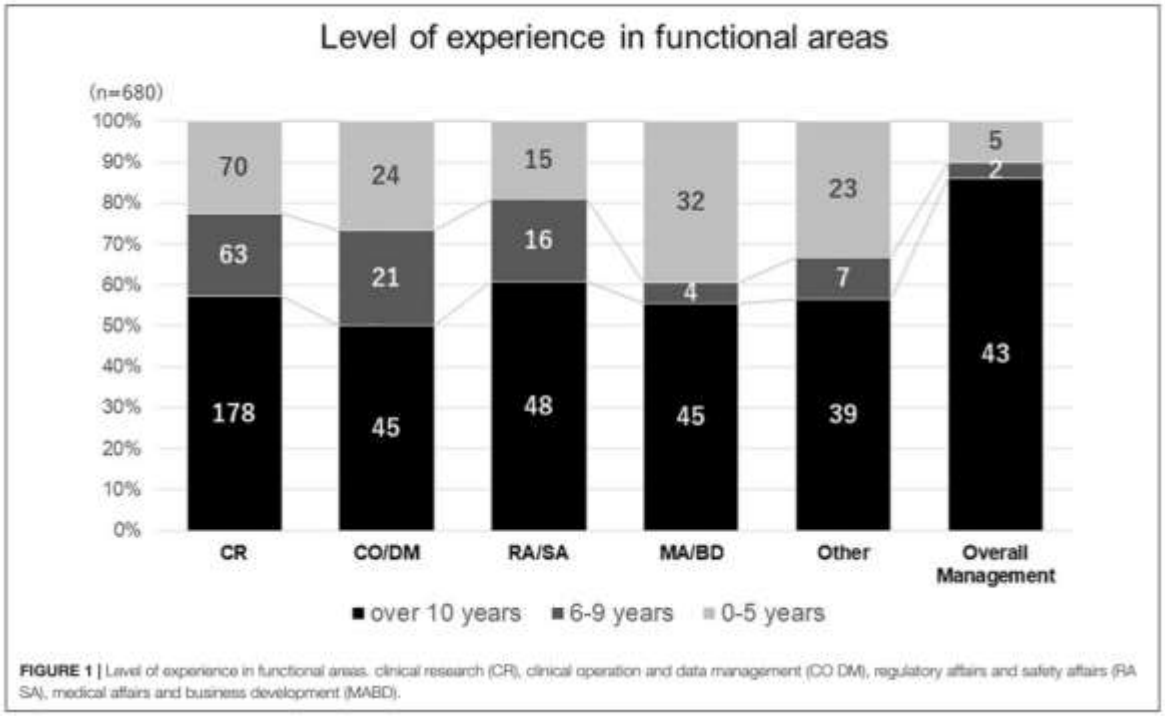


FIGURE 1 | Level of experience in functional areas. clinical research (CR), clinical operation and data management (CO DM), regulatory affairs and safety affairs (RA SA), medical affairs and business development (MABD).

Front. Pharmacol., 05 March 2019 | https://doi.org/10.3389/fphar.2019.00188

Δεξιότητες &Εκπαιδευτικές Ανάγκες Επιστημόνων Χορηγών

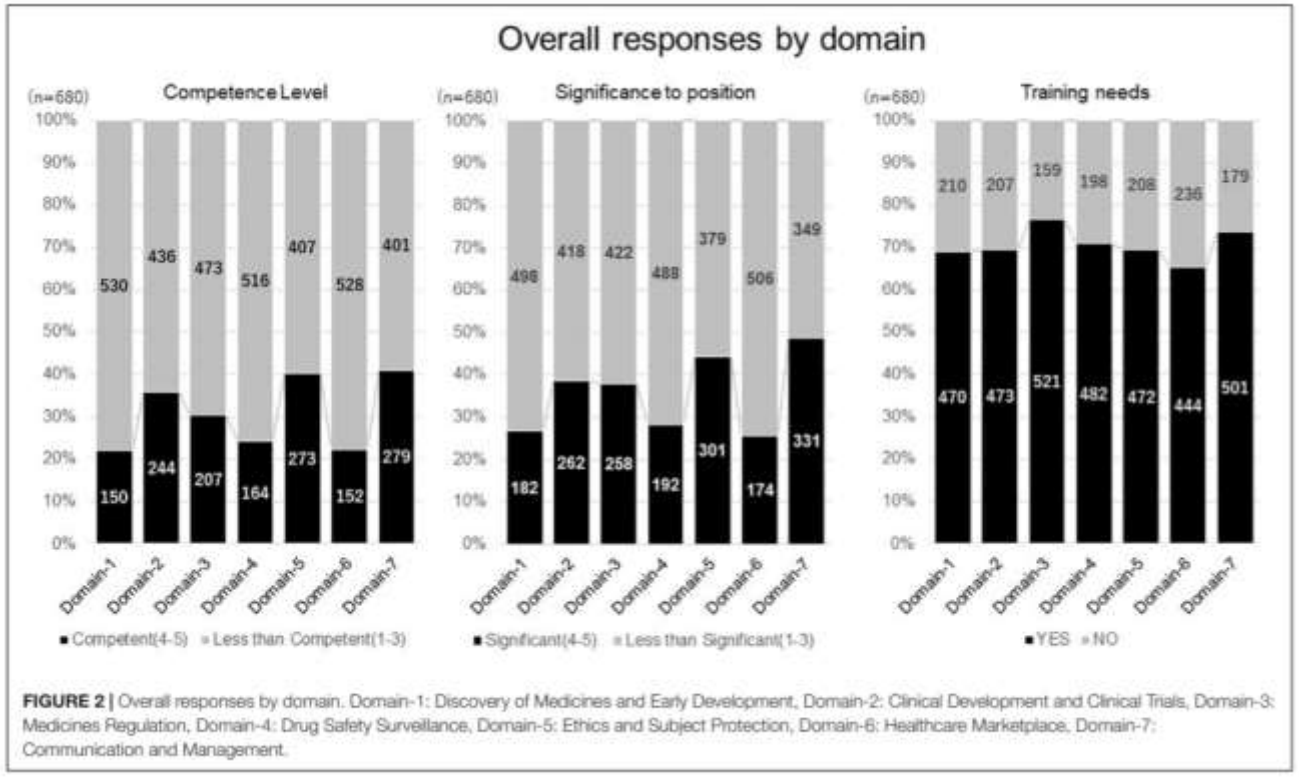


FIGURE 2 | Overall responses by domain. Domain-1: Discovery of Medicines and Early Development, Domain-2: Clinical Development and Clinical Trials, Domain-3: Medicines Regulation, Domain-4: Drug Safety Surveillance, Domain-5: Ethics and Subject Protection, Domain-6: Healthcare Marketplace, Domain-7: Communication and Management.

Front. Pharmacol., 05 March 2019 | https://doi.org/10.3389/fphar.2019.00188

Magnin et al. Trials (2019) 20:616
https://doi.org/10.1186/s13063-019-3702-z

Trials

RESEARCH Open Access

European survey on national training activities in clinical research

A. Magnin[1], V. Cabral Iversen[2], G. Calvo[3], B. Čečetková[4], O. Dale[2], R. Demlova[5], Gy. Blasko[6], F. Keane[7], G. L. Kovacs[6], C. Levy-Marchal[8], E. C. Monteiro[9], L. Palmisano[10], D. Pella[4], A. Portolés Pérez[3], O. Rascol[8], C. Schmid[1], F. Tay[1], H. von der Leyen[11] and C. Ohmann[12*]

Table 2 Overview of the training activities for clinical research in each country

Training activity	Country										
	CZE	FRA	DEU	HUN	IRL	ITA	NOR	PRT	SVK	ESP	CHE
GCP	X	X	X	X	X		X	X	X	X	X
Study nurse/coordinator	X		X	X	X	X	(X)	X	(X)	X	X
Investigator	X	X	X	X	X	X		X	X	X	X
Monitoring	X	X	X	X			X	X		X	X
PV/clinical pharmacology	X		X	X				X	(X)	X	X
Principal investigator	X	X	X	X				X	X		X
CRO operators			X			X		X			
Methodology		X			X			X		X	X
QMS	X	X	X		X			X			
Postgraduate	X		X	X	X		X	X	X		X
Other		X	X	X	X						X

X = available, (X) = planned
CZE Czech Republic, *FRA* France, *DEU* Germany, *HUN* Hungary, *IRL* Ireland, *ITA* Italy, *NOR* Norway, *PRT* Portugal, *SVK* Slovakia, *ESP* Spain, *CHE* Switzerland, *GCP* Good Clinical Practice, *PV* pharmacovigilance, *CRO* clinical research organization, *QMS* quality management system

Average self-assessed competency rating by role and by domain

Role	Number of respondents	Scientific concepts and research design	Ethical and safety considerations	Investigational product development and regulation	Clinical study operations	Study and site Mgt	Data Mgt and informatics	Leadership and professionalism	Communications and teamwork
Clinical research associate/monitor	52	6.9	7.4	7.3	7.9	7.7	7.3	7.9	7.5
Clinical research coordinator/study nurse	183	6.4	7.5	6.1	7.6	6.9	7.1	7.4	6.7
Educator/trainer	51	7.8	8.4	7.8	8.5	8.3	7.4	8.5	8.8
Principal investigator/co-investigator	51	7.5	8.0	6.9	7.7	7.0	6.8	8.0	7.7
Project manager/research manager	164	7.5	8.2	7.9	8.3	8.8	7.8	8.6	8.3
Regulatory affairs professional (49)	46	6.8	8.3	7.5	7.8	6.8	6.6	8.1	6.8
Average of all roles	661	6.9	7.8	7.1	8.0	7.5	7.1	8.0	7.6

Therapeutic Innovation &regulatory Science (2022) 56:607-615
https://link.springer.com/article/10.1007/s43441-022-00395-z
The Joint Task Force for Clinical Trial Competency (JTF) conducted a global survey of clinical research professionals requesting respondents to self–assess their competencies in each of the eight domains of its Core Competency Framework version 3.1.

Average self-assessed competency rating by experience &professional certification

Self-assessed competency rating by experience

Years of experience	Number of respondents	Scientific concepts and research design	Ethical and safety considerations	Investigational product development and regulation	Clinical operations (GCPs)	Study and site management	Data management and informatics	Leadership and professionalism	Communications and teamwork
0–2	78	5.2	5.9	4.9	5.5	4.9	5.6	6.3	5.9
3–5	95	6.4	6.9	6.4	7.0	6.7	7.1	7.4	7.0
6–10	102	6.7	7.7	6.7	7.8	7.2	6.5	7.8	7.2
>10	386	7.8	8.6	7.9	8.9	8.4	7.7	8.6	8.2
Average of total	661	6.9	7.8	7.1	8.0	7.5	7.1	8.0	7.6

Self-assessed competency by professional certification

	Number of respondents	Scientific concepts and research design	Ethical and safety considerations	Investigational product development and regulation	Clinical study operations	Study and site management	Data management and informatics	Leadership and professionalism	Communication and teamwork
ACRP and/or SoCRA Certified	274	7.3	8.3	7.7	8.8	8.4	7.8	8.3	7.8
No professional certification	306	6.8	7.4	6.4	7.4	6.8	6.7	7.7	7.2

Therapeutic Innovation &regulatory Science (2022) 56:607-615
https://link.springer.com/article/10.1007/s43441-022-00395-z

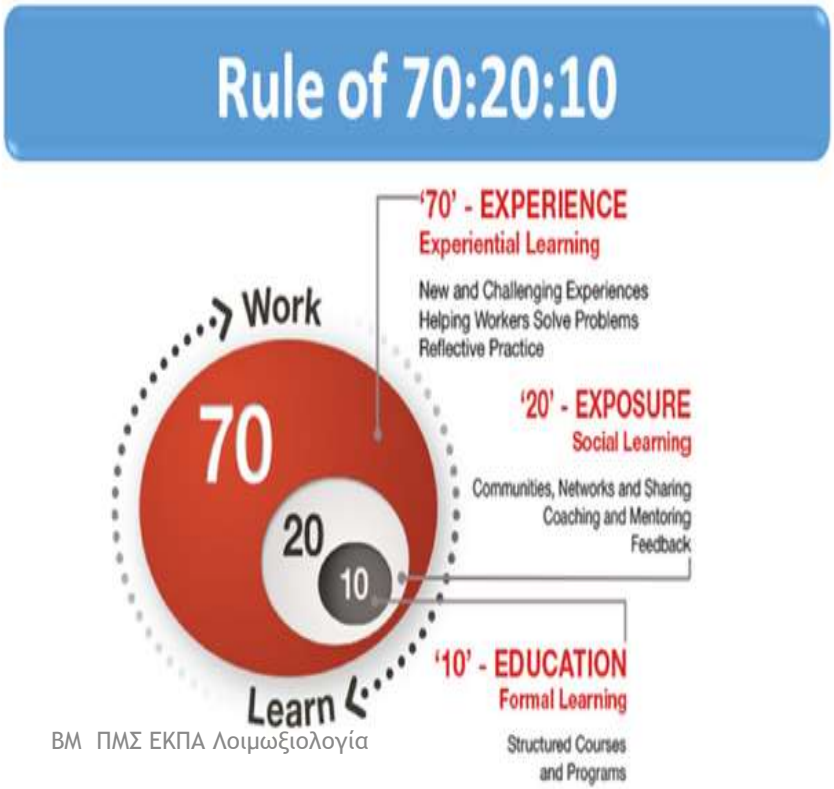
ΗΠΑ ενδεικτικά προγράμματα εκπαίδευσης κλινικών ερευνητών

Sample online offerings:

- Northwestern University, Clinical and Translational Sciences Institute *Introduction to Clinical Research* Online Modules
- University of Washington, Institute of Translational Health Sciences (ITHS), Self-Directed Learning Center
- Office of Research Integrity: *The Lab*, *The Research Clinic*
- NIH: *Teaching the Responsible Conduct of Research*
- ACRP: *GCP—An introduction to ICH GCP Guidelines*
- Collaborative Institutional Training Initiative (CITI): *Populations in Research Requiring Additional Consideration*
- UC Davis: *Strengthening Provider Patient Communication Skills in Clinical Trials.*

- ***Tufts University Center for the Study of Drug Development***

Δια βίου εκπαίδευση ερευνητών

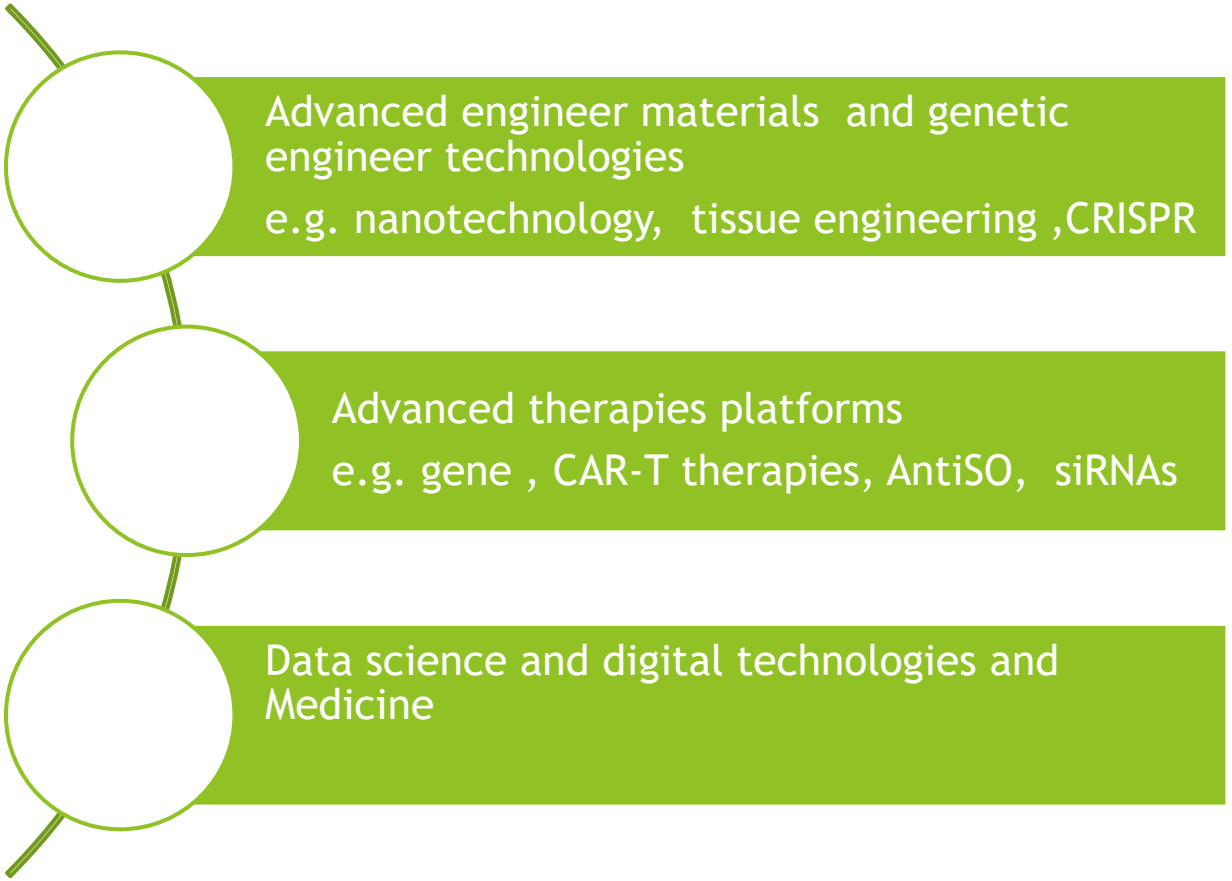


Experience	• Sabbatical
Exposure	Exchange program
Network	• Collaborative projects

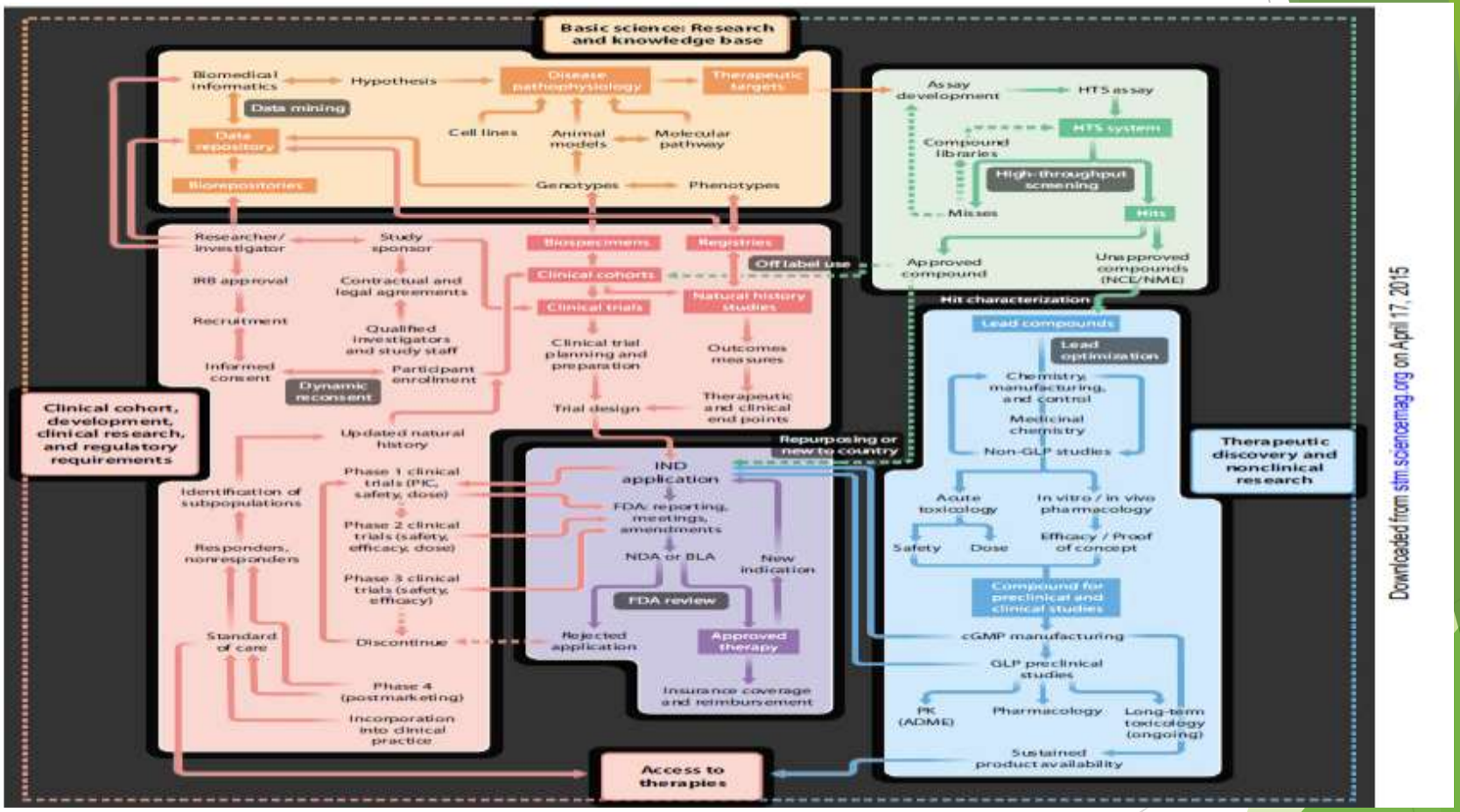
Τάσεις στην Κλινική Ερευνα

Οικοσύστημα καινοτομίας και έρευνας

The Changing Face of Innovation : 21st century model



Μοντέλο R&D

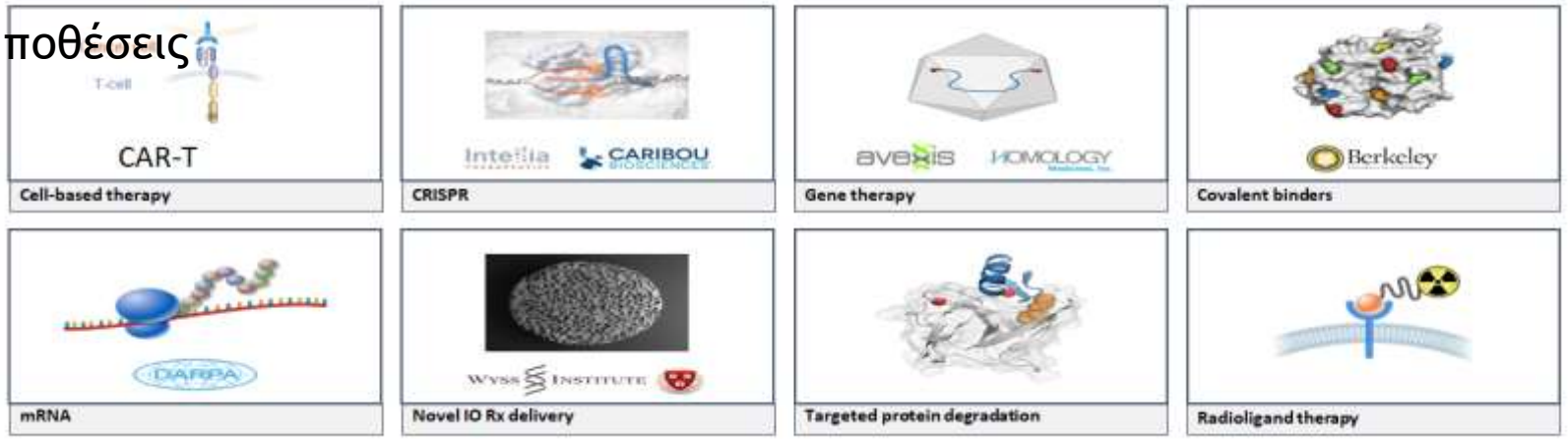


Kristin Baxter,[1,2] Elizabeth Horn,[1] Neely Gal-Edd,[1] Kristi Zonno,[1,3] James O'Leary,[1] Patrick F. Terry,[4] Sharon F. Terry[1]*

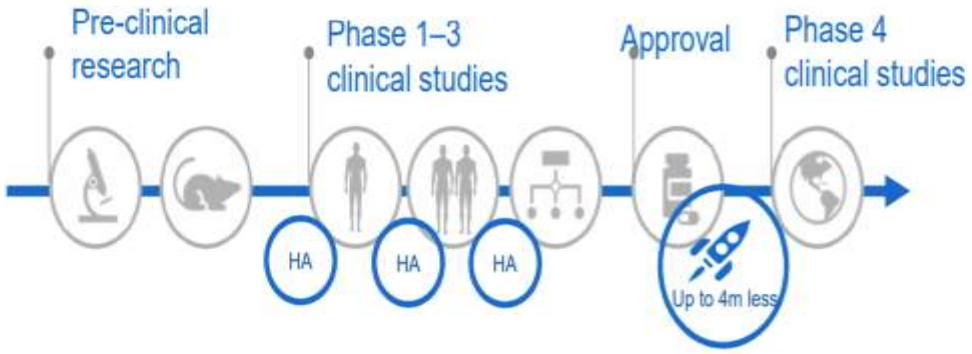
www.ScienceTranslationalMedicine.org 6 February 2013 Vol 5 Issue 171 171cm1

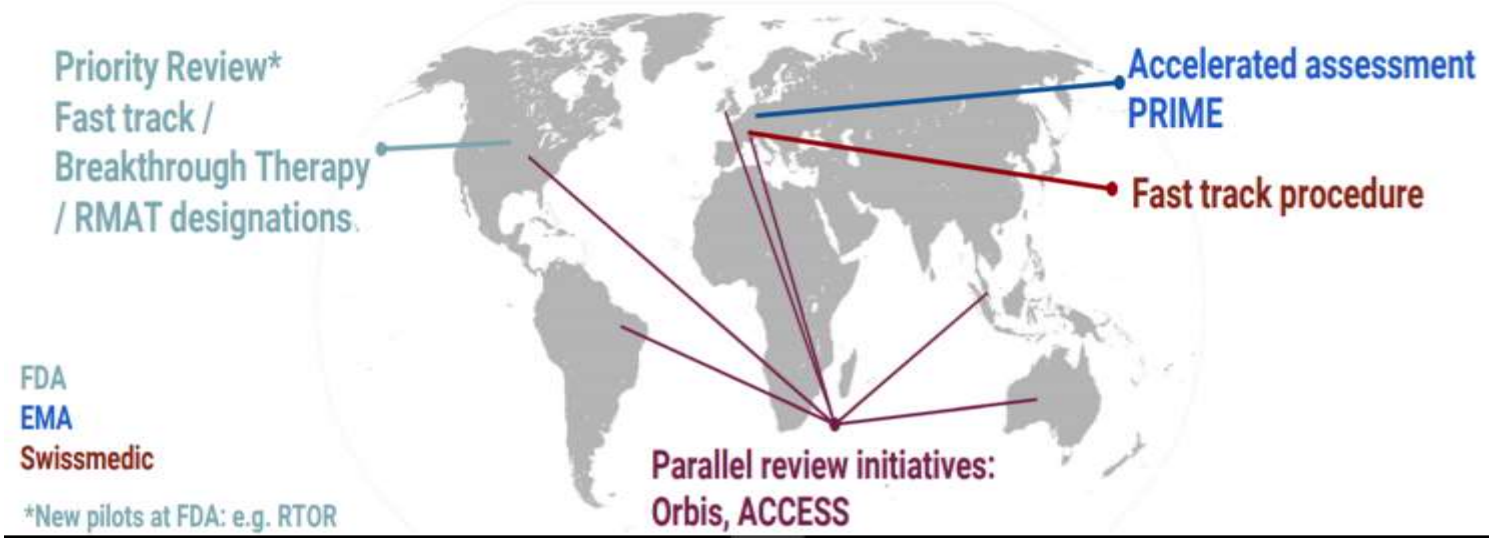
Το Αναδυόμενο Μοντέλο Υπέρ -Καινοτόμου Έρευνας και Ανάπτυξης του 21ου αιώνα

*Υπό Προϋποθέσεις

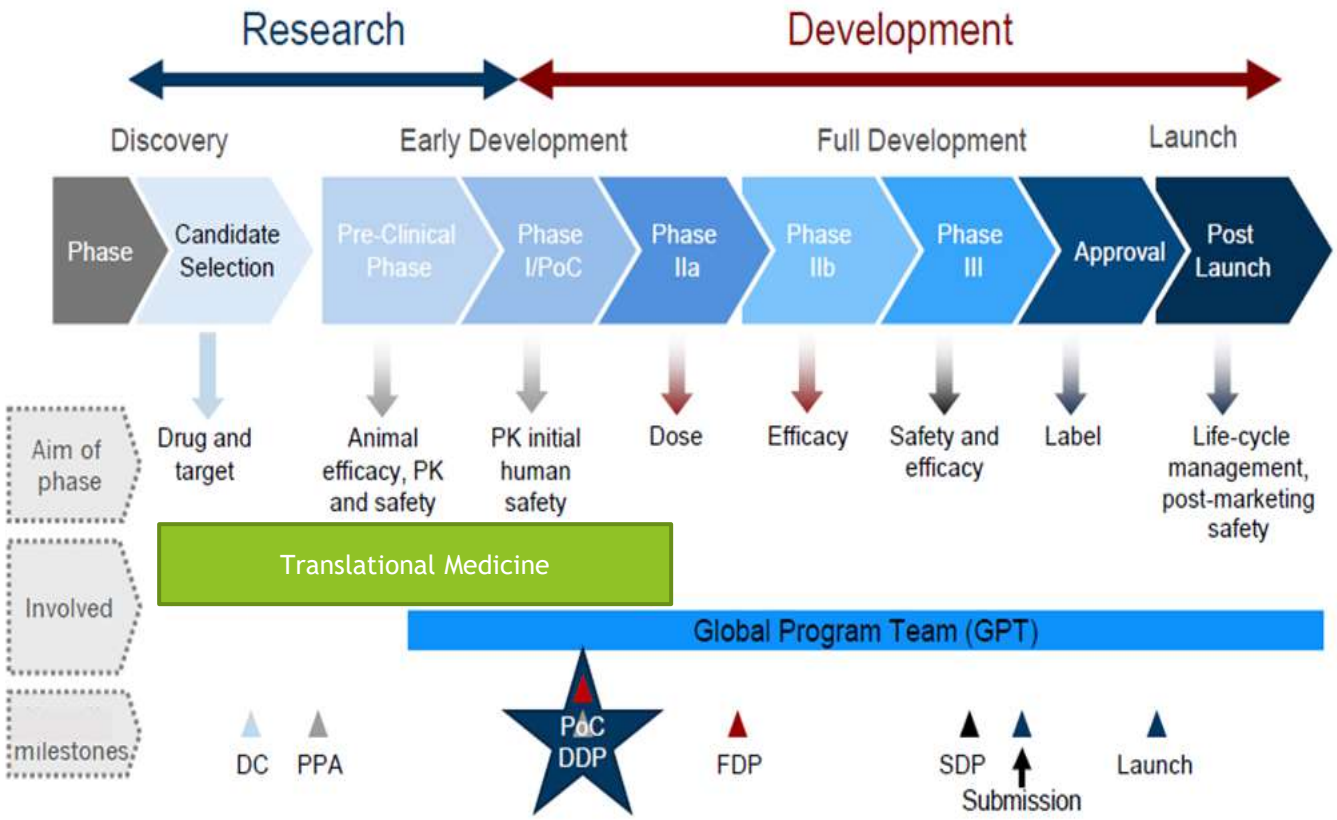


Εγκριτικές εξελίξεις στην Ευρωπαϊκή Ένωση και οι επισπεύδουσες διαδικασίες για καινοτόμες θεραπείες με πρώιμα σημαντικά δεδομένα

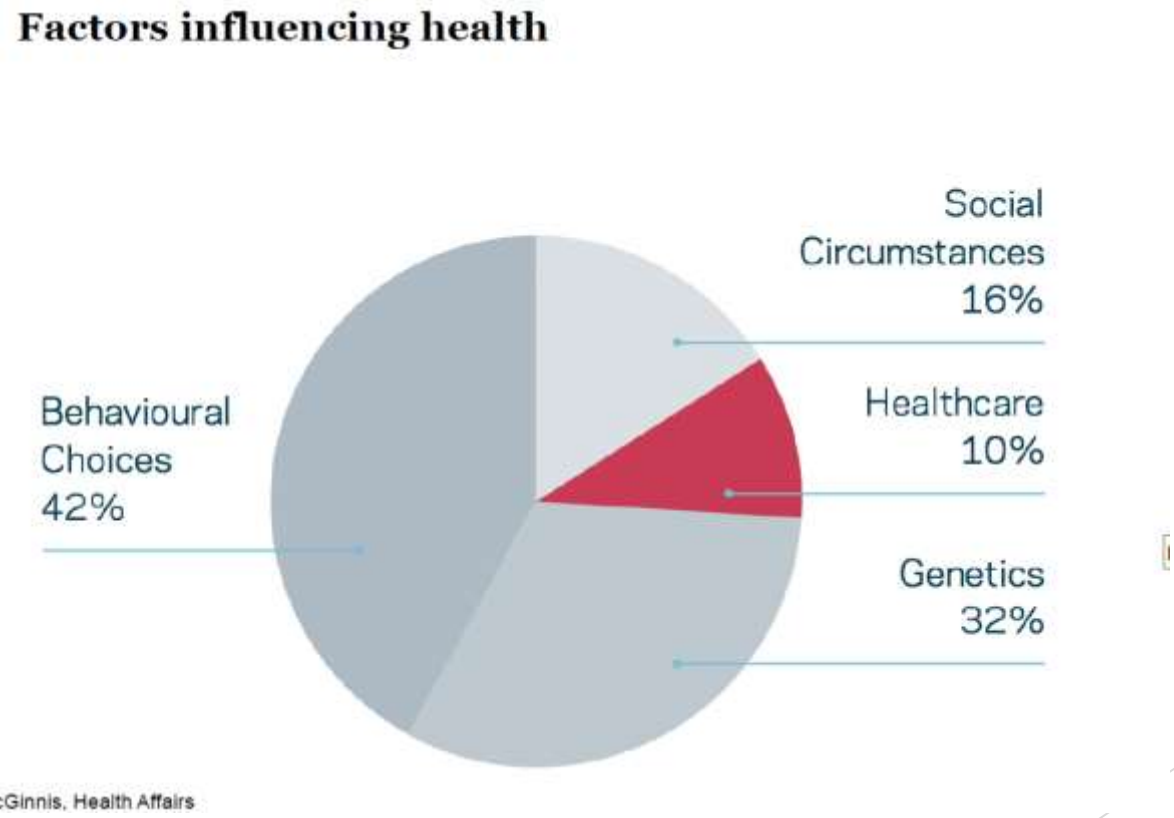




The Changing Face of Innovation : 21st century R&D model



Προς την Εξατομικευμένη Ιατρική



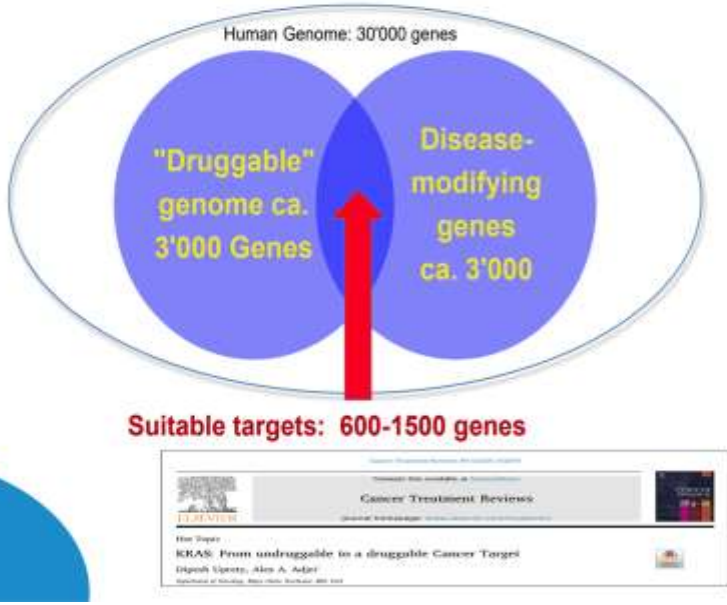
Γονιδιωματική και Θεραπείες Στόχευσης

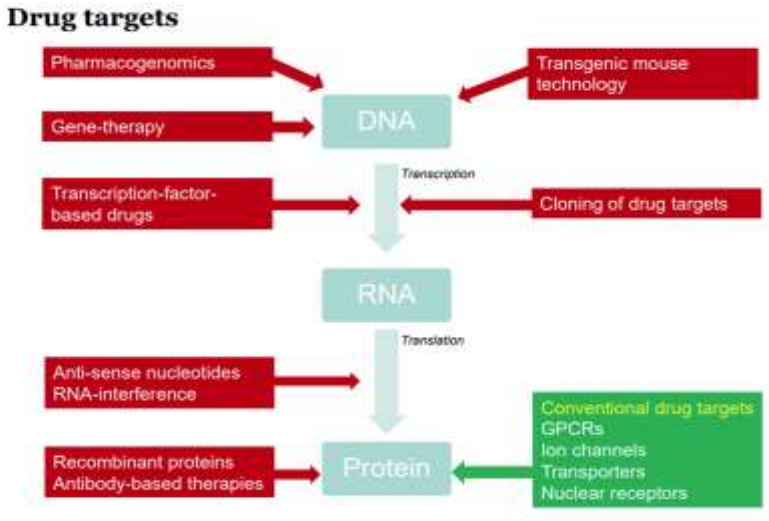
Genomics and therapeutics

Identifying new drug **targets** using genomic information	**Repurposing** existing drugs for new indications basedon new genomic information	Developing drugs **targeted** at specific mutations
Using genomic technologies to **stratify** the intensity of drug therapy	Using genomic information to improve drug **dosing**	Using genomic information to **prevent adverse drug reactions**

Γονιδίωμα και θεραπευτικοί στόχοι

Genome and Drug targets





Εγκριτικές εξελίξεις στις ΗΠΑ και στην Ευρώπη

Clinical Pharmacology & Therapeutics

Review | Open Access

Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth

Hans-Georg Eichler, Francesco Pignatti, Brigitte Schwarzer-Daum, Ana Hidalgo-Simon, Irmgard Eichler, Peter Arlett, Anthony Humphreys, Spiros Vamvakas, Nikolai Brun, Guido Rasi

First published: 16 October 2020 | https://doi.org/10.1002/cpt.2083

Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth

Hans-Georg Eichler[1,2,*], Francesco Pignatti[1], Brigitte Schwarzer-Daum[2,3], Ana Hidalgo-Simon[1], Irmgard Eichler[1], Peter Arlett[1,4], Anthony Humphreys[1], Spiros Vamvakas[1], Nikolai Brun[5] and Guido Rasi[1,6]

Compared with drugs from the blockbuster era, recently authorized drugs and those expected in the future present a heterogenous mix of chemicals, biologicals, and cell and gene therapies, a sizable fraction being for rare diseases, and even individualized treatments or individualized combinations. The shift in the nature of products entails secular trends for the definitions of "drugs" and "target population" and for clinical use and evidence generation. We discuss that the lessons learned from evidence generation for 20th century medicines may have limited relevance for 21st century medicines. We explain why the future is not about randomized controlled trials (RCTs) vs. real-world evidence (RWE) but RCTs and RWE—not just for the assessment of safety but also of effectiveness. Finally, we highlight that,

Outline of emerging clinical trials designs

DCTs* and hybrid trials

Adaptive trials with bio markers / translational research trials

Pragmatic trials

In silico trials

Pharmacoepidemiology post approval trials and studies

Externally controlled trials FDA draft guidance Feb 2023

Why: To optimize knowledge gain and reduce uncertainty

What we need is : Shorter CT* times, improved patient safety, less biased endpoints , fewer ethical concerns , more risk modification by using specific biomarkers

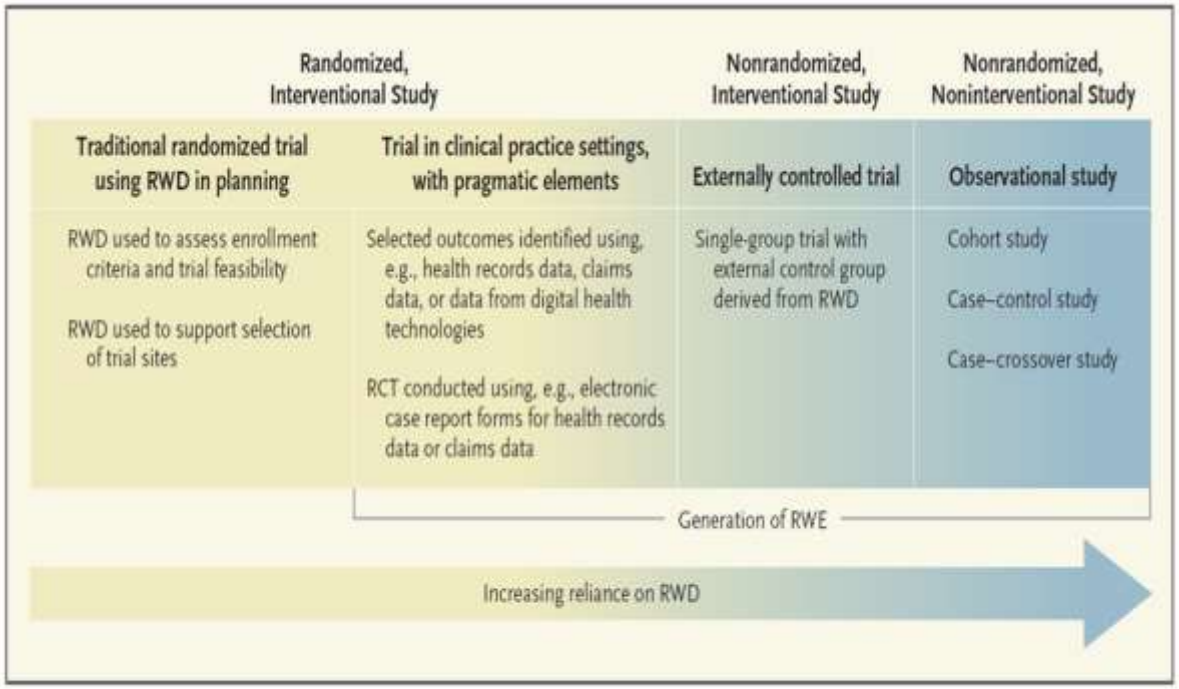
How : with the right CT design ,appropriate ethics and biostatistics to achieve highest possible evidence.

In fact, we cannot eliminate uncertainty.

* DCT : Decentralised Clinical Trial

**CT: Clinical Trial

Increasing reliance on RWD in study designs



Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

n engl j med 386;18 nejm.org May 5, 2022

FDA 2022 Novel Drug approvals: less rigorous evidence-37 approvals- 413 Clinical trials

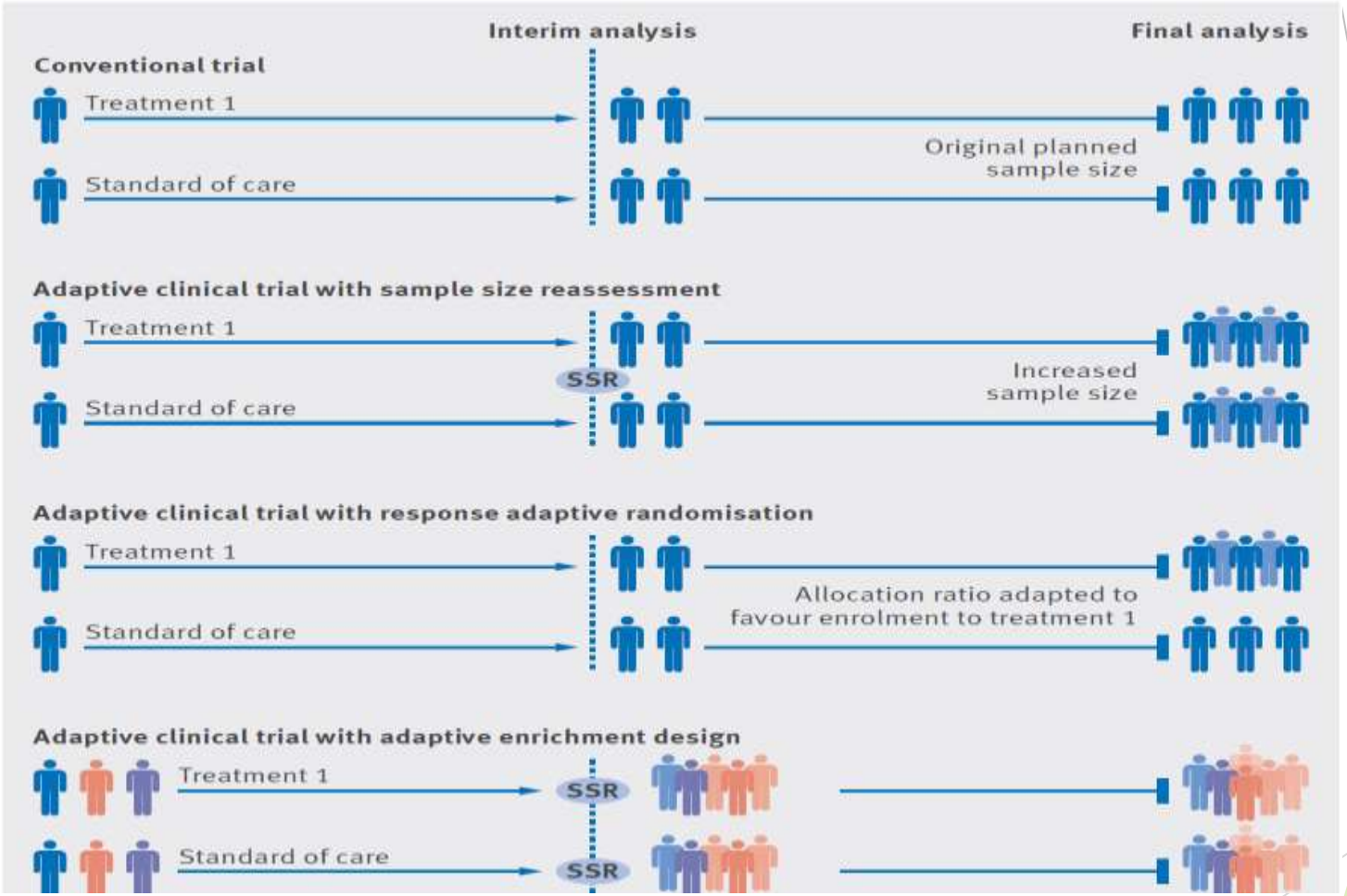
Table. Summary of Frequencies and Percentages From 413 Studies Used to Evaluate the 37 Novel Drugs Approved by the Food and Drug Administration in 2022

Variable	Frequency (%)
Industry sponsored	326 (79)
Randomized clinical trials	227 (55)
Single group design	87 (21)
Completed studies	165 (40)
Results posted	103 (25)
Result posted after approval[a]	24 (23)

Published: August 8, 2023. doi:10.1001/jamanetworkopen.2023.27650 JAMA Network Open. Corresponding Author: Robert M. Kaplan, PhD, Clinical Excellence Research Center, Stanford University

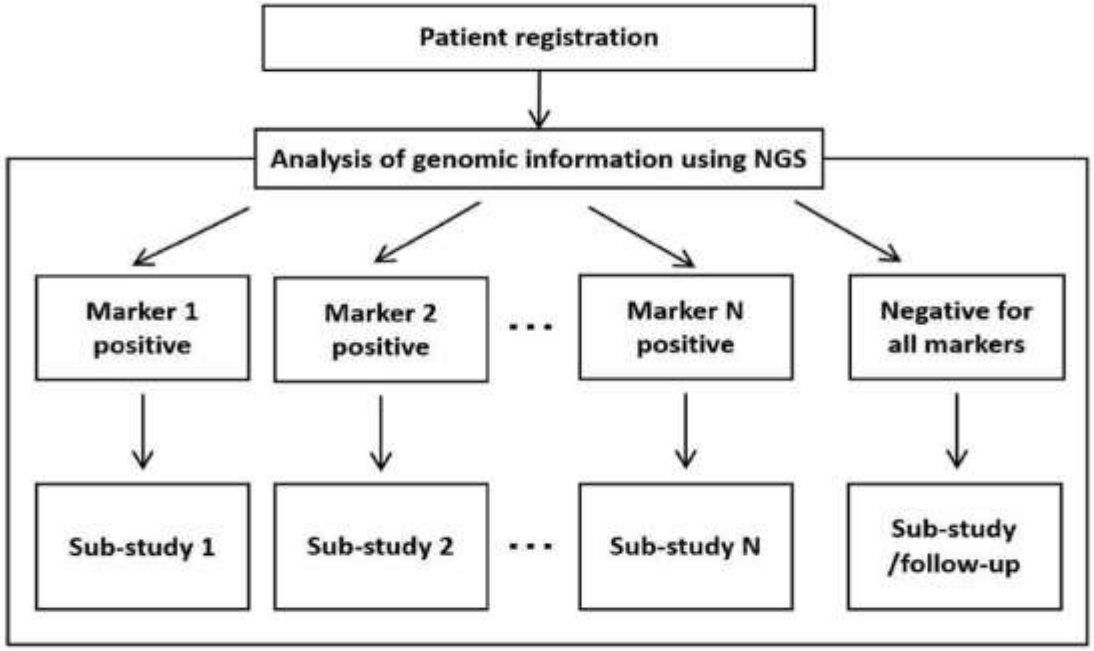
https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2022

Adaptive protocols : Μελέτες Προσαρμοστικού Σχεδιασμού



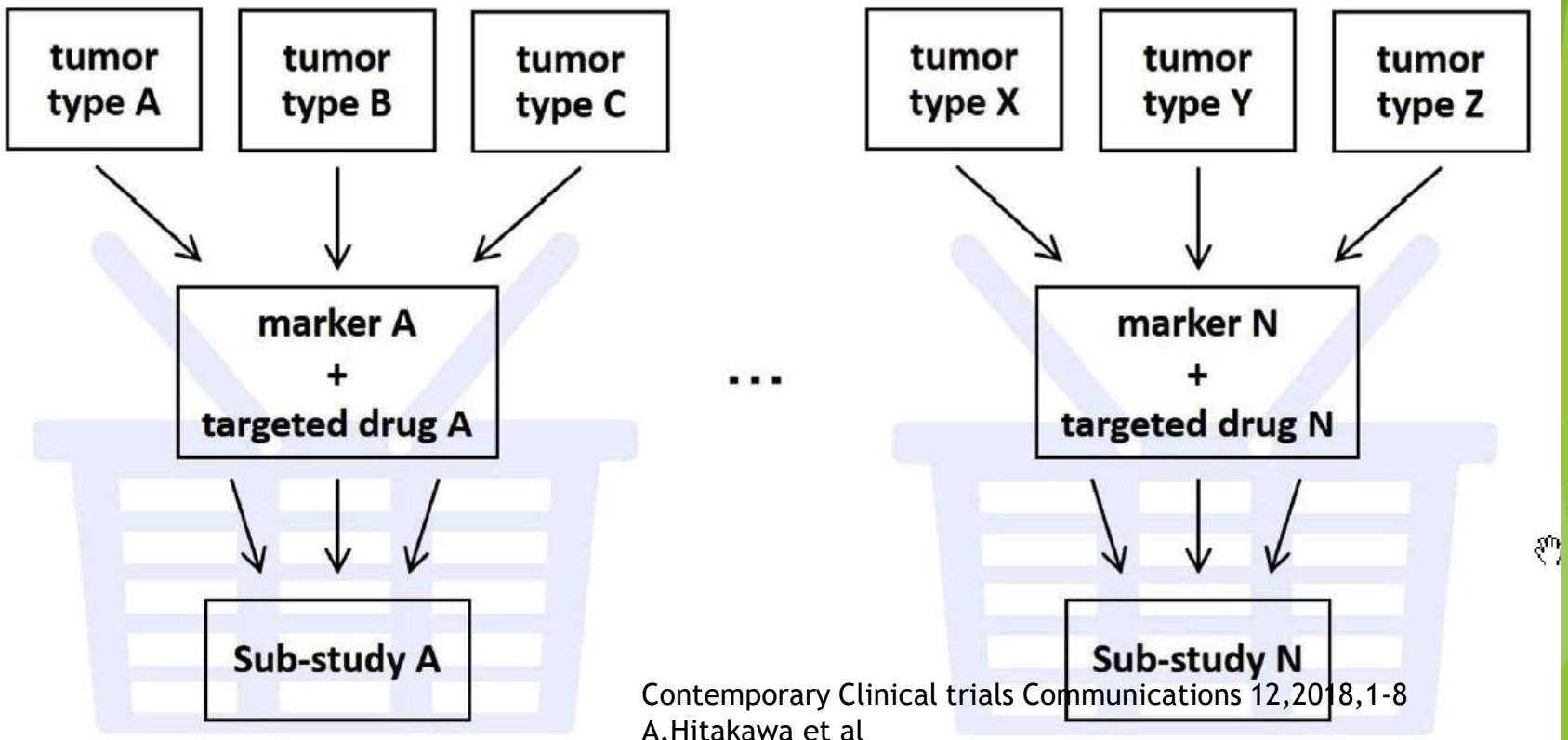
BMJ 2018;360:k698 | bmj

Master protocols -Platform



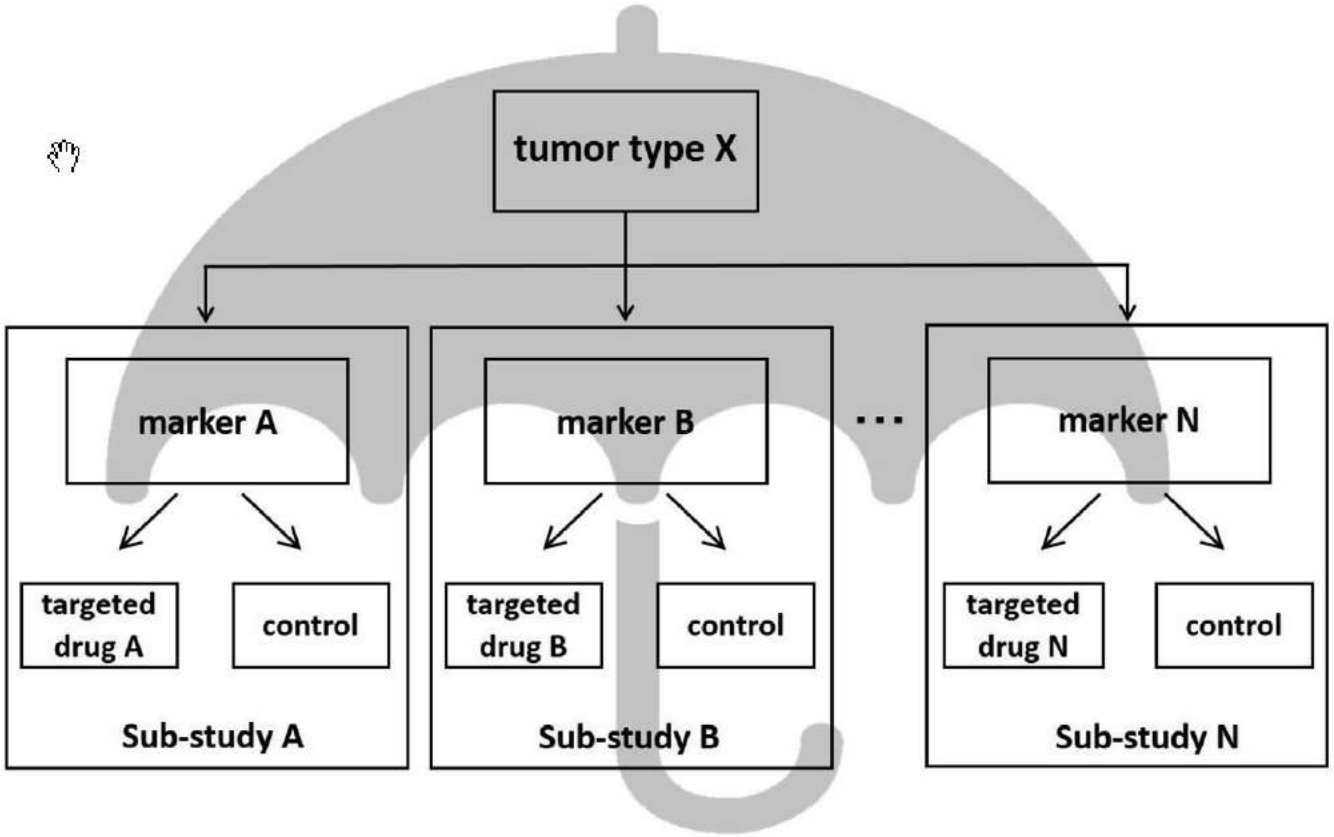
Contemporary Clinical trials Communications 12,2018,1-8
A.Hitakawa et al

Basket protocols



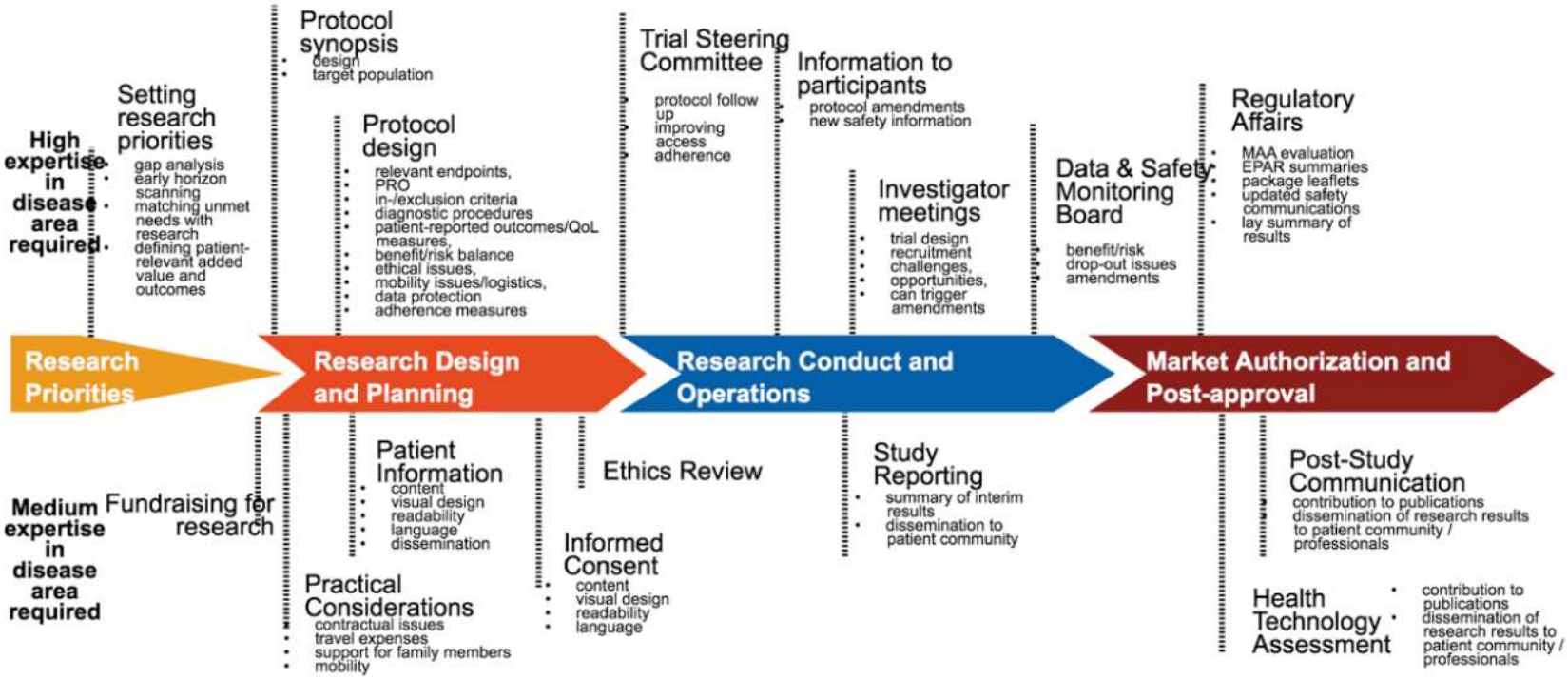
Contemporary Clinical trials Communications 12,2018,1-8
A.Hitakawa et al

Umbrella trials



- Contemporary Clinical trials Communications 12,2018,1-8 A.Hitakawa et al

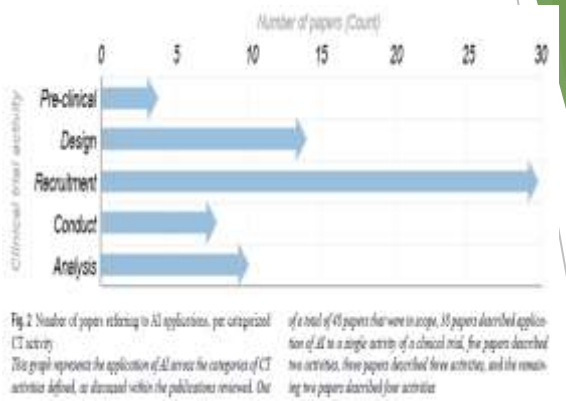
Patient involvement in medicines R&D: a practical roadmap

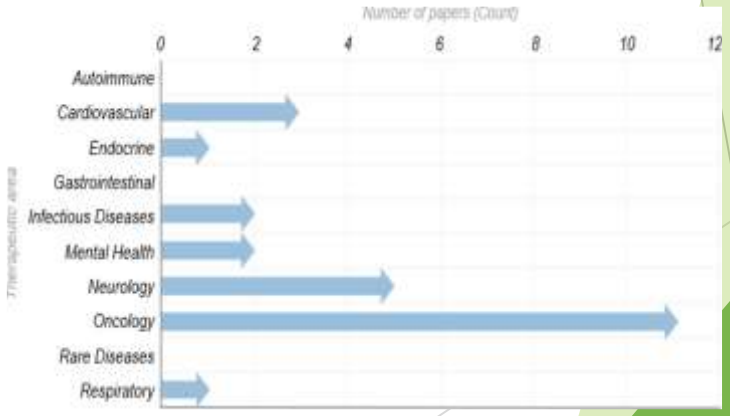


Improving Patient Involvement in Medicines Research and Development: A Practical Roadmap. Geissler, Ryll, Leto, Uhlenhopp, Therapeutic Innovation & Regulatory Science (2017), doi: 10.1177/2168479017706405, and at www.eupati.eu

AI in R&D

Pre-clinical research	*Early use of AI in pre-clinical research, impacting subsequent CTs.*
Design	*Use of AI enabling prediction of outcomes and disease progression to shape or improve Design of CTs.*
Recruitment	*Use of AI in Recruitment, which includes Enrollment, defined as the identification of eligible participants and onboarding them into suitable CTs.*
Conduct	*Use of AI in Conduct refers to the period following a participant's enrollment into the trial, up to the trial database lock, prior to statistical analysis.*
Analysis	*Use of AI in Analysis relates to activities performed by statisticians after a trial has achieved database lock, as part of statistical analysis for the trial.*





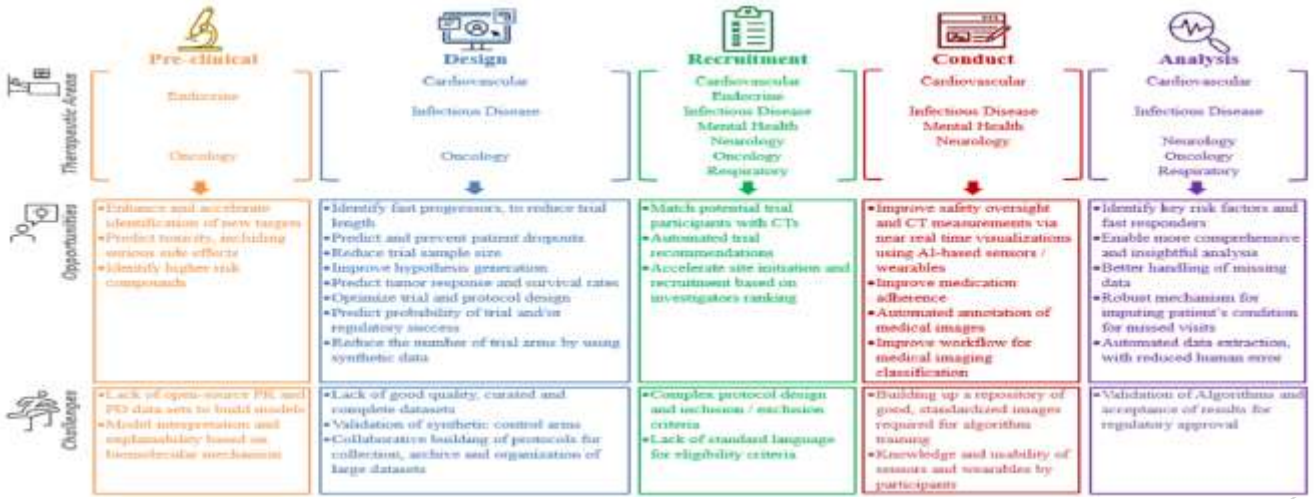
Health Technology,2023, 13, 203-213

Opportunities &Challenges

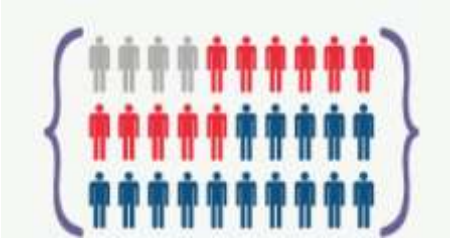
- Health Technology ,2023, 13, 203-213

Table 2 Examples of AI applications within Recruitment

Opportunity	*Therapeutic Area*	*AI application*
Patient selection and access fairness	*Oncology and Cardiovascular*	• Oncology: • Facilitation of cohort selection (e.g., AI technology applied to medical records to ameliorate recruitment and identification of suitable patients) [20, 44] • An AI-enabled clinical decision support system (CDSS) -based on natural language processing of cancer specific values and ML methods- to accurately identify eligible subjects with a high degree of sensitivity and specificity during a retrospective review of four breast cancer focused trials [20, 45] • Cardiovascular: AI ML-based fairness metrics established for the purpose of equity in trial access [21]
Biomarker refinement	*Neurology (Alzheimer) and Amyotrophic Lateral Sclerosis (ALS))*	• In Alzheimer disease: an AI classifier was optimized to detect asymptomatic cases for CT recruitment (otherwise not identified using the biomarker amyloid plagne) [19] • In ALS: It has been shown that a robust ML survival model includes a broader approach to patient inclusion in CTs, by identifying patients that could have still benefitted from a trial despite originally being excluded [18]
Large scale analytics to support trial matching search engine	*Infectious diseases (HIV)*	• Large public database of interventional trials developed using AI, to support a search engine for a trial matching system to be used by HIV patients [22]



Η Επιδημιολογία & Φαρμακοεπιδημιολογία την E&A



Epidemiology*

Prospective

What are tomorrow's medical unmet needs?

- Prevalence
- Incidence
- Population studies

Market Research

- what are the evidence gaps?
- what are the treatment options?

Pharmaco-economics

- Cost effectviness
- Cost benefit
- Cost-utility

Real life= Pharmaco-epi

- Efficacy
- Tolerability
- Proper Use
- Performance

EMA
PASS, PAES

Licensing | Price | Reinscription

Animal Tox — **I** — **II** — **III** — **IV** — **Post-licensing**

12 years

5/10/15 years

FDA postmarketing studies

* Types of Studies

There are four primary types of epidemiology studies. They are:

1. **Cohort studies** — A cohort (group) of individuals with exposure to a chemical and a cohort without exposure are followed over time to compare disease occurrence.
2. **Case control studies** — Individuals with a disease (such as cancer) are compared with similar individuals without the disease to determine if there is an association of the disease with prior exposure to an agent.
3. **Cross-sectional studies** — The prevalence of a disease or clinical parameter among one or more exposed groups is studied, such as:
   - The prevalence of respiratory conditions among furniture makers.
4. **Ecological studies** – The incidence of a disease in one geographical area is compared to that of another area, such as:
   - Cancer mortality in areas with hazardous waste sites as compared to similar areas without waste sites.

Μέρος 2

Πανδημία COVID-19

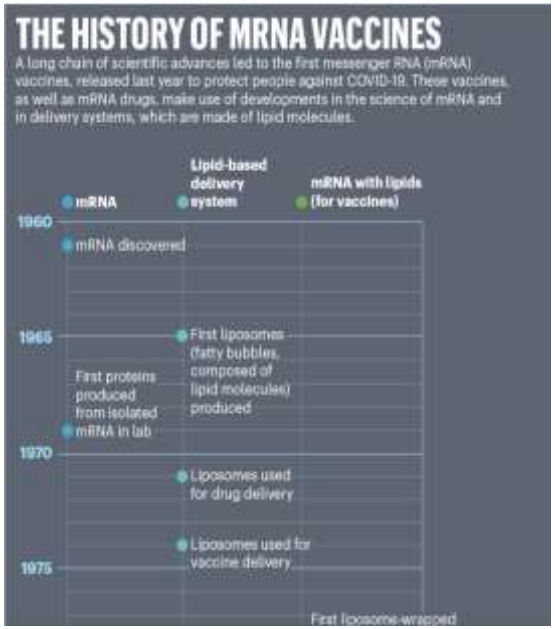
Επιδράσεις στην Ε&Α και ανάπτυξη εμβολίων

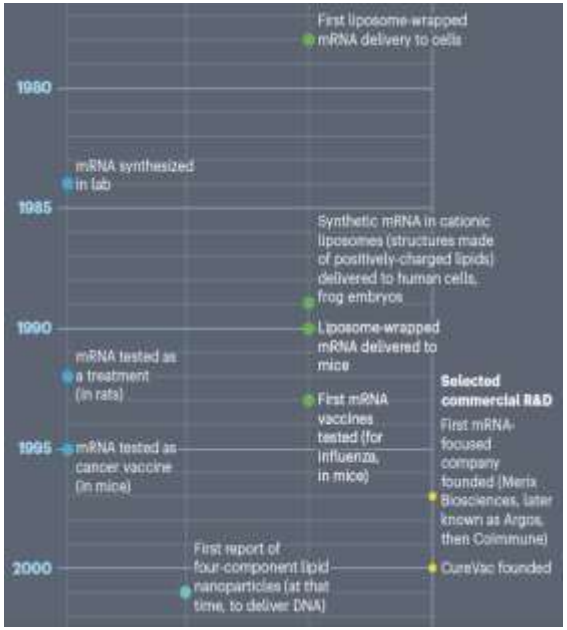
Η πανδημία και ανάπτυξη των εμβολίων έναντι της COVID-19

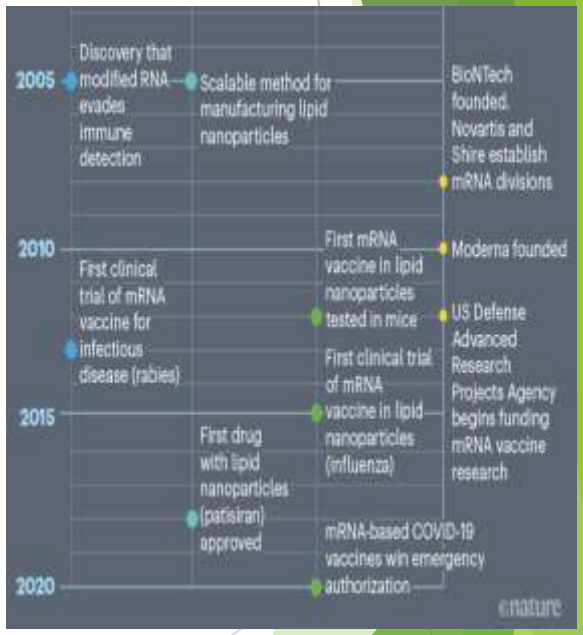
Χρόνοι ανάπτυξης και επιτάχυνση διαδικασιών

- Διαφορές Μοντέλου Ερευνας

Η έρευνα των MRNA εμβολίων ξεκινά το 1960

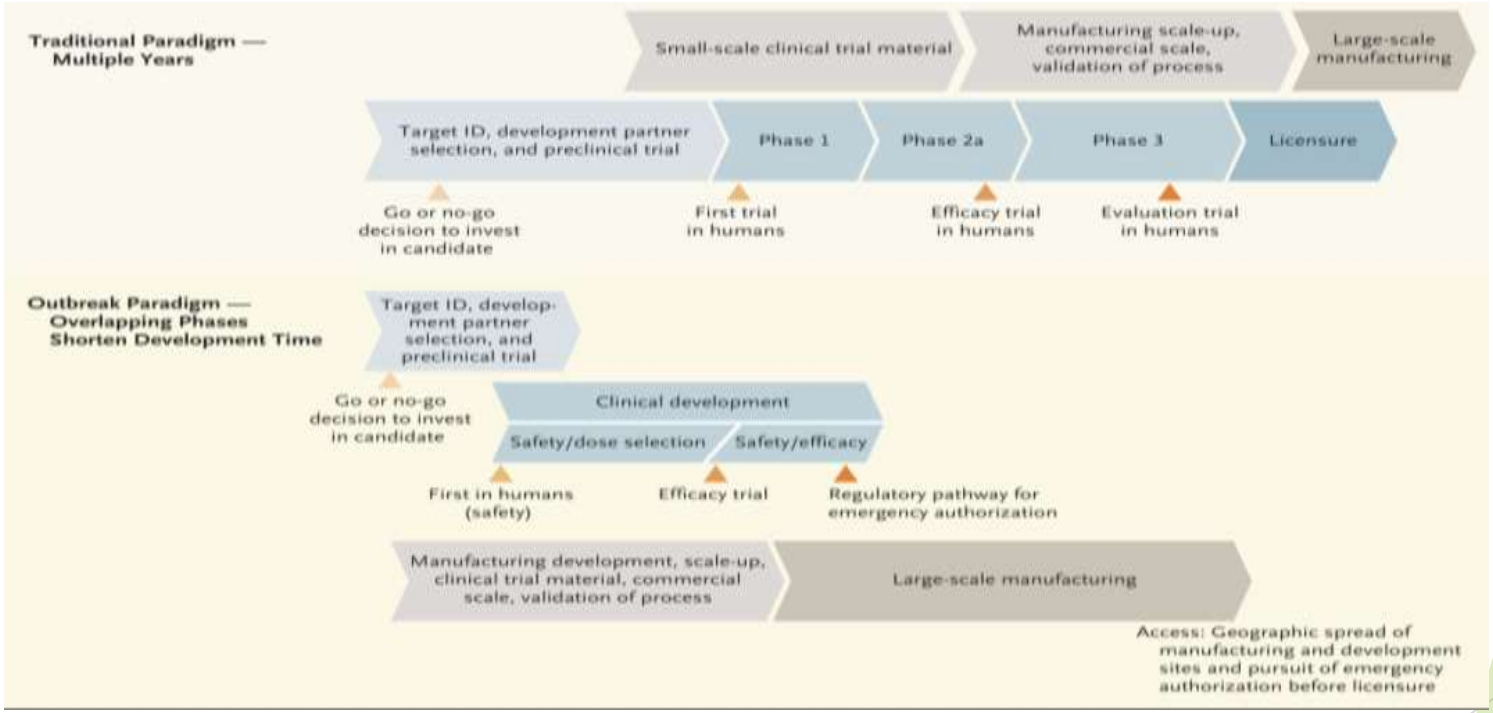






https://www.nature.com/articles/d41586-021-02483 Oct 22, 2021
w?utm_source=Nature+Briefing&utm_campaign=41794890cb-briefing-dy-20210914&utm_medium=email&utm_term=0_c9dfd39373-41794890cb-44721677

R&D paradigm shift with Covid-19



https://www.nejm.org/doi/full/10.1056/NEJMp2005630
NEJM May 2020

Εξαιρετικά πρωτόγνωρη ευρύτατη ερευνητική συνεργασία

- Unprecedented levels of collaboration, information-sharing, innovation
- Permanent adoption of R+D-accelerating COVID-19 measures is a top FDA priority[1]
- Active discussions regarding how to sustain the momentum to ensure rapid vaccine/therapeutic development
- Many lessons learned about the need for better preparedness

World Health Organization

Commitment and call to action: Global collaboration to accelerate new COVID-19 health technologies

A Global Collaboration to Accelerate the Development, Production and Equitable Access to New COVID-19 diagnostics, therapeutics and vaccines

A Happy Exception: The Pandemic Is Driving Global Scientific Collaboration

BY JOSE GUIMON, RAJNEESH NARULA

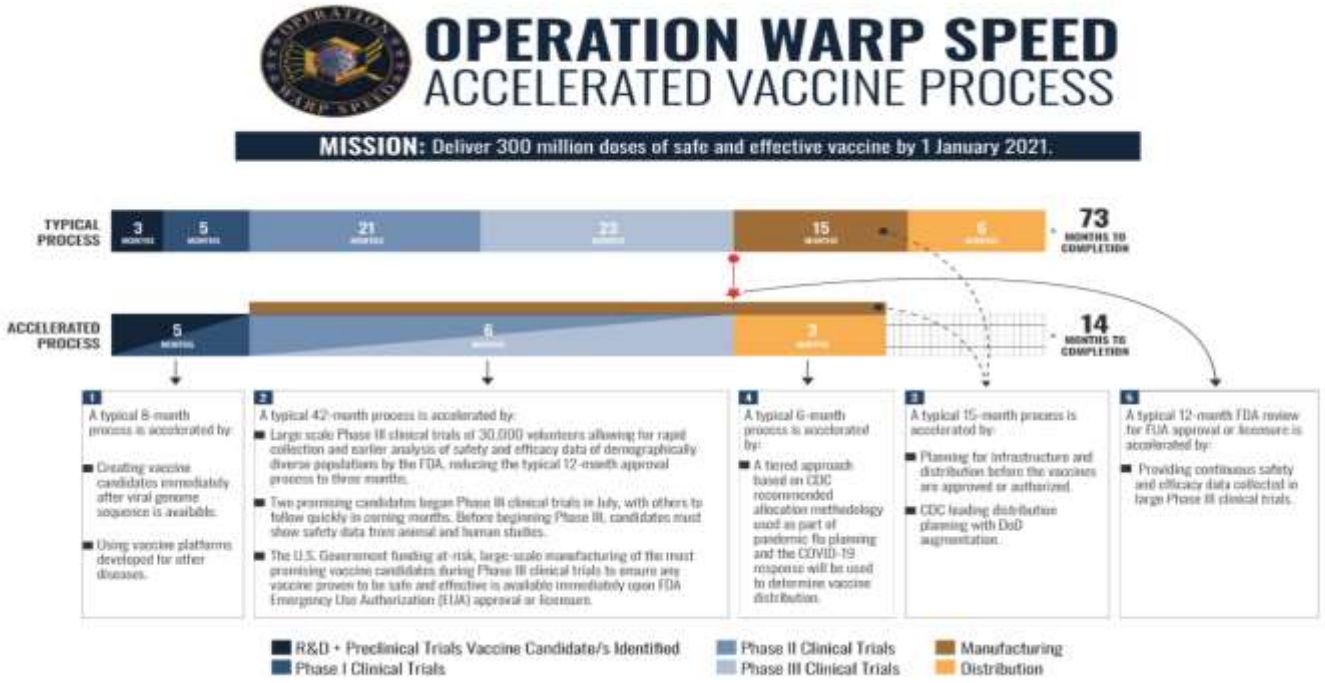
Issues in Science and Technology

COVID-19: Collaboration is the engine of global science – especially for developing countries

World Economic Forum

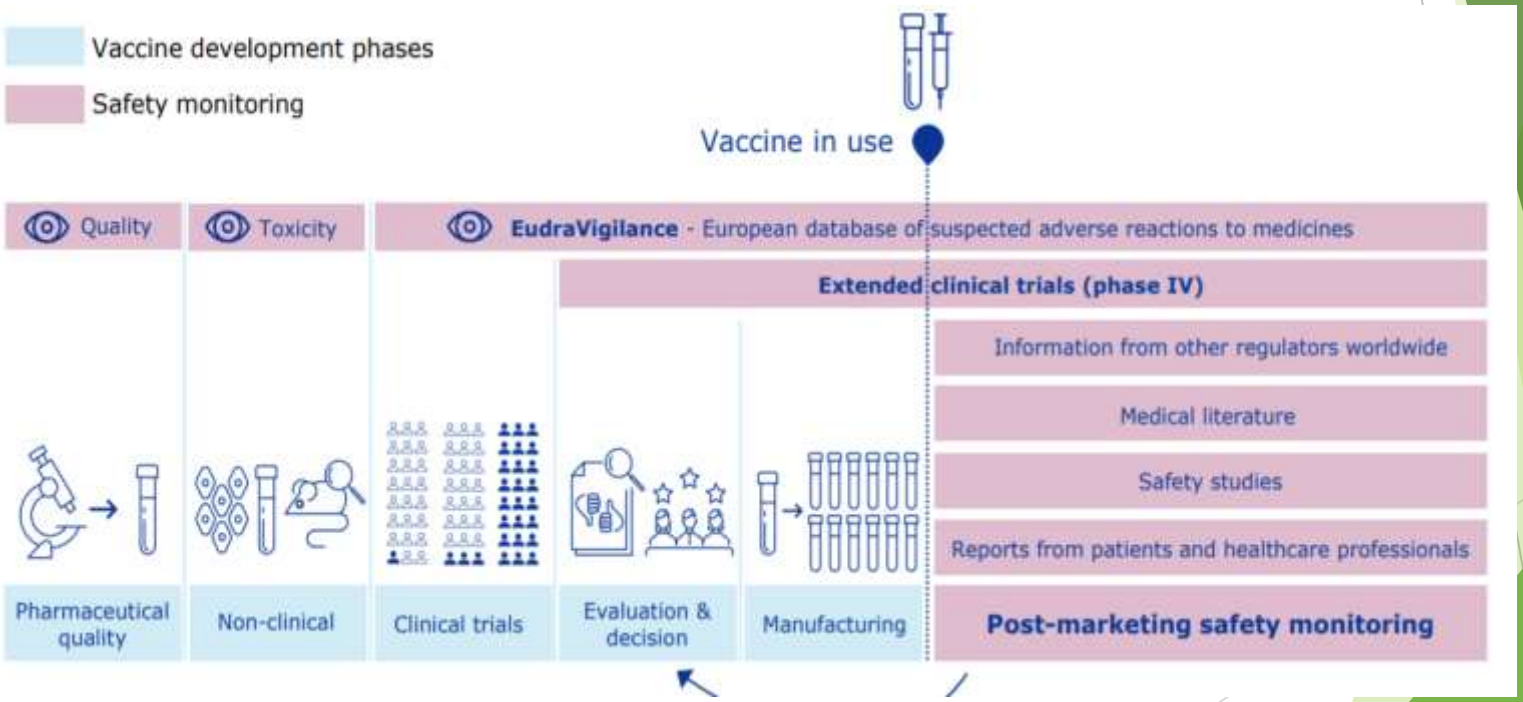
Operations Warp Speed- under NIH

- "Very rapid vaccine development without inappropriate corners cut"



All risk taken is financial, logistical, resourcing and not on safety and efficacy. Bureaucratic obstacles removed and saving time from gaps between phases .

Προεγκριτική και Μετεγκριτική παρακολούθηση ασφάλειας εμβολίων

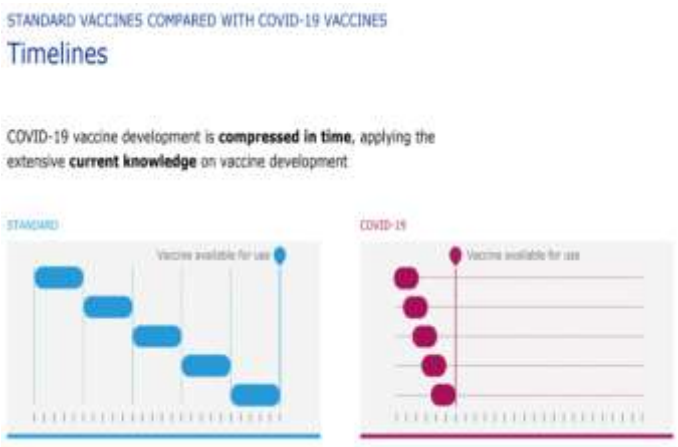


EMA Public Stakeholders Meeting 11/12/2020

Ταχεία ανάπτυξη εμβολίων έναντι COVID-19

- Νέες πλατφόρμες για την παραγωγή εμβολίων είχαν ήδη τεκμηρίωση και προ-κλινικές μελέτες
- Υπερταχεία αλληλούχηση του ιού για την επείγουσα ανάπτυξη αντιγόνων για ενσωμάτωση στα εμβόλια
- Τα στάδια ανάπτυξης των εμβολίων εξελίσσονταν παράλληλα
- Ο επιπολασμός της νόσου ήταν πολύ υψηλός και η νοσηρότητα και θνητότητα απειλητική
- Τάχιστη εθελοντική εισαγωγή/στρατολόγηση ατόμων στις Κλινικές δοκιμές
- Η παραγωγή των εμβολίων εξελισσόταν παράλληλα με την διεξαγωγή των Κλινικών Δοκιμών

EMA Public Stakeholders Meeting
Dec 11, 2020



Παραγωγή των εμβολίων ξεκινά νωρίτερα για να είναι άμεσα διαθέσιμα

STANDARD VACCINES COMPARED WITH COVID-19 VACCINES

Manufacturing

Companies are **expanding** manufacturing and production **capacity** to ensure efficient vaccine deployment

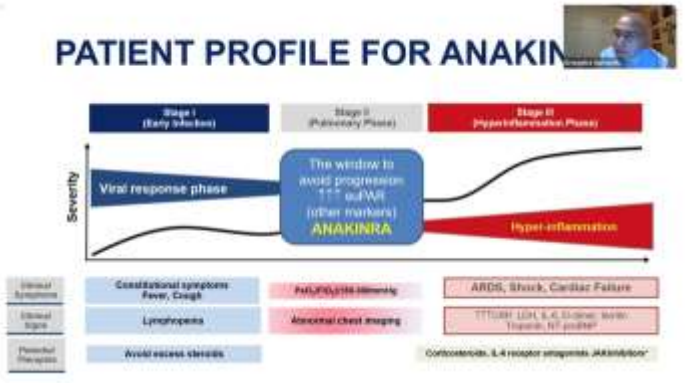
EMA Public Stakeholders Meeting
11/12/2020

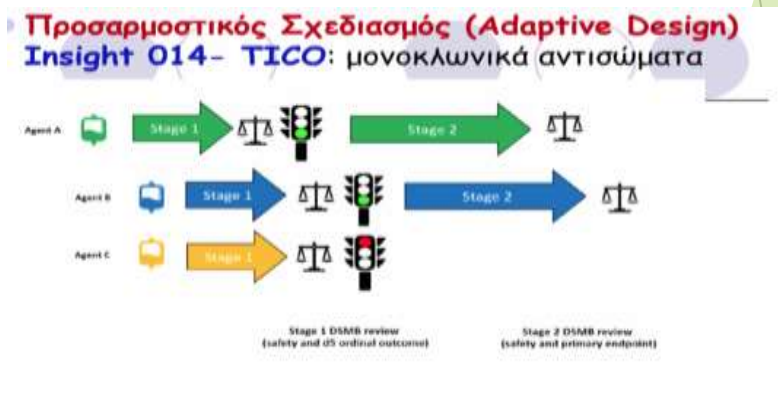
STANDARD

COVID-19

COVID-19 therapies efforts

- WHO Solidarity adaptive trials
- Oxford UK Recovery adaptive tria
- Monoclonal antibodies
- Antiviral Rx
- Repurposing efforts
  - Anakinra





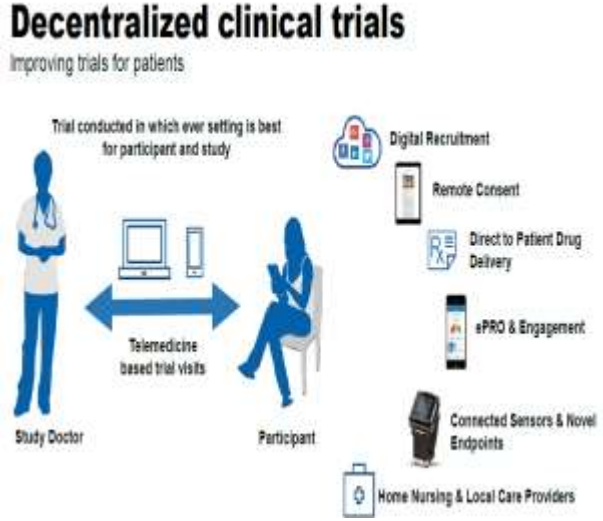
Επιπτώσεις στις κλινικές μελέτες στην διάρκεια της πανδημίας

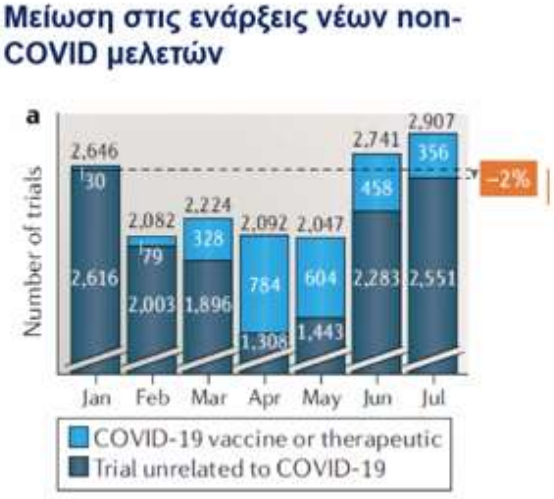
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

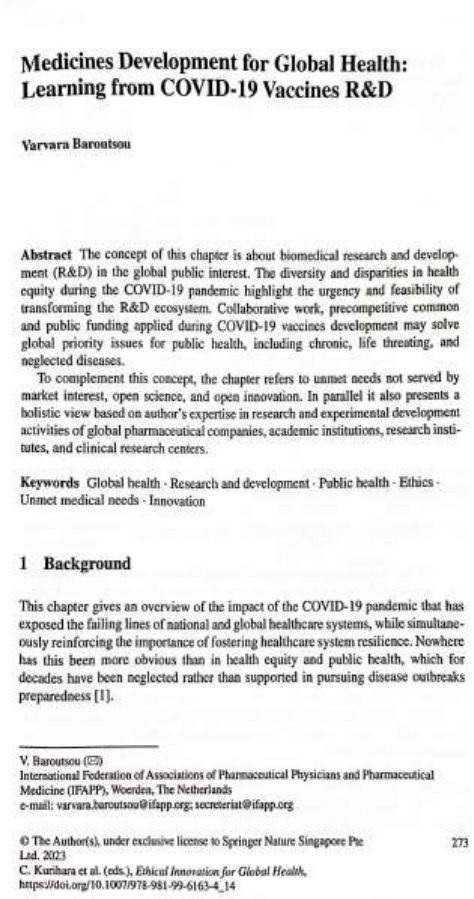
Νέα Πραγματικότητα
Τηλεϊατρική ,Registries, RWE,PROs,
Εξ αποστάσεως μελέτες





Springer Nature Book -My Chapter

- **Ethical innovation for global health: pandemic, democracy and research ethics**
  - Editor: Chieko Kurihara, Japan /Ames Dhai, South Africa /Dirceu Greco, Brazil
  - **Medicines Development for Global Health**
  - **Varvara Baroutsou**
  - Published;
- https://link.springer.com/book/10.1007/978-981-99-6163-4



Medicines Development for Global Health: Learning from COVID-19 Vaccines R&D

Varvara Baroutsou

Abstract The concept of this chapter is about biomedical research and development (R&D) in the global public interest. The diversity and disparities in health equity during the COVID-19 pandemic highlight the urgency and feasibility of transforming the R&D ecosystem. Collaborative work, precompetitive common and public funding applied during COVID-19 vaccines development may solve global priority issues for public health, including chronic, life threating, and neglected diseases.

To complement this concept, the chapter refers to unmet needs not served by market interest, open science, and open innovation. In parallel it also presents a holistic view based on author's expertise in research and experimental development activities of global pharmaceutical companies, academic institutions, research institutes, and clinical research centers.

Keywords Global health · Research and development · Public health · Ethics · Unmet medical needs · Innovation

1 Background

This chapter gives an overview of the impact of the COVID-19 pandemic that has exposed the failing lines of national and global healthcare systems, while simultaneously reinforcing the importance of fostering healthcare system resilience. Nowhere has this been more obvious than in health equity and public health, which for decades have been neglected rather than supported in pursuing disease outbreaks preparedness [1].

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International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP), Woerden, The Netherlands
e-mail: varvara.baroutsou@ifapp.org; secreteriat@ifapp.org

C. Kurihara et al. (eds.), *Ethical Innovation for Global Health*,
https://doi.org/10.1007/978-981-99-6163-4_14

GOOD CLINICAL TRIALS COLLABORATIVE

The Good Clinical Trials Collaborative, established in 2020, is a not-for-profit organization focused on promoting new guidance to enable better randomized controlled trials (RCTs) globally. It is led by Professor Sir Martin Landray, co-architect of the Covid-19 RECOVERY trial and supported by Wellcome and the Bill & Melinda Gates Foundation.

https://www.goodtrials.org/who-we-are/about-good-trials-collaborative/

https://www.goodtrials.org/wp-content/uploads/2023/04/GCTC-guidance-ENG.pdf

Bad Research

- 96 reviews authored by 546 reviewers from 49 Cochrane Review Groups of 1659 trials done in 84 countries.
- Of the 1640 trials providing risk of bias information,
  - 1013 (62%) were high risk of bias (bad), 494 (30%) unclear and
  - 133 (8%) low risk of bias.
- Bad trials were spread across all clinical areas and all countries.
- Well over 220,000 participants (or 56% of all participants) were in bad trials.
- The low estimate of the cost of bad trials was £726 million; our high estimate was over £8 billion.

Pirosca et al. Trials (2022) 23:458
https://doi.org/10.1186/s13063-022-06415-5

Trials

COMMENTARY Open Access

Tolerating bad health research: the continuing scandal

Stefania Pirosca[1], Frances Shiely[2,3], Mike Clarke[4] and Shaun Treweek[1*]

Abstract

Background: At the 2015 REWARD/EQUATOR conference on research waste, the late Doug Altman revealed that his only regret about his 1994 *BMJ* paper 'The scandal of poor medical research' was that he used the word 'poor' rather than 'bad'. But how much research is bad? And what would improve things?

Main text: We focus on randomised trials and look at scale, participants and cost. We randomly selected up to two quantitative intervention reviews published by all clinical Cochrane Review Groups between May 2020 and April 2021. Data including the risk of bias, number of participants, intervention type and country were extracted for all trials included in selected reviews. High risk of bias trials was classed as bad. The cost of high risk of bias trials was estimated using published estimates of trial cost per participant.

We identified 96 reviews authored by 546 reviewers from 49 clinical Cochrane Review Groups that included 1659 trials done in 84 countries. Of the 1640 trials providing risk of bias information, 1013 (62%) were high risk of bias (bad), 494 (30%) unclear and 133 (8%) low risk of bias. Bad trials were spread across all clinical areas and all countries. Well over 220,000 participants (or 56% of all participants) were in bad trials. The low estimate of the cost of bad trials was £726 million; our high estimate was over £8 billion.

We have five recommendations: trials should be neither funded (1) nor given ethical approval (2) unless they have a statistician and methodologist; trialists should use a risk of bias tool at design (3); more statisticians and methodologists should be trained and supported (4); there should be more funding into applied methodology research and infrastructure (5).

Conclusions: Most randomised trials are bad and most trial participants will be in one. The research community has tolerated this for decades. This has to stop: we need to put rigour and methodology where it belongs — at the centre of our science.

Keywords: Randomised trials, Research waste, Risk of bias, Statisticians, Methodologists

Five recommendations: trials should be neither funded (1) nor given ethical approval (2) unless they have a statistician and methodologist; trialists should use a risk of bias tool at design (3); more statisticians and methodologists should be trained and supported (4); there should be more funding into applied methodology research and infrastructure (5).

The WHO guidance lists 12 features needed for strong trials : July 19, 2023

public consultation: ended Sept 15,2023

1. Appropriate trial populations;
2. Robust randomization;
3. Adequate size;
4. Blinding and masking of the intervention(s);
5. Adherence to the trial intervention(s);
6. Completeness of participant follow-up;
7. Relevant measures of outcomes;
8. Proportionate, efficient and reliable data capture;
9. The same outcome assessments for all randomized groups;
10. Statistical analysis;
11. Assessment of beneficial and harmful intervention effects; and
12. Data monitoring for safety and effectiveness.

https://www.who.int/news-room/articles-detail/public-consultation-on-who-guidance-for-best-practices-for-clinical-trials?utm_campaign=pharmalittle&utm_medium=email&_hsmi=267652943&_hsenc=p2ANqtz--uc-i2prVEdGaoixZuVRgrkCElzQBpnvf8G_mNlIZpj52fptrbIkRyikPonlNoKT5cwGM5ztyQ0lzrUIrc6lEI8eGc9Q&utm_content=267652943&utm_source=hs_email

The remit includes, for example:

• **any design for a clinical trial**: including comparisons of two or more interventions (one of which may be to provide no additional active intervention beyond usual practice/standard care); blinded or not; parallel, cluster, crossover or other design;

• **any health intervention:** including (but not limited to) pharmaceutical and biological therapies; use of medical devices; surgical procedures; vaccination; nutritional measures; cognitive, behavioural and psychological interventions; physical therapy interventions; digital and public health approaches;

- **any purpose:** including (but not limited to) guidelines processes; recommendations for clinical practice or public health strategies; health technology assessments – there is some relevance to regulatory submissions noting the central role of the guidance issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which this document does not replace;
- **any setting:** any geographical, economic or societal context; and any context including clinical trials based in hospital, primary care or community settings; or where the intervention is delivered directly to participant
- **any role:** including researchers and clinicians; patient and public groups (including trial participants); regulators and other national health authorities; ethics committees and institutional review boards; research funders; trial sponsors (both academic and commercial).

Important clinical trials requirements

Declaration of Helsinki (DoH): High Level Ethical Principles

CIOMS* Guidelines : Implementation Guidelines

ICH** Documents : Professional Standards

*Council for International Organizations of Medical Sciences (CIOMS)
**International Conference Harmonisation (ICH)

Declaration of Helsinki

- Ethical principles for medical research involving human subjects
- ***Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:***
  29th WMA General Assembly, Tokyo, Japan, October 1975
  35th WMA General Assembly, Venice, Italy, October 1983
  41st WMA General Assembly, Hong Kong, September 1989
  48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
  52nd WMA General Assembly, Edinburgh, Scotland, October 2000
  53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
  55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
  59th WMA General Assembly, Seoul, Republic of Korea, October 2008
  64th WMA General Assembly, Fortaleza, Brazil, October 2013

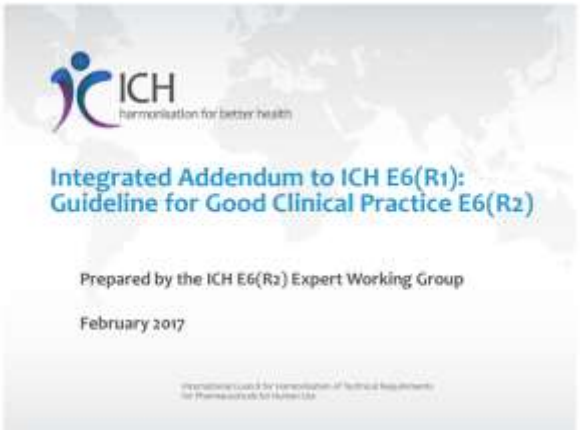
WORLD MEDICAL ASSOCIATION

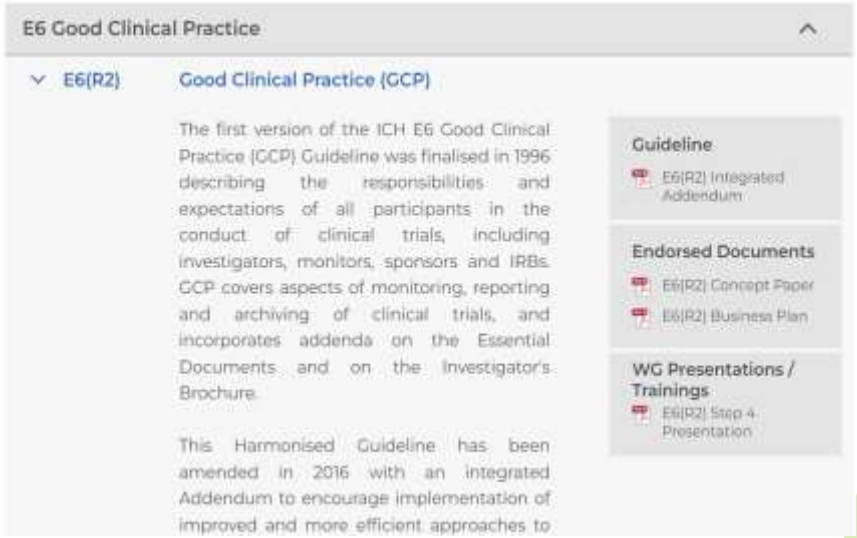
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

ICH Guidelines

- E1 Clinical Safety for Drugs used in Long-Term Treatment
- E2A - E2F Pharmacovigilance
- E3 Clinical Study Reports
- E4 Dose-Response Studies
- E5 Ethnic Factors
- E6 Good Clinical Practice
- E7 Clinical Trials in Geriatric Population
- E8 General Considerations for Clinical Trials
- E9 Statistical Principles for Clinical Trials
- E10 Choice of Control Group in Clinical Trials
- E11 - E11A Clinical Trials in Pediatric Population
- E12 Clinical Evaluation by Therapeutic Category
- E14 Clinical Evaluation of QT
- E15 Definitions in Pharmacogenetics / Pharmacogenomics
- E16 Qualification of Genomic Biomarkers
- E17 Multi-Regional Clinical Trials
- E18 Genomic Sampling
- E19 Safety Data Collection
- E20 Adaptive Clinical Trials
- E21 Inclusion of Pregnant and Breastfeeding Individuals in Clinical

https://www.ich.org/page/efficacy-guidelines





https://database.ich.org/sites/default/files/E6_R2_Step_4_Presentation_0.pdf

ICH Reflection on "GCP Renovation": Modernization of ICH E8 and Subsequent Renovation of ICH E6

ICH is inviting public review and comment on a reflection paper on Good Clinical Practice (GCP) "Renovation", which contains the ICH proposal for further modernization of the ICH Guidelines related to clinical trial design, planning, management, and conduct. The scope of the proposed renovation includes the current E8 General Considerations for Clinical Trials and further revision to the E6 Guideline for Good Clinical Practice, which is already undergoing modernization with the recent production of ICH E6(R2).

The reflection paper is available for download via the following link:

- Reflection paper on GCP Renovation

The goal of the potential renovation is to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of study types and data sources that are being employed to support regulatory and other health policy decisions, as appropriate. The underlying principles of human subject protection and data quality would remain. ICH's decision to invite stakeholder comment on the

E6(R3) EWG Good Clinical Practice (GCP)

This topic was endorsed by the ICH Assembly in June 2019.

ICH E6(R3) Principles, Annex 1 and Annex 2

The E6(R3) EWG is working on the revision of the E6(R2) Guideline *"Good Clinical Practice"* (GCP) with a view to addressing the application of GCP principles to the increasingly diverse trial types and data sources being employed to support regulatory and healthcare related decision-making on drugs, and provide flexibility whenever appropriate to facilitate the use of technological innovations in clinical trials. Additional information may also be found in ICH Reflection Paper on *"GCP Renovation"* on the ICH Reflection Paper page. When complete, E6(R3) will be composed of an overarching principles and objectives document, Annex 1 and Annex 2.

While the original E6(R3) Concept Paper stated that before the drafting of Annex 2, its

Guideline
- E6(R3) Draft Guideline

Guidance for Stakeholder Public Consultation
- E6(R3) Guideline Availability Notice
- E6(R3) Explanatory Video
- E6(R3) Stakeholder Engagement

Endorsed Documents
- E6(R3) Concept Paper
- E6(R3) Annex 2 Concept Paper
- E6(R3) Business Plan
- E6(R3) Work Plan

WG Presentations/ Trainings
- E6(R3) Step 2 Presentation

https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step%202_Presentation_2023_0613.pdf

Μέρος 3

Ρυθμιστικό πλαίσιο στην Ευρωπαική Ενωση και την Ελλάδα

Clinical Trials in the EU – what has changed over time?

…Before May 2004

National rules, different processes/requirements for authorisation in each EU Member States

…resulted in delays and

…Directive 2001/20/EC

(since 1 May 2004)

First step to harmonise processes and requirements for clinical trial authorisations

Introduction of e-application form

…Regulation (EU) No. 536/2014

(published May 2014)

Full harmonisation and combined assessment of multinational trials (after full functionality of the EU portal and EU database)

e-submission

Διεθνώς το Πρόβλημα είναι :

- 80% των ΚΔ καθυστερούν λόγω μη επαρκούς εισαγωγής κατάλληλων ασθενών
- 30% των ασθενών διακόπτουν την συμμετοχή τους στις ΚΔ
- 85% των ΚΔ δεν επιτυγχάνουν τον προβλεπόμενο αριθμό ασθενών
- 70 % των συμμετεχόντων ζουν σε απόσταση > 2ωρών από το κέντρο της ΚΔ

Κλινικές Δοκιμές: ΚΔ

Regulators considering new ways of evidence generation and ways of decision-making

- **IMI/IHI:** *Novel designs (including endpoints), patient-centric conduct, infrastructure, and capability to modernize clinical trials*

- **Modernizing Clinical Trial Conduct (MCTC):** *Develop practical guidance and solutions to implement modern approaches to ensuring clinical trial continuity*

- **Digital Endpoints Ecosystem & Protocols:** *Facilitate the development of novel clinical endpoints for clinical trials, and standardize digital measure*

European Parliament

Artificial Intelligence Act: deal on comprehensive rules for trustworthy AI

Press Releases IMCO LIBE 09-12-2023 - 00:04

For boosting innovation and making Europe a leader in the field.

- Safeguards agreed on general purpose artificial intelligence
- Limitation for the of use biometric identification systems by law enforcement
- Bans on social scoring and AI used to manipulate or exploit user vulnerabilities
- Right of consumers to launch complaints and receive meaningful explanations
- Fines ranging from 35 million euro or 7% of global turnover to 7.5 million or 1.5% of turnover

MEPs reached a political deal with the Council on a bill to ensure AI in Europe is safe, respects fundamental rights and democracy, while businesses can thrive and expand.

Further information

> Committee on the Internal Market and Consumer Protection

> Committee on Civil Liberties, Justice and Home Affairs

Μέρος 4

Συμπεράσματα

Συζήτηση

Συμπερασματικά

- Μεταφραστική έρευνα- πανεπιστημιακά κέντρα
- Επιδημιολογική έρευνα για τα χρόνια νοσήματα και προτεραιότητες στην έρευνα
- Ενίσχυση Μητρώων Ασθενών- Χρήση (EMR) ΑΗΦΥ ή εθνικό ηλεκτρονικό φάκελο Υγείας
- RWD – RWE για την διαμόρφωση τοπικών οδηγιών
- Διασύνδεση με διεθνή και τοπικά Δίκτυα Ερευνητών
- Συμμετοχή σε Consortia με Βιοφαρμακευτική και Ιατροτεχνολογική έρευνα , μη κερδοσκοπικούς φορείς & ευρωπαϊκούς φορείς,& ενώσεις ασθενών
- Συνεχιζόμενη εκπαίδευση των ερευνητών
- Κουλτούρα διαχείρισης αλλαγών και καινοτομίας

- Σας ευχαριστώ πολύ για την προσοχή σας
- varvara.baroutsou@ifapp.org

- https://www.linkedin.com/company/65277832/admin/feed/posts/