NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES

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The WHO action plan to improve clinical trials and implications for family medicine and primary care in sub-Saharan Africa

Chris Butler
Professor of Primary Care, University of Oxford
Clinical Director, Primary Care Clinical Trials Unit

PRIMAFAMED
25 June 2025

NIHR | National Institute for Health Research

Inverse funding and potential health gain law

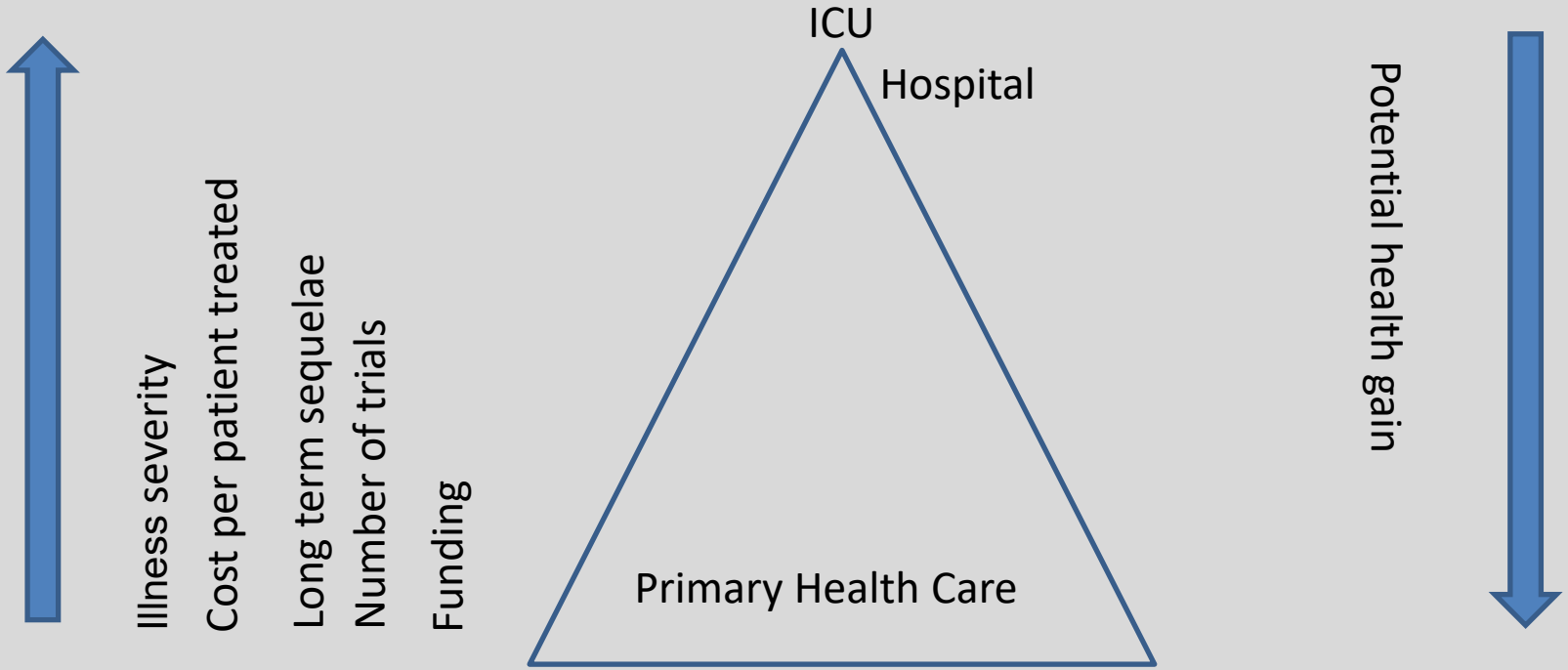
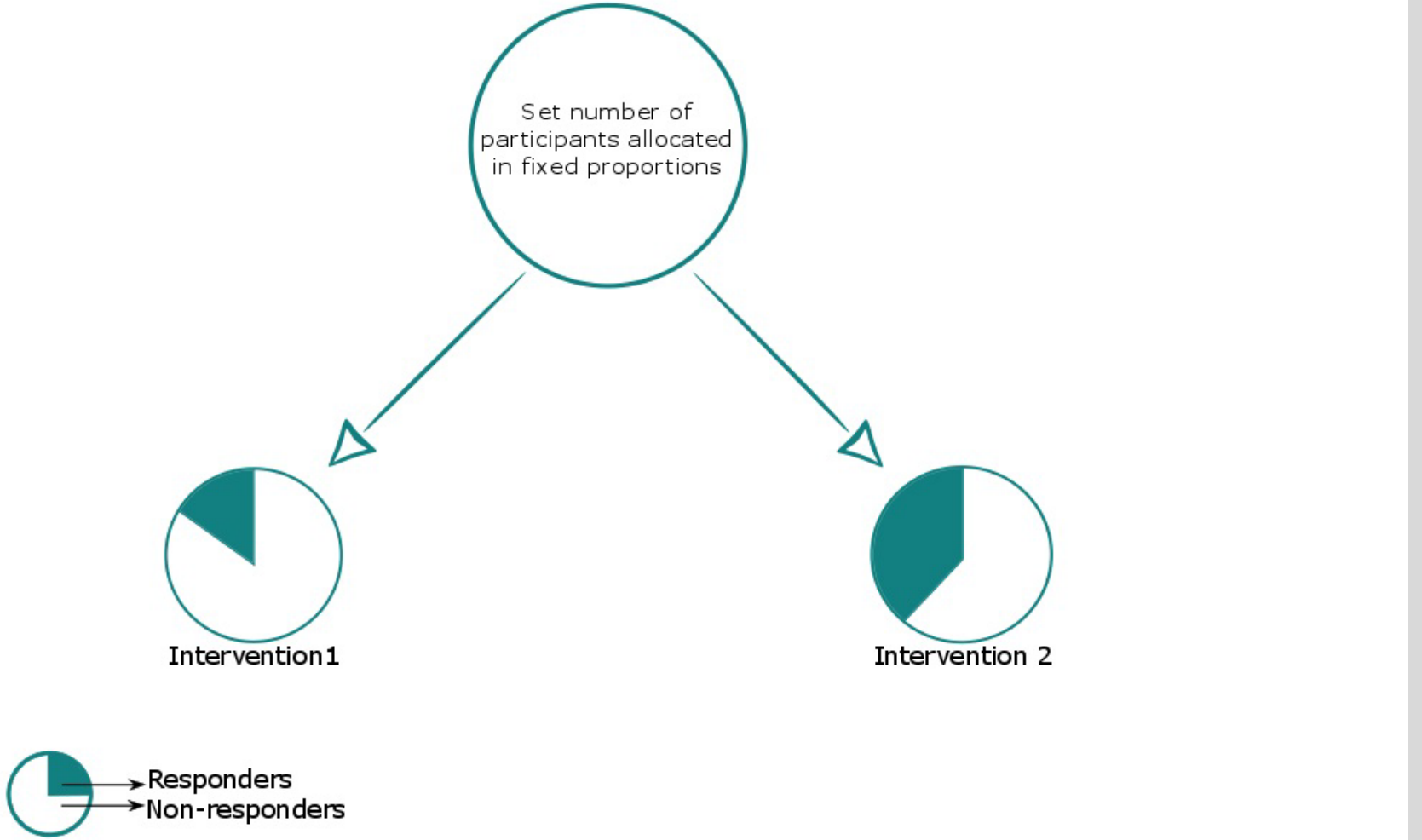


Figure 1: The two arm, fixed proportion allocation Trial: What is the average effect?



World Health Assembly Resolution 75.8 on strengthening clinical trials..

World Health Organization

SEVENTY-FIFTH WORLD HEALTH ASSEMBLY
Agenda item 16.2

WHA75.8
27 May 2022

Strengthening clinical trials[1] to provide high-quality evidence on health interventions and to improve research quality and coordination

The Seventy-fifth World Health Assembly,

Recalling resolutions WHA58.34 (2005) acknowledging that high-quality, ethical research and the generation and application of knowledge are critical in achieving internationally agreed health-related development goals, WHA63.21 (2010) outlining WHO's role and responsibilities in health research, WHA66.22 (2013) and WHA69.23 (2016) on the follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, WHA67.20 (2014) on regulatory system strengthening for medical products, WHA67.23 (2014) on health intervention and technology assessment in support of universal health coverage, WHA74.6 (2021) on strengthening local production of medicines and other health technologies to improve access, and WHA74.7 (2021) on strengthening WHO preparedness for and response to health emergencies, which notes the importance of basic and clinical research and recognizes the critical role of international collaboration in research and development, including in multicountry clinical and vaccine trials, as well as rapid diagnostics test and assay development, while acknowledging the need for further rigorous scientific evidence;

- "…that clinical trials on new health interventions are likely to produce the clearest result when carried out in diverse settings, including all major population groups the intervention is intended to benefit, with a particular focus on under-represented populations"

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Julian Tudor Hart: Clinician and clinical scientist

The Lancet · Saturday 27 February 1971

THE INVERSE CARE LAW

JULIAN TUDOR HART

Glyncorrwg Health Centre, Port Talbot, Glamorgan, Wales

Summary The availability of good medical care tends to vary inversely with the need for it in the population served. This inverse care law operates more completely where medical care is most exposed to market forces, and less so where such exposure is reduced. The market distribution of medical care is a primitive and historically outdated social form, and any return to it would further exaggerate the maldistribution of medical resources.

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Patient's agency

The abilities and capabilities of patients to act, contribute, influence and make decisions within the healthcare system in which they find themselves.

Five components of health care improvement

WHO: Guidance for best practices for clinical trials

1. Measuring the magnitude and distribution of the health problem;
2. Understanding the diverse causes or the determinants of the problem, whether they are due to biological, behavioural, social or environmental factors;
3. Developing solutions or interventions that will help to prevent, mitigate or cure the problem;
4. Implementing or delivering solutions through policies and programmes; and
5. Evaluating the impact of these solutions on the level and distribution of the problem.

Patients and public should contribute all along this line

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Patient's agency in health care improvement limited by

- Inadequate patients/public inclusion in all 5 phases of research
- Limited representation of intended-use population
- Mismatch between problem prevalence and where research is done
- Inability to think beyond inefficient single question trials and consider other designs e.g., adaptive platform studies
- Prioritisation of *studies for profit* over *systems strengthening studies for health gain* (inequity by indication)
- Disproportionate regulation that makes researchers, HCPs and patients walk through glue to contribute
- Requirements for patient information limit informed consent and frightens people off (*50-page PILs 20-clause ICFs*)

Cont.: Patient's agency in health care improvement limited by

- Addiction to placebo-control, rather than 'standard of care' as comparator. Q=What is the effect of adding in this intervention over and above best practice vs. performance against an inert version? (No routine use of placebos in PHC)
- Limited acceptance of self sampling by regulators and reviewers despite evidence of adequate equivalence with HCP sampling
- Poor understanding of probability by regulators, editors and guideline developers
- Inflexible delivery protocols (PHC is a distributed, complex adaptive system)
- Inefficient and disproportionate contracting!!!!
- Data protection that undermines patient autonomy (can't access records for eligibility check and seamless follow-up using routinely collected data and even with patient signed consent)
- Requirement for individual consent in comparative effectiveness studies
- Trying to ensure "quality by inspection" rather than "quality by design" (Martin Landray)

Case Study 1: STRETCH

Articles

Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa (STRETCH): a pragmatic, parallel, cluster-randomised trial

Lara Fairall, Max O Bachmann, Carl Lombard, Venessa Timmerman, Kerry Uebel, Merrick Zwarenstein, Andrew Boulle, Daniella Georgeu, Christopher J Colvin, Simon Lewin, Gill Faris, Ruth Cornick, Beverly Draper, Mvula Tshabalala, Eduan Kotze, Cloete van Vuuren, Dewald Steyn, Ronald Chapman, Eric Bateman

- Question arose from patient activism and agency
- Embedded in routine systems
- No individual consent
- Routinely collected data as follow up
- Results embedded into routine care, strengthening PHC system
- Influenced policy to save many lives

***Panel 2:* Innovation in HIV care delivery**

The Streamlining Tasks and Roles to Expand Treatment and Care for HIV trial addressed the urgent problem in South Africa of high mortality and morbidity among people with HIV whose initiation of antiretroviral treatment (ART) was delayed by shortages of doctors authorised to prescribe it. The trial evaluated a complex intervention comprising nurse initiation and monitoring of ART (NIMART), supported by a clinical decision guide, staff training, organisational strengthening, and managerial and clinical support. The trial was conducted in all 31 primary health-care clinics that provided ART in one province, 16 of which were randomised to receive the intervention. Use of electronic medical records to identify eligible participants and measure outcomes enabled rapid recruitment of over 15 000 participants and completion of the trial in 2 years. With research ethics committee approval, participants' consent was not sought because it was not feasible and because it would not affect the care individuals received. The trial showed that the intervention did not affect mortality or virological suppression but was associated with better health and HIV programme outcomes. These improvements were despite unanticipated real-world problems including some intervention clinics being unable to deliver NIMART, and a temporary moratorium on ART initiation because of financial restrictions. The trial results coincided with and supported the change of national policy on NIMART, leading to rapid expansion of ART to millions of people with HIV in South Africa, and task shifting in HIV care in other low-income and middle-income countries. Policy relevance and effect was strengthened by long-standing engagement between the researchers and provincial and national health departments, with senior government officials represented on the trial steering committee. This primary care trial exemplifies pragmatic design, efficient use of medical records, appropriate ethical regulation, and timely production of results to influence policy.[23]

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Case study 2: PRINCIPLE and PANORAMIC trials of community treatment for COVID-19: Innovation in

Trial design: adaptive platform trial

Implementation: taking trials research to the peole

Impact: affected guidelines worldwide

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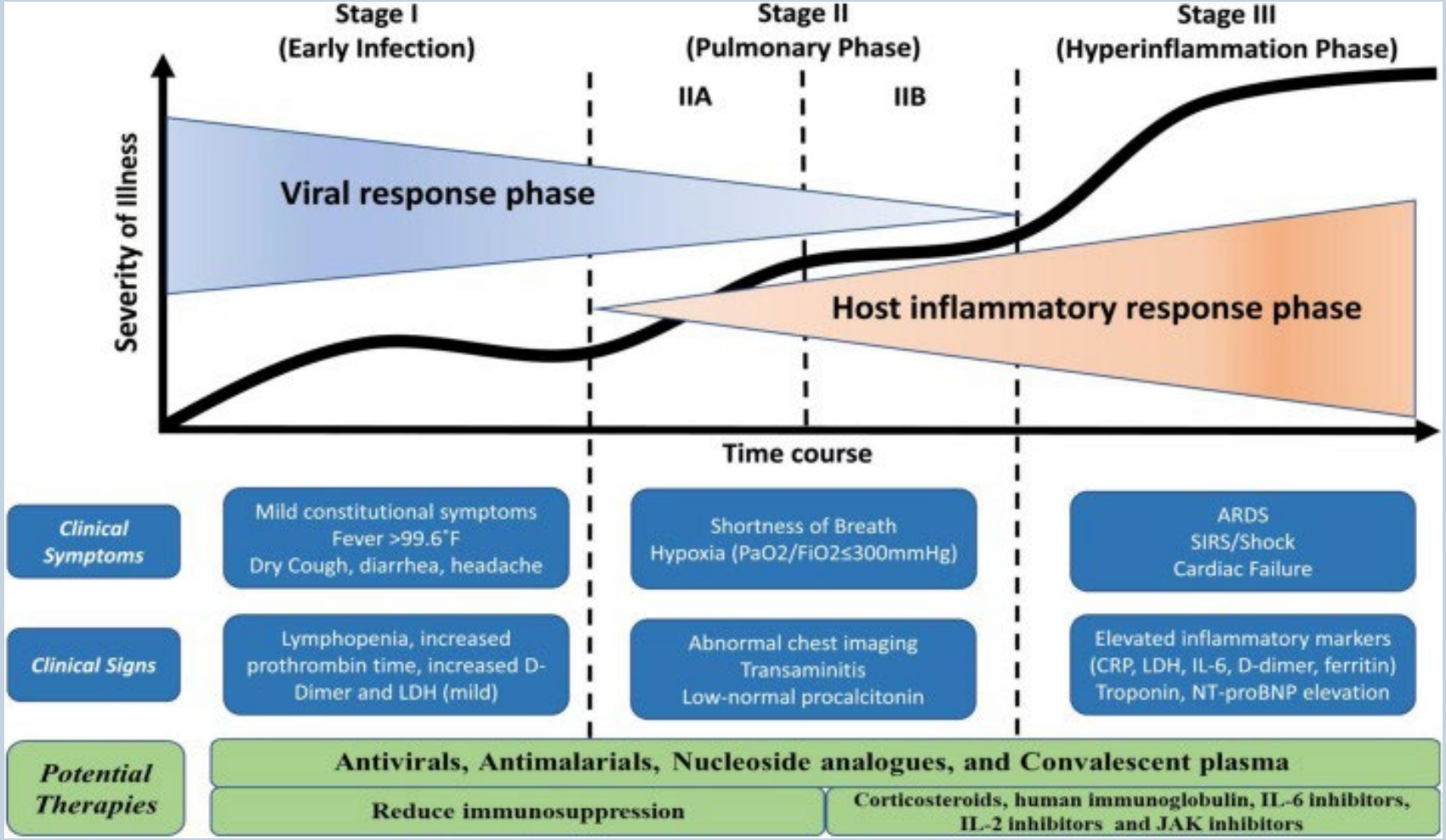
”Hand me down evidence” from hospitals to primary care particularly inappropriate in primary care



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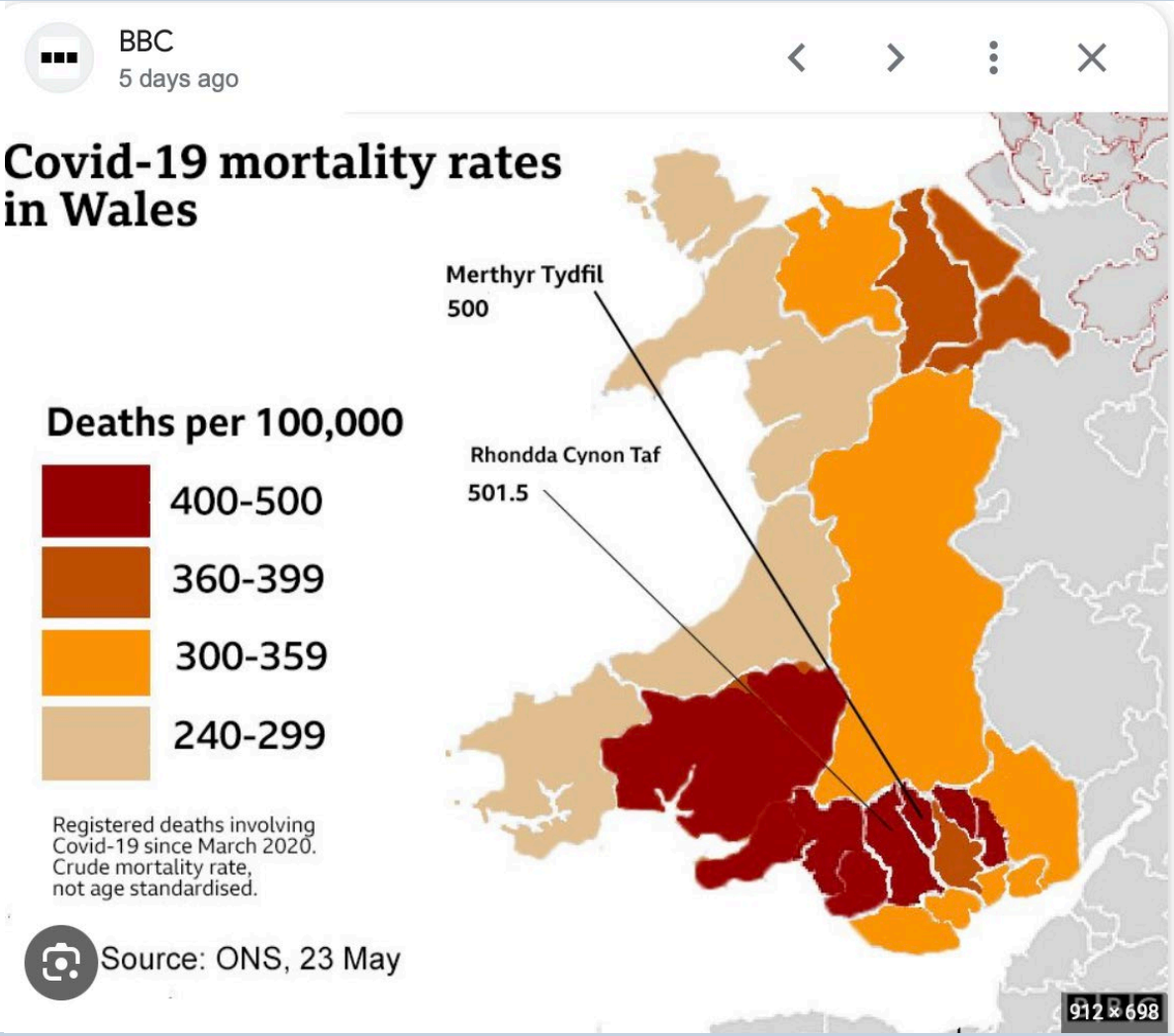
Nile, Cytokine & Growth Factor Reviews Volume 53, June 2020, Pages 66-70

Health inequalities: Deprivation and poverty and COVID-19

The unequal impact of the coronavirus in our communities can be measured by rates of mortality among the most deprived. Deprivation underpins almost all inequalities.

Eas

Office for National Statistics (ONS) data shows that people who live in the most deprived areas of England and Wales are around twice as likely to die after contracting COVID-19. The data released in August 2020, when cases and mortality rates were relatively low reveal that in England, the age-standardised mortality rate for deaths involving COVID-19 in the most deprived areas in July 2020 was 3.1 deaths per 100,000 population; as seen in previous months, this was more than double the mortality rate in the least deprived areas (1.4 deaths per 100,000 population).



Disease incidence and severity is contiguous with deprivation: example of COVID mortality highest in South Wales coalfield

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27 March 2020

Cardiff Road Medical Centre,
Mountain Ash
Cynon Valley
South Wales

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Managing uncertainty… ???

Only just

No treatment, no research opportunity

Inverse research participation law

Access to research is often inversely proportional to a participants' potential contribution to research, and to where the research findings should be most applicable

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Adaptive Design Trials

- Flexible design
- More commonly seen in early phase trials but also applies to Phase III trials
- Clinical trial design that uses accumulating data to decide on how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial

  (Gallo P et al, J Biopharm Stat 2006)

- Optimise cost and process of drug development

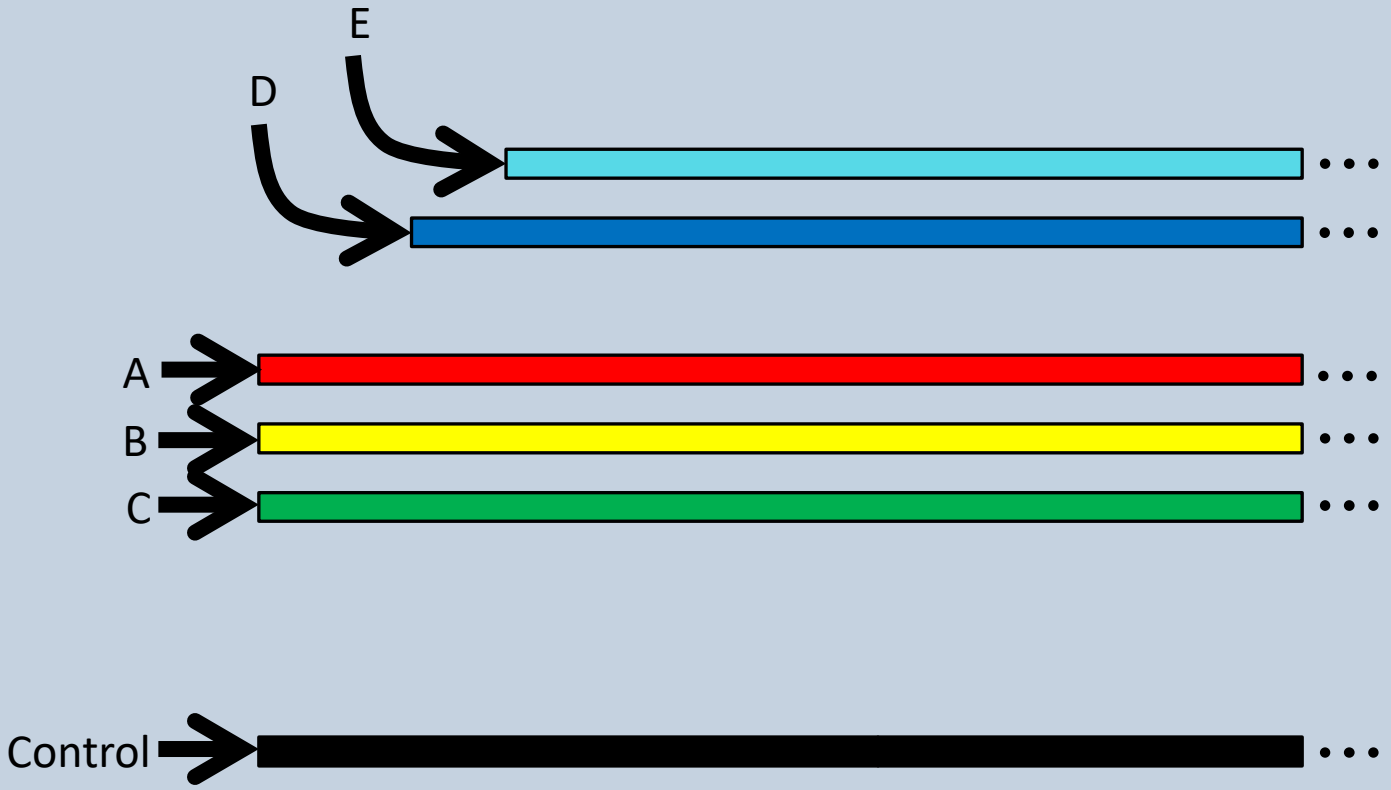
Platform trial

A **platform trial** is an adaptive clinical trial in which multiple treatments for the same disease can be tested at the same time, and allows for additional treatments to be added while the trial is in progress and for futile interventions to be dropped via frequent interim analyses that ensure each drug remains in the trial only until pre-specified thresholds for futility, success or safety concerns are met.

A **master protocol** that describes the overall study design, with **intervention specific appendices** that provide each drug's details, including additional inclusion criteria and specific monitoring requirements.

Platform Trial Vs **Trial Platform**

Potential Features of an Adaptive Platform Trial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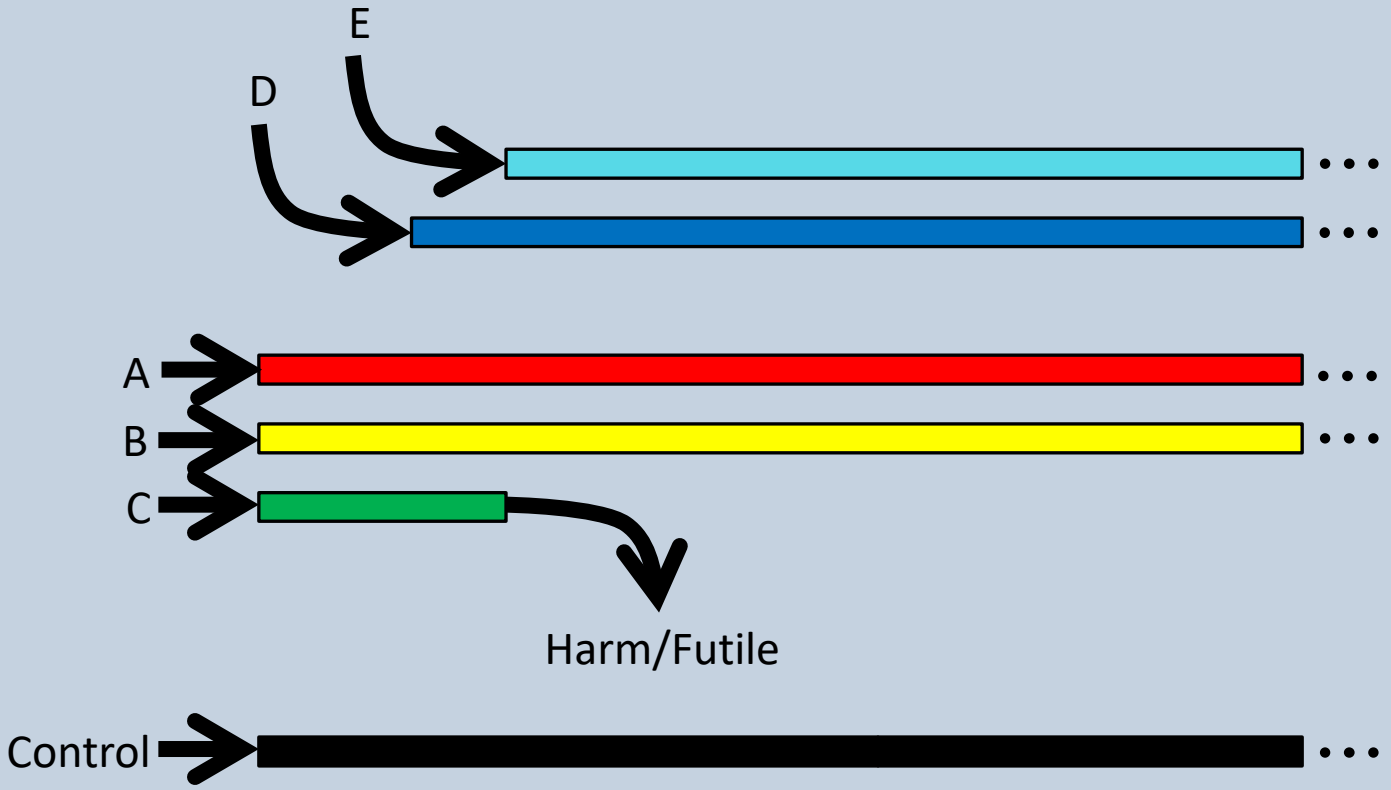
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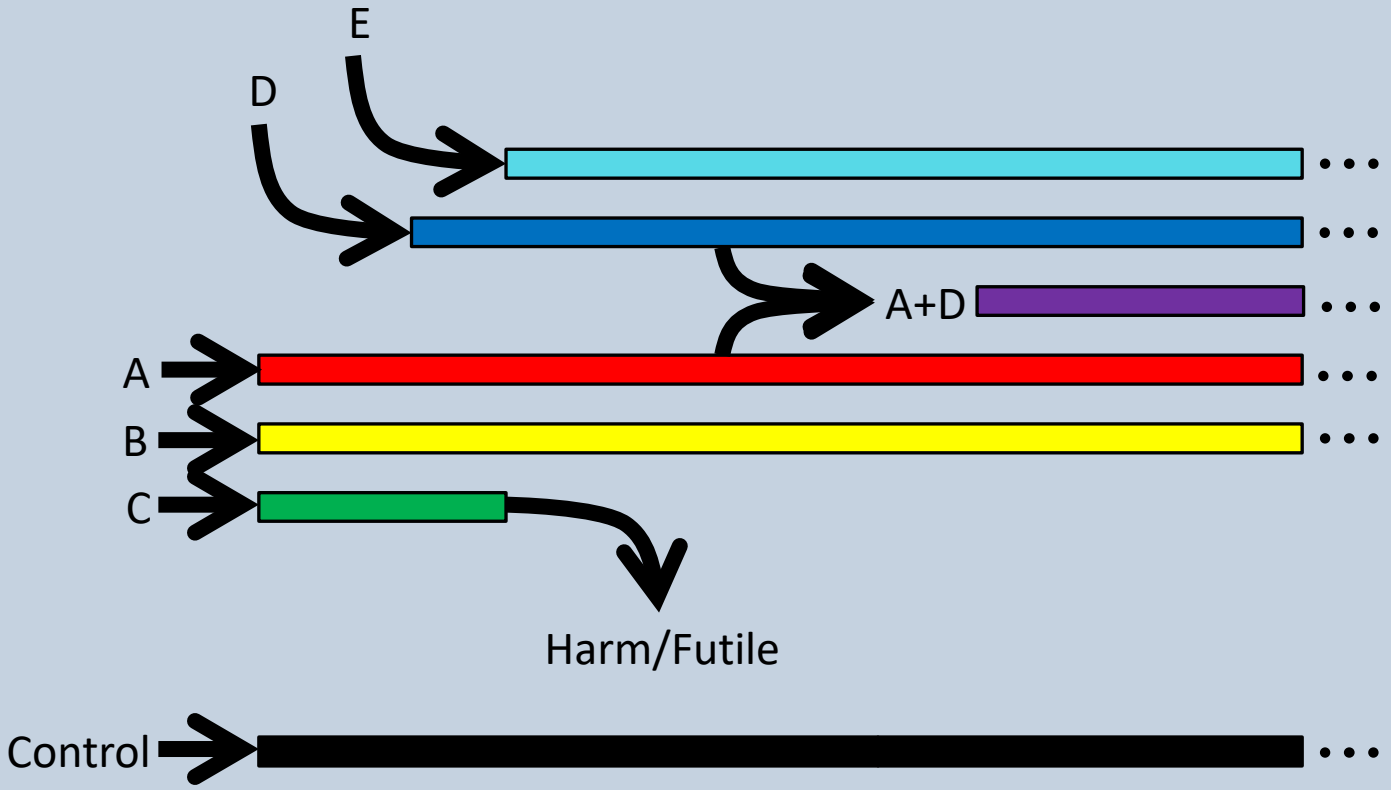

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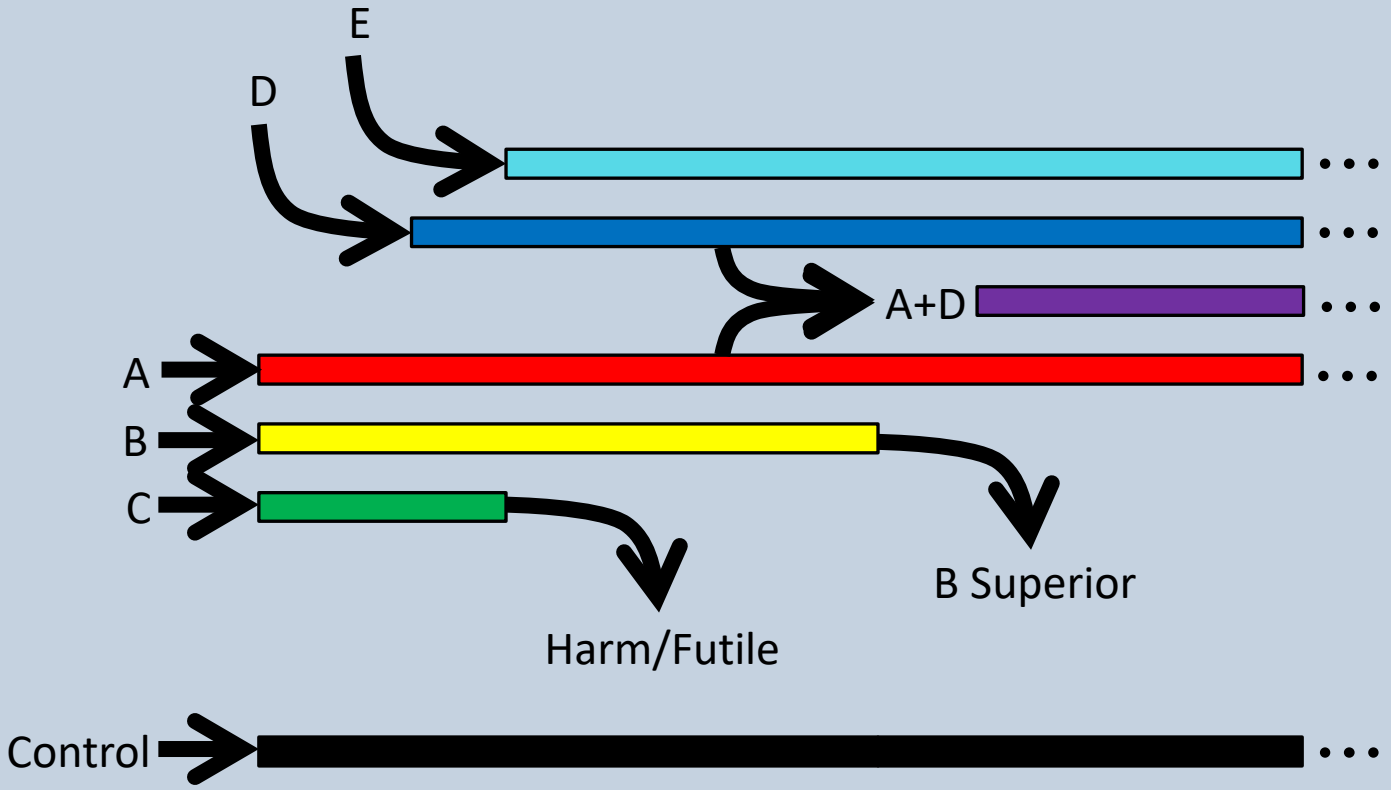
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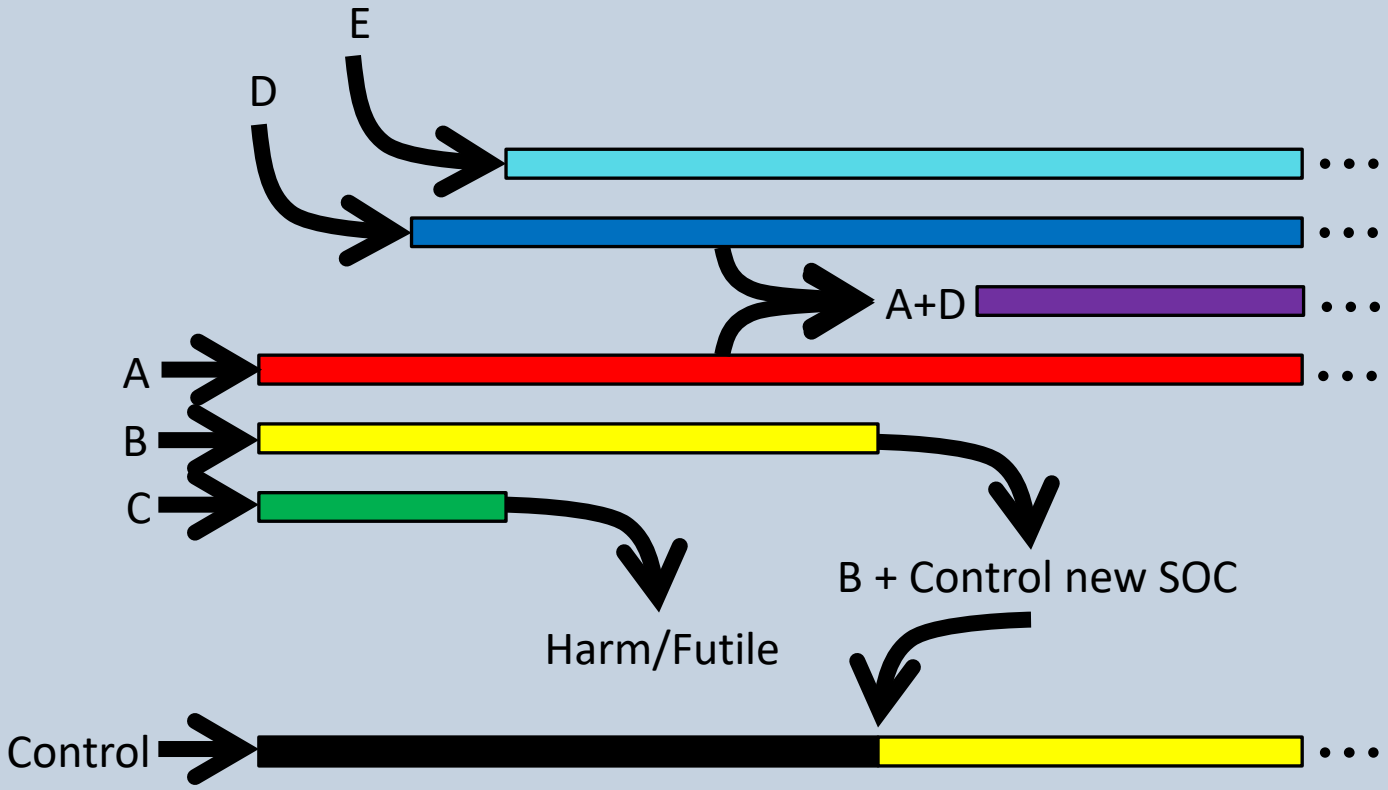
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Harm/Futile
Control

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Primary Care Clinical Trials Unit

Recruitment timeline in PRINCIPLE (n=11,768)

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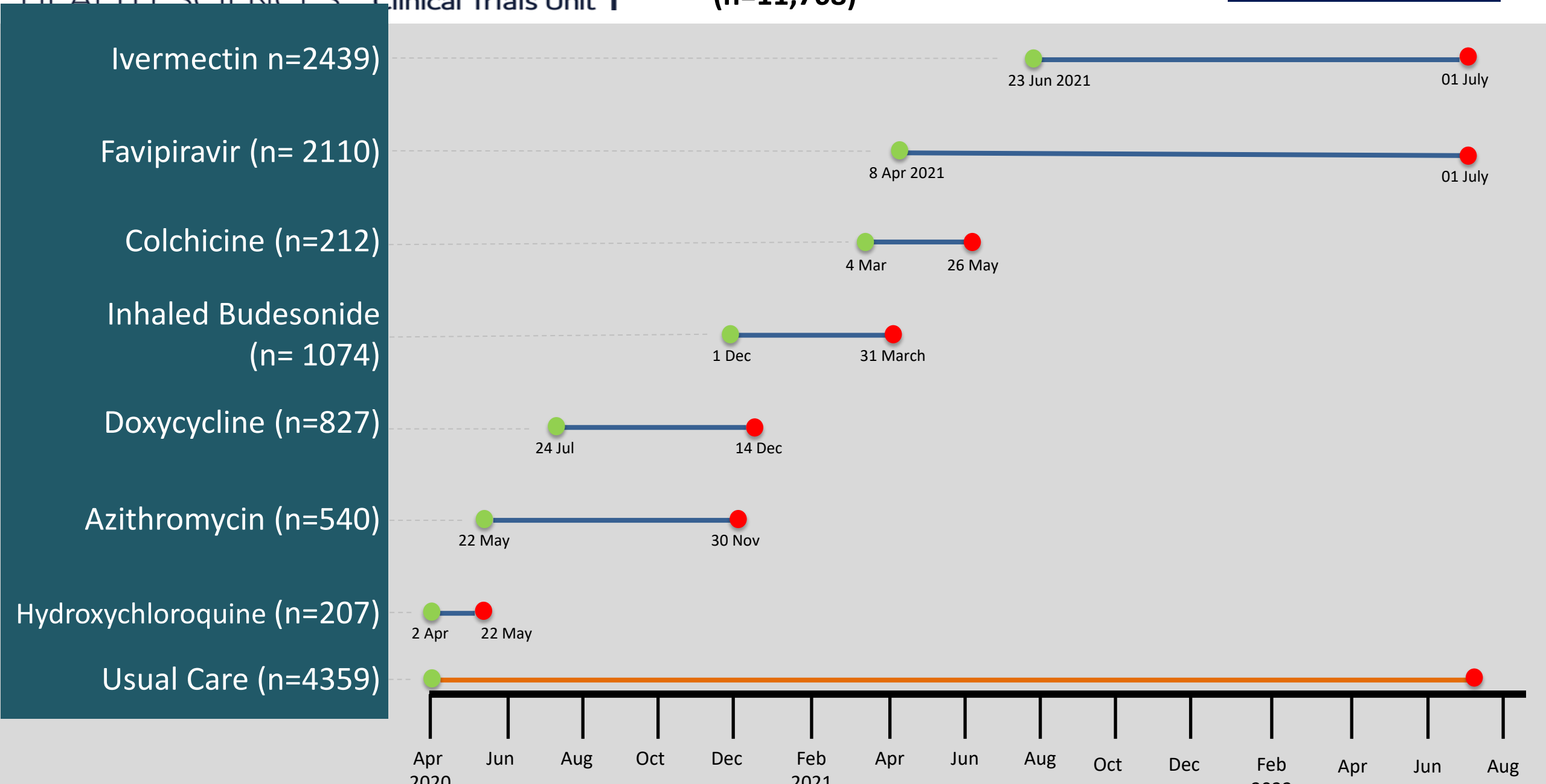

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PANORAMIC
Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community

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Platform Adaptive trial of Novel antiviRals for eArly treatment of COVID-19 in the Community (PANORAMIC)

Network and Support	
Sponsor	University of Oxford
Funder(s)	NIHR Evaluation, Trials and Studies Co-…
Lead Admin	England
Lead LCRN	Thames Valley and South Midlands
Managing Specialty	Primary Care
All Specialties	Infection, Primary Care
Primary Sub-Specialty	Infection
All Sub-specialties	Infection, Respiratory infections, Virolog…

UCL
University of Southampton
University of Glasgow
Cardiff University / Prifysgol Caerdydd
University of Liverpool

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Primary Care Clinical Trials Unit

65 Hubs, 4509 GP practices

>120,000 Screened

25,708 randomised to molnupiravir vs usual care

Traditional Clinical Trial Participant Journey

Site-based & site-dependent process

Recruitment
conducted opportunistically through GPs and requires proximity to trial sites

Screening
Requires in-person visits for physical assessment & interviews

Informed consent
Obtained in-person with site staff to explain study procedures

Randomisation
Managed by trial staff during in-person visit using computerised system or manual methods

Intervention
Participants receive interventions or controls during site visits

Monitoring & Follow up
Scheduled visits for assessments & data collection

ecraid
Prime

Funded by the European Union

Challenges of Traditional Clinical Trials in Primary Care (PC)

- GP's excessive clinic-level workflow & workload crisis
- Lack of time, funding, resources & research experience
- Failure to recruit sufficient participants – opportunistic recruitment
- Geographical constraints – smaller scope of recruitment
- The need for patients to travel to a specific location
- Processes are too manual

ecraid Prime

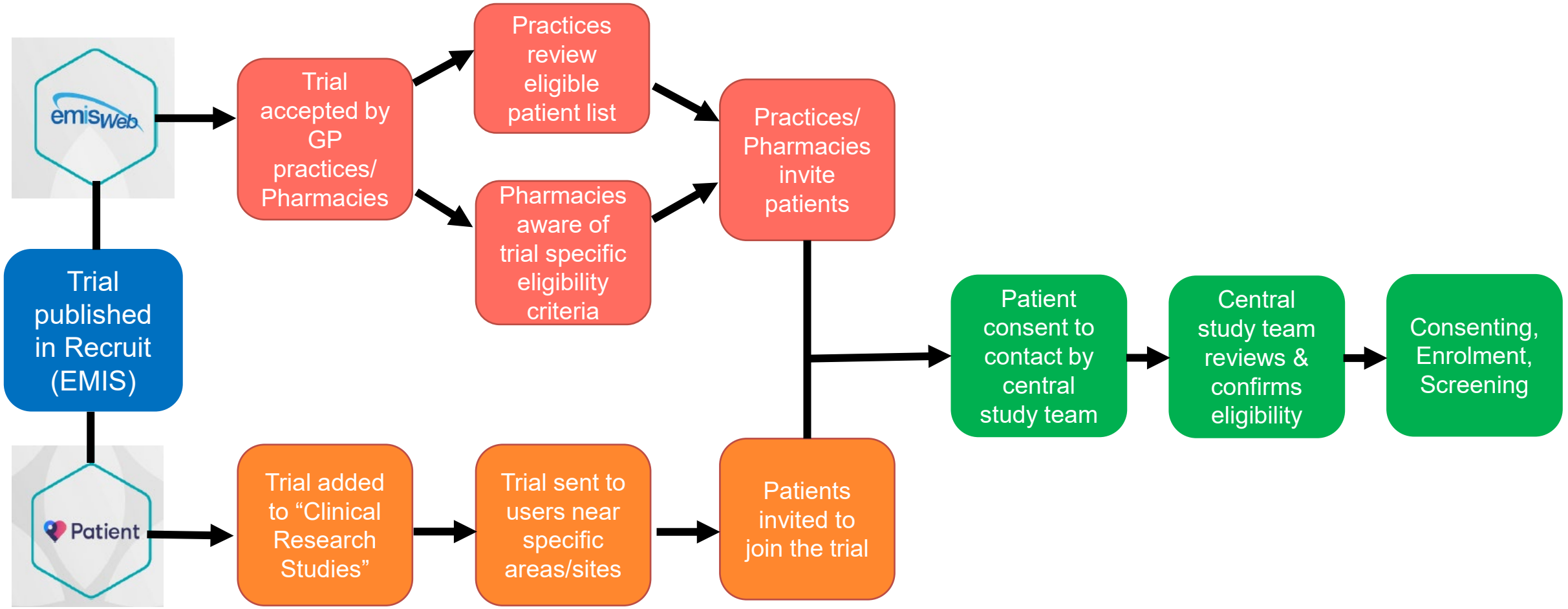
Funded by the European Union

‘Bringing research to the patients’

participant doesn’t need to travel → improves patient access to the research → reduces the burden on the participant → improves recruitment and retention

increases diversity of participants

Decentralised Recruitment (1)



Follow-ups


Daily diary
(online and/or phone)
Nurse home visit
Participant
Questionnaires
(online or phone)
Source System
(EHR/eSource)
Electronic medical
notes review
Safety phone calls

Participate without leaving your sick bed

A meeting room was converted to be functional space for carrying out overlabelling, storage and trial dispensing for use in PRINCIPLE trial

Drug labelling and delivery

- Over-labelling IMPs by clinicians
- Assembly and packaging
- Storage and handling (including distribution)
- Temperature controlled
- Need for exemption for each IMP within same trial
- MHRA exemption in place for over-labelling
- Couriered to patient's home UK-wide by next morning

4,582 GP practices recruited at least one participants to PRINCIPLE

Impact

Department of Health & Social Care

NHS

COVID-19 Therapeutic Alert

CEM/CMO/2021/003 28 January 2021

Antimicrobials (azithromycin and doxycycline) Not Beneficial in the Management of COVID-19 (SARS-CoV-2) Positive Patients

Recommendation

It is recommended that:

Azithromycin should NOT be used in the management of confirmed or suspected COVID-19 infection either within primary care or in hospitalised patients, unless there are additional indications for which its use remains appropriate (see Product Details).

Doxycycline should NOT be used in the management of confirmed or suspected COVID-19 infection within primary care, unless there are additional indications for which its use remains appropriate (see Product Details).

PRINCIPLE's interim analysis also concluded that doxycycline (administered as 200mg on the first day, followed by 100mg a day for 6 days) offered no meaningful beneficial effect compared to standard of care in patient aged over 50 who are treated at home in the early stages of COVID-19. The estimated clinical benefit in terms of both time to recovery and hospital admission were small.

Chief Medical Officer Directorate
Pharmacy and Medicines Division

Scottish Government
Riaghaltas na h-Alba
gov.scot

Dear Healthcare Professional,

COVID-19 THERAPEUTIC ALERT – ANTIMICROBIALS (AZITHROMYCIN AND DOXYCYCLINE) NOT BENEFICIAL IN THE MANAGEMENT OF COVID-19 (SARS-CoV-2) POSITIVE PATIENTS

Please see attached CMO letter about the results from the RECOVERY trial, and interim analysis from the PRINCIPLE trial which demonstrated that azithromycin should **NOT** be used in the management of confirmed or suspected COVID-19 infection either within primary care or in hospitalised patients. Doxycycline should **NOT** be used in the management of confirmed or suspected COVID-19 infection within primary care. I would be grateful if you could cascade this information to relevant colleagues.

NICE National Institute for Health and Care Excellence

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Home > NICE Guidance > Conditions and diseases > Infections > Antimicrobial stewardship

COVID-19 rapid guideline: managing COVID-19

NICE guideline [NG191] Published: 23 March 2021 Last updated: 08 May 2024

Guidance | Tools and resources | Evidence | History

World Health Organization

Health Topics | Countries | Newsroom | Emergencies | Data | About WHO

Home / Publications / Overview / Living guidance for clinical management of COVID-19

Living guidance for clinical management of COVID-19

23 November 2021 | COVID-19: Clinical care

NIHR | National Institute for Health Research

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GCTF Global clinical trials forum

World Health Organization

Global action plan for clinical trial ecosystem strengthening

A vision for the future of global clinical trials, emphasizing the need for local relevance, streamlined frameworks for ethical and regulatory oversight in accordance with international standards, and sustained functioning capacities

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Global action plan for clinical trial ecosystem strengthening

Strengthen local leadership and national support for sustained infrastructure and funding

Enhance involvement and engagement with patients, communities and the public in clinical trial lifecycle

Address barriers to clinical trials in under-represented populations

Enable effective trials through adoption of innovative designs and digital technologies

Accelerate access to fit-for-purpose training packages for clinical trials

Improve coordination and streamlining regulatory and ethics review

Engage clinical practitioners to integrate clinical trials into health systems and practices

Step up the use of trial registries to improve research transparency

Expand international health research and clinical trial collaboration

Outcome measures to monitor how reforms can accelerate generation of quality evidence

World Health Organization

Comparison: WHO Guidance vs ICH-GCP

Dimension	WHO Guidance	ICH-GCP
Origin	World Health Organization (2020)	International Council for Harmonisation (E6 R2)
Purpose	Global ethical guidance, esp. for public health and LMIC settings	Regulatory trials for new drug/device approval
Trial Types	All types (including pragmatic, adaptive, cluster RCTs)	Primarily drug/device registration RCTs
Target Settings	Global, incl. LMICs and public health systems	High-income, regulated research environments
Focus	Equity, ethics, inclusivity, and access	Regulatory compliance, pharma-oriented
Flexibility	Proportionate to risk and context	More prescriptive, less flexible (but evolving)
Community Engagement	Strong emphasis on local and community involvement	Not a core focus
Informed Consent	Context-appropriate and culturally sensitive	Formal and standardised, with less flexibility
Monitoring Approach	Risk-based, supports innovative/remote monitoring	Traditional, on-site focused monitoring
Data Sharing	Encouraged for public health benefit	Not addressed directly
Modern Methods	Supports digital, adaptive, decentralised designs	Being updated to include (E6 R3 in development)
Participant Protection	Emphasizes equitable participant inclusion	Focus on individual rights, not equity per se

ICH GCP E6(R3) Draft – Considerations for Decentralized, Pragmatic & RWD Trials

Decentralized Elements:

- Home visits, local care, digital health technologies (DHTs)
- Ensure data integrity, validation, and patient confidentiality

Pragmatic Designs:

- Embedded in routine care settings
- Streamlined protocols that align with clinical workflows

Real-World Data (RWD) or Routinely Collected Data:

- Sources include EHRs, registries, and claims data
- Protocol should address data access, variability, and linkage strategies

GCP Considerations:

- Informed consent (e.g. eConsent), identity verification, and data clarity
- Risk-based oversight, adapted monitoring, and ethics committee engagement
- Safety reporting from decentralized sources must be clearly defined

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Implications…

- **Question identification: Bottom up, patent agency, role of PRIMAFAMED….?**
- **Study design**
- **Funding**
- **Team**:
    - Citizens
    - Clinicians
    - Methodologists
    - data management
    - Statisticians
    - Collaborations; South to South, North to South

- **Dissemination; embedding, "systems strengthening…"**

Clinical Trials in Global Health 4

Democratising clinical trials research to strengthen primary health care

Christopher C Butler, Robert Mash, Nina Gobat, Paul Little, Mpundu Makasa, Martha Makwero, Edward J Mills, Regina Wing-Shan Sit, Max O Bachmann

The World Health Assembly has called for clinical trials to be strengthened, with broader demographic and geographical inclusion of populations. The objective of this paper is to highlight the importance of rigorous evidence to maximise the health gains of primary health care, and to identify strategies for strengthening clinical trials in primary care. Clinical trials should evaluate interventions of all kinds, including preventive manoeuvres, diagnostics, health service research questions, behavioural and educational interventions, vaccines, therapeutics, and policies. Single question trials can be inefficient and seldom strengthen health systems. New approaches that develop or strengthen health research infrastructure and embed research in primary care will identify effective interventions faster, how to deliver them better, and more accurately determine to whom they should be applied. When patients and community members, together with researchers, contribute to conception, design, and delivery, research will result in more useful, relevant evidence. Traditional site-based recruitment (where the participant comes to the trial) can be complemented by approaches that give people the opportunity to contribute regardless of where they live and receive their health care (taking the trials to the people). However, this cannot be done until regulation is modernised to make it easier for health-care professionals, researchers, and research participants to co-design, deliver, and implement such trials, and to develop processes to coordinate and monitor progress against goals for budget shifts, delivery, engagement, trials activity, and impact. Strengthening primary care trials is especially important in those regions where primary care is most under-resourced and is key to pandemic preparedness. Not doing so risks widening inequities further.

Lancet Glob Health 2025

This is the fourth in a Series of six papers on clinical trials in global health. All papers in the

Lancet Glob Health 2025; 13: e749–58

Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK (Prof C C Butler FMedSci); Division of Family Medicine and Primary Care, Stellenbosch University, Stellenbosch, South Africa (Prof R Mash PhD); Community Readiness and Resilience Unit, World Health Organisation, Geneva, Switzerland (N Gobat PhD); Primary Care Research Centre, University of Southampton,

Diolch yn fawr

The ALIC4E study was funded by EU 7th Funding Program as part of the PREPARE Network of Excellence, ECRAID-Prime is funded by the European Union's HORIZON 2021 – 2027 Research and Innovation Programme, under Grant Agreement number 101046109. The PRINCIPLE trial was funded by the UK National Institute for Health and Care Research/United Kingdom Research Innovation (MC_PC_19079), and PANORAMIC was funded by the UK National Institute for Health and Care Research

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