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Anticipating Market Authorization for MASH Drugs:

Impact on MASH Drug Development Programs

March 22, 2024

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Berkeley Public Health

Congratulations

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FDA NEWS RELEASE

FDA Approves First Treatment for Patients with Liver Scarring Due to Fatty Liver Disease

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For Immediate Release: March 14, 2024

Español

Today, the U.S. Food and Drug Administration approved Rezdiffra (resmetirom) for the treatment of adults with noncirrhotic non-alcoholic steatohepatitis (NASH) with moderate to advanced liver scarring (fibrosis), to be used along with diet and exercise.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REZDIFFRA safely and effectively. See full prescribing information for REZDIFFRA.

REZDIFFRA (resmetirom) tablets, for oral use
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------

REZDIFFRA is a thyroid hormone receptor-beta (THR-beta) agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).

This indication is approved under accelerated approval based on improvement of NASH and fibrosis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1)

Limitations of Use
Avoid use of REZDIFFRA in patients with decompensated cirrhosis. (1)

Remaining unmet medical need

Benefit-Risk-Uncertainty

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- General context:
  - Seriousness of disease
  - Therapeutics landscape
- MASH context:
  - Multi-factorial disease
  - Combination MOA's likely needed
  - Precision medicine approaches?

Therefore

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- Additional drugs needed to meet needs of all patients
  - diversity of affected patient populations
- MASH drug development programs must continue
  - "drug development" includes non-invasive biomarkers for all COU's

MASH Development Programs

Existing challenges exacerbated by availability of marketed drugs

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- Patient perspective
  - Understanding benefit-risk wrt options
  - Biopsy requirement
  - Length of follow-up
- Sponsor perspective
  - Recruitment/retention in clinical trials
  - Resources for larger, >larger trials
- Clinician perspective
  - Diminishing equipoise

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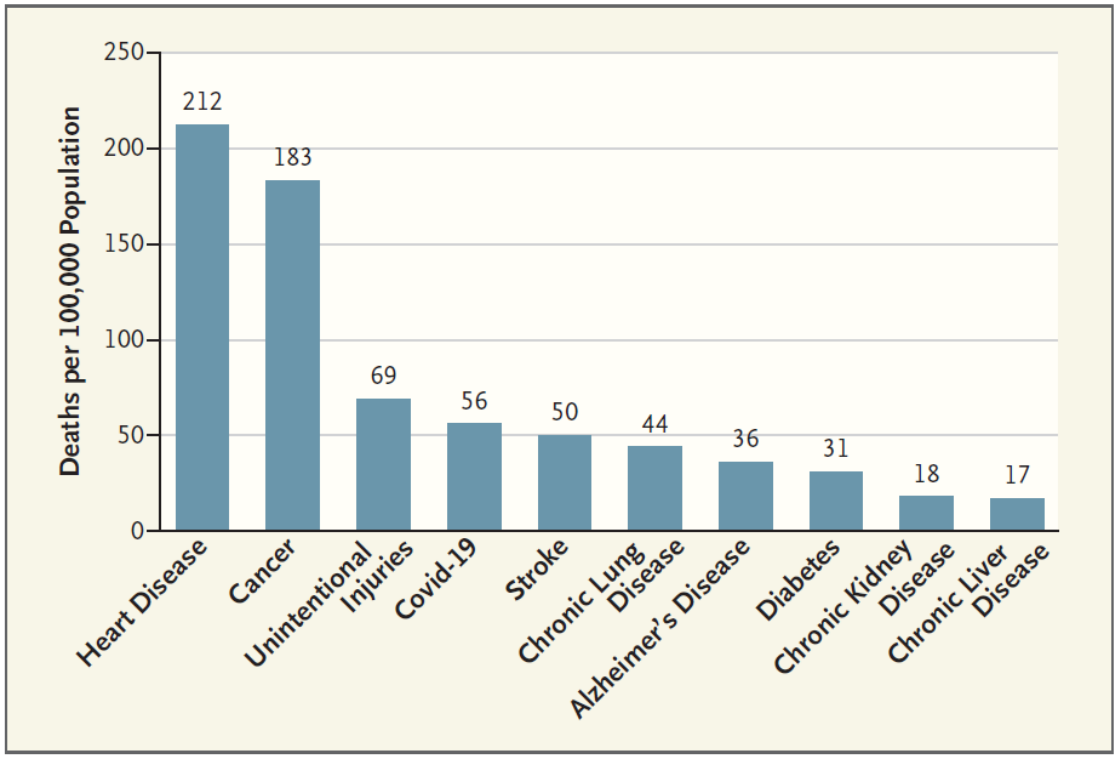
Addressing the Challenge of Common Chronic Diseases — A View from the FDA

Haider J. Warraich, M.D., Hilary D. Marston, M.D., M.P.H., and Robert M. Califf, M.D.



Crude Mortality for the 10 Leading Causes of Death in the United States, 2022.

Preliminary data are from the Centers for Disease Control and Prevention's WONDER database.

N ENGL J MED 390;6 NEJM.ORG FEBRUARY 8, 2024

- Wide disparities in prevalence and outcomes
- FDA: regulatory, scientific, and public health agency
  - Support development of effective and accessible interventions
  - Improve the way evidence is generated
  - Collaboration among stakeholders

Strategies:

- Transform evidence-generating methods
- Make better use of technology
- Develop coherent approaches to issues across chronic diseases
- Foster patient-centered innovation

"There is an urgent need for a research environment that facilitates prospective development and evaluation of reliable biomarkers and surrogate end points for outcomes of interest to overcome the challenge that many candidate therapeutics with promising results in phase 2 trials aren't found to effective in phase 3 trials"

"Requires a broad coalition"

Evidence requirements across research generations

Traditional design schema

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- First generation drugs (no SOC)
  - Placebo control RCT appropriate
  - Effect size large(r): efficacy easy (easier) to demonstrate

- Second generation drugs (SOC defined)
  - Superiority design
    - Comparative effect size small(er): superiority more difficult to demonstrate
  - Non-inferiority design
    - Issues with constancy assumptions, margins, etc.

Focus our attention

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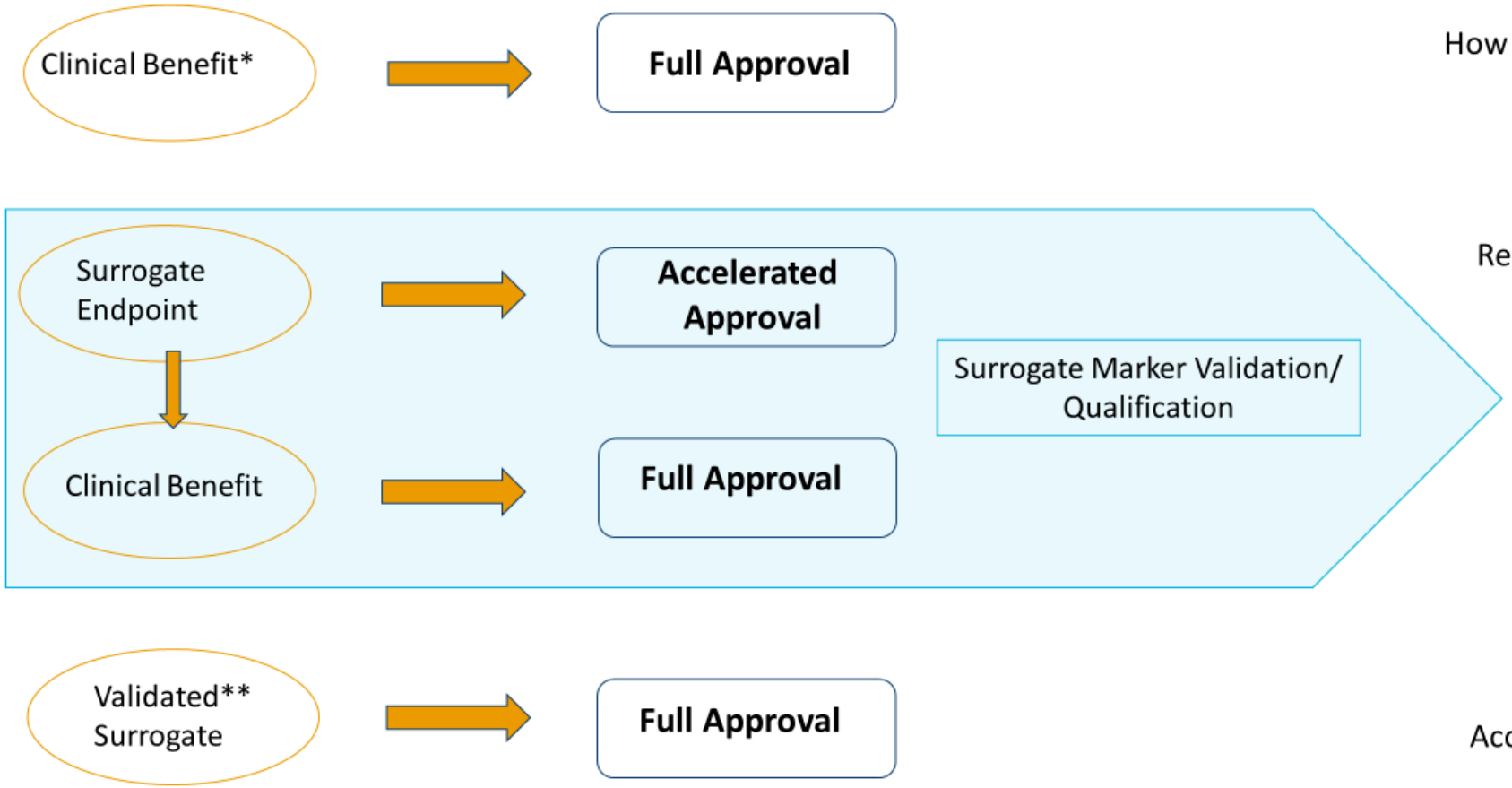
Immediate

- Subpart H obligations
  - Surrogate endpoint validation with clinical endpoints requires long-term outcome studies
    - Histology
    - Non-invasive "holy grail"

Near future

- Surrogate (histology) will be validated for traditional (full) approval?
- New SOC?
- Trial design?

Need to plan now



*Primary endpoint

**For specific disease setting and class of interventions
**Recognized as validated by definitive studies
**Primary endpoint

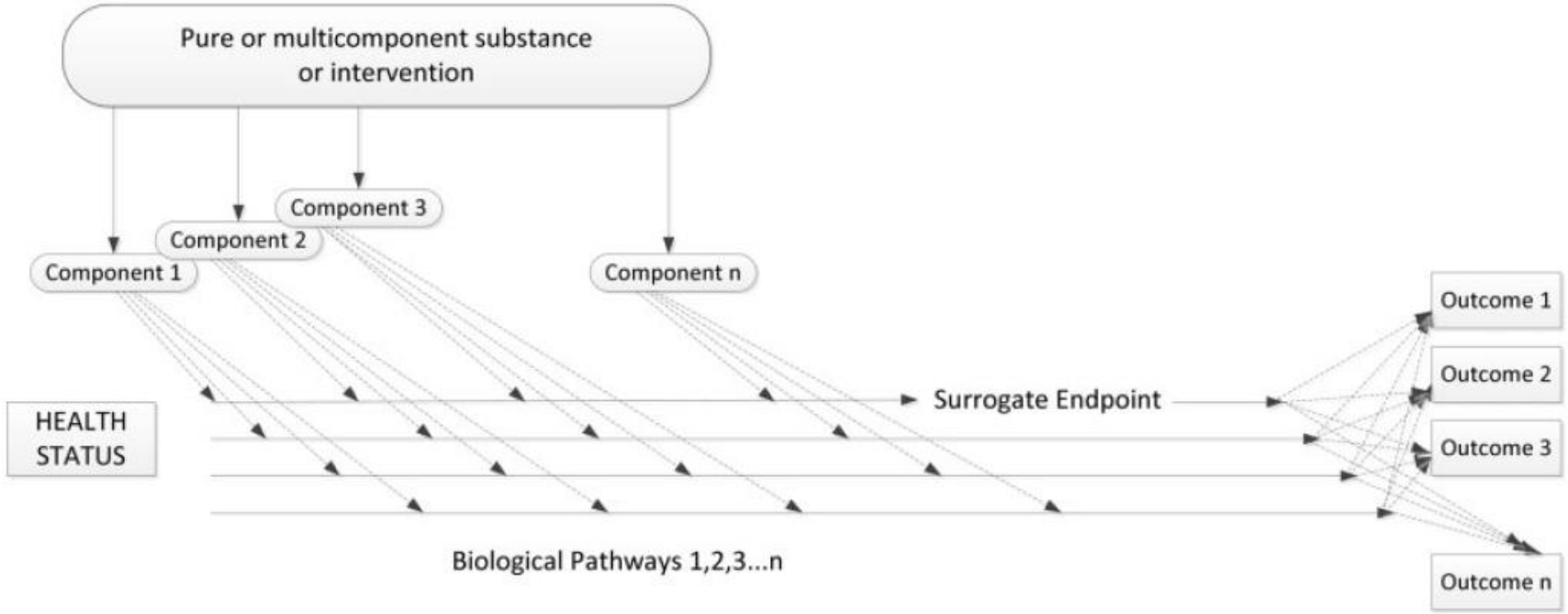
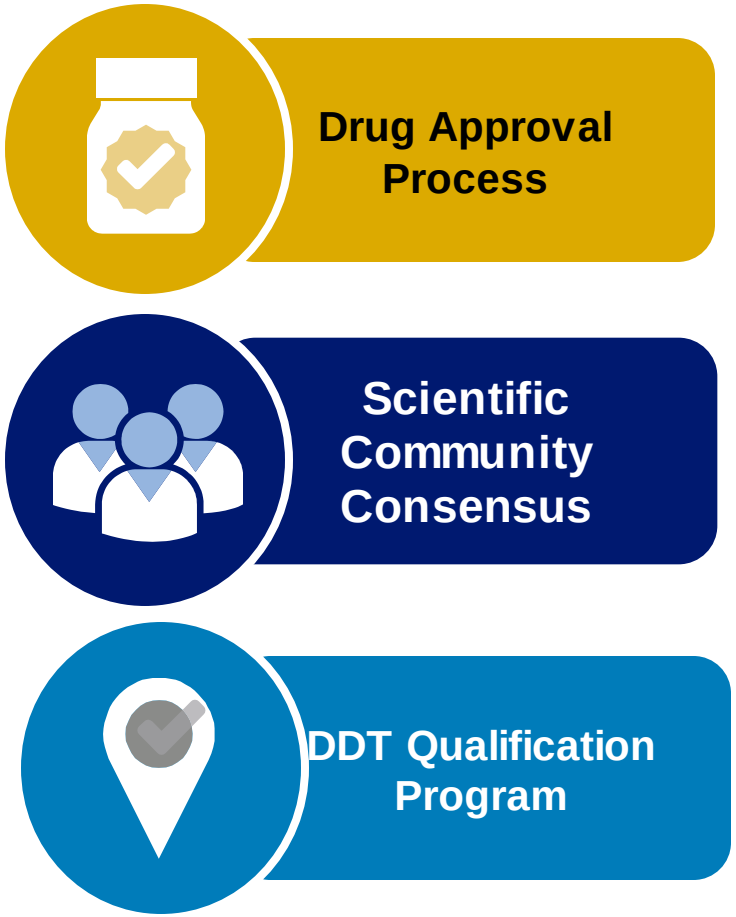


Figure 3. Multiple components, biological pathways, and outcomes all contribute to the complexity of using biomarkers and surrogate endpoints in the context of chronic disease. Adapted from: Institute of Medicine. *Evaluation of biomarkers and surrogate endpoints in chronic disease*. Summary. Washington, D.C.: National Academies Press, 2010.

Experimental Biology and Medicine **2018; 243: 213–221. DOI: 10.1177/1535370217750088**

Opportunities for Improved Integration of Biomarker Development Activities within Drug Development



Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.

What are the options?

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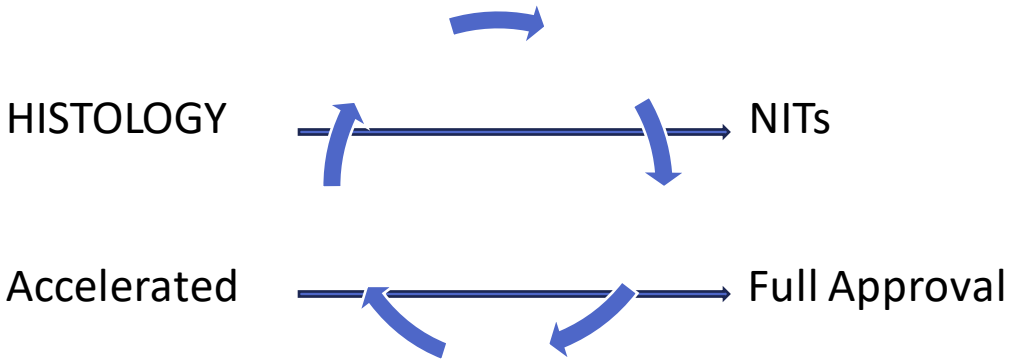

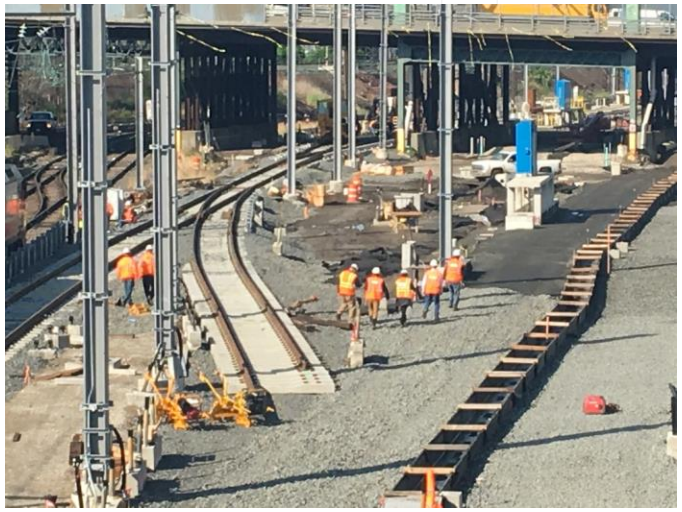

"Requires a broad coalition"

Strategies

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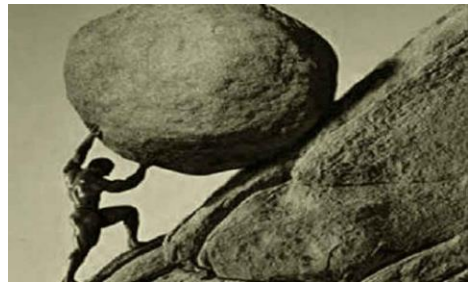
- Continue as is
  - Each sponsor on their own, "work really hard" to recruit/retain patients in long-term placebo-controlled studies



- Innovate
  - Trial design
  - Analytics

- Collaborate
  - Master protocols
  - Shared placebo arms
  - Cross-company meta-analyses

Potential Strategies - 1

To alleviate challenges in patient recruitment-retention

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- External comparator
  - Claims data
  - Electronic health records
- Shared placebo arm
  - Retrospective
  - Concurrent
- Master protocols

Table 1. 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

Areas of Innovation

Infrastructure
- Common screening platform for biomarker identification
- Governance
  - Steering committee
  - Adjudication committee
  - Data monitoring committee
  - Central institutional review board
- Trial networks and clinical centers
- Processes
  - Randomization
  - Data and safety capture and management
  - Quality-control oversight

Trial Design
- Adaptive randomization and other adaptive design features
- Longitudinal modeling to determine probabilities of success or failure
- Shared control patients
- Natural-history cohort
- Biomarker qualification

Figure 3. Areas of Innovation in Master Protocols.

Simplifying “master protocol”

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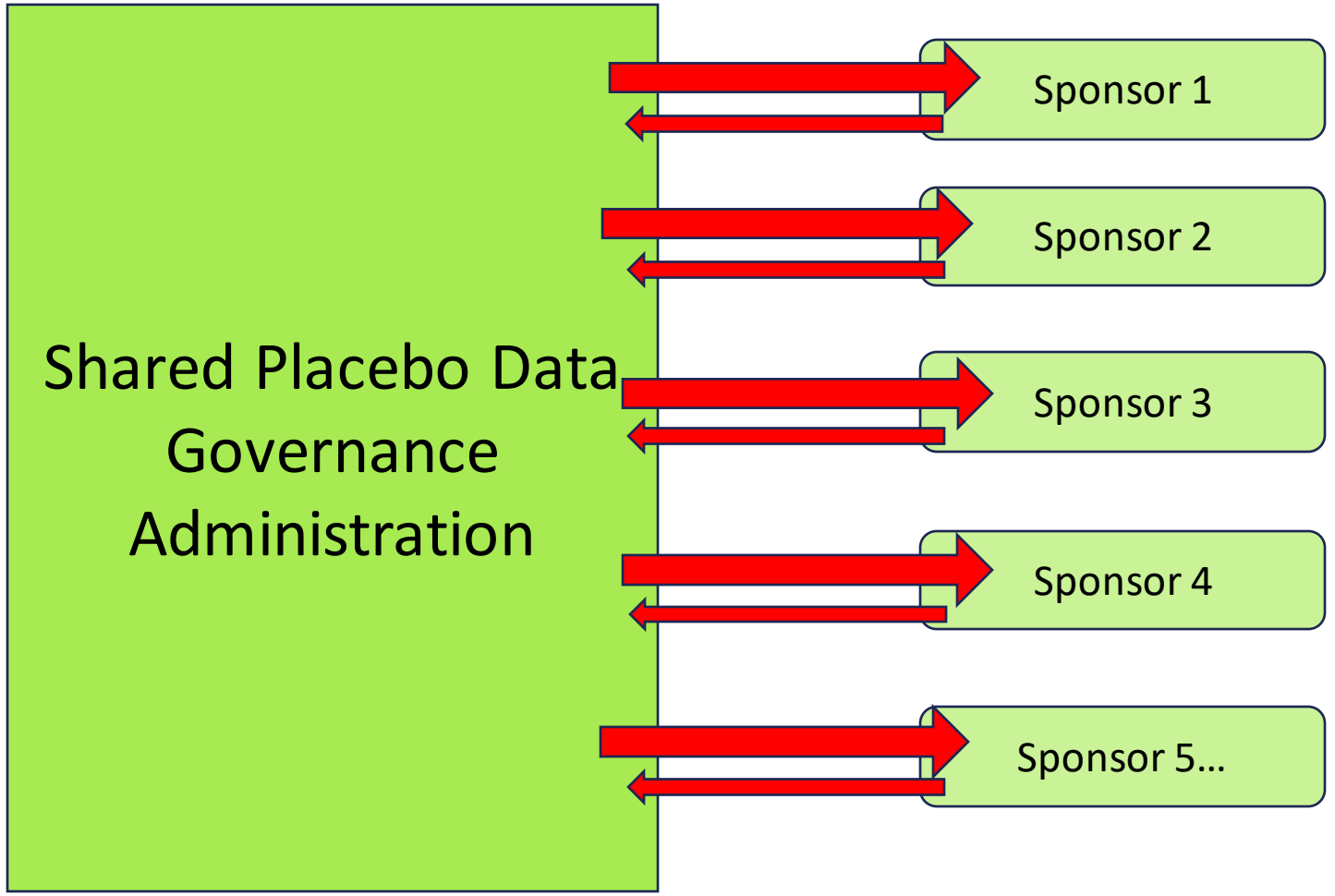
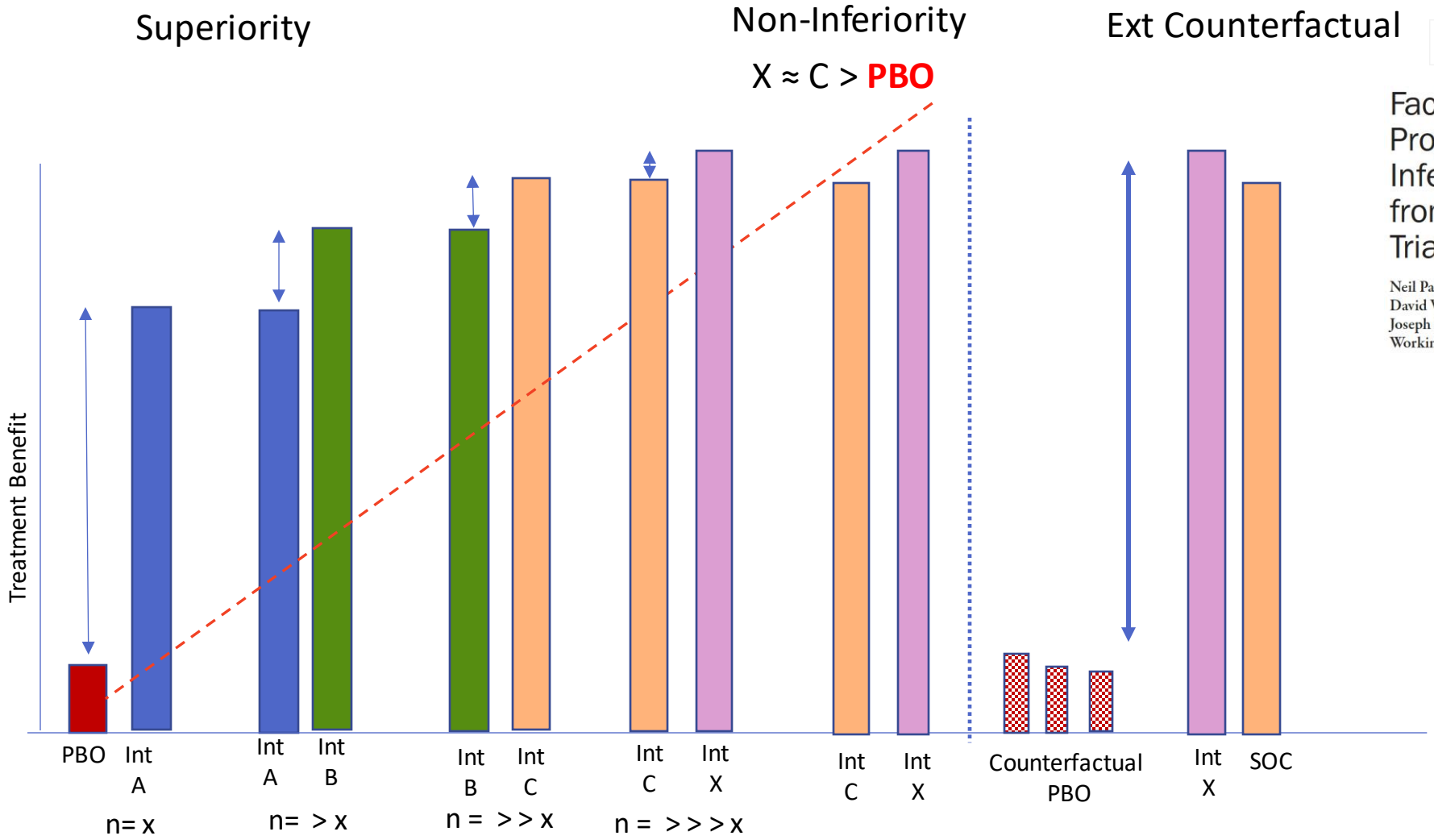
Master Protocol
One protocol
Steering Committee
Governance
Administration
Research Organization
Sponsor 1
Sponsor 2
Sponsor 3….





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Facilitating Next-Generation Pre-Exposure Prophylaxis Clinical Trials Using HIV Recent Infection Assays: A Consensus Statement from the Forum HIV Prevention Trial Design Project

Neil Parkin[1], Fei Gao[2], Eduard Grebe[3,4], Amy Cutrell[5], Moupali Das[6], Deborah Donnell[2], Ann Duerr[2], David V. Glidden[4], James P. Hughes[7], Jeffrey Murray[8], Michael N. Robertson[9], Joerg Zinserling[10], Joseph Lau[11], and Veronica Miller[11,*] for the Forum for Collaborative Research Recency Assay Working Group

Berkeley Public Health

Potential Strategies - 2

To increase chances of sufficient clinical endpoints

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- Pool endpoints from trials in F2/F3 and F4 pts
  - Individual sponsor
    - LF Working Group
- Standardize clinical endpoints assessment
  - New working group?
- Meta-analysis across trials – collaboration amongst sponsors
  - New working group?

Potential Strategies - 3

To increase chances for non-invasive surrogate endpoint

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- Standardize NIT's across programs
- Meta-analysis across programs
- Consider all three approaches
  - Drug development
  - Expert consensus
  - Biomarker qualification

Potential Strategies - 4

To increase value of each data point – improve precision

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- Responsible re-use of data
  - Placebo data base project
- Application of novel analytics
  - ML/AI, TML/causal inference
- Consider Bayesian approaches?

nature reviews drug discovery
https://doi.org/10.1038/s41573-023-00638-0

Perspective

Check for updates

Application of Bayesian approaches in drug development: starting a virtuous cycle

Stephen J. Ruberg[1], Francois Beckers[2], Rob Hemmings[3], Peter Honig[4], Telba Irony[5], Lisa LaVange[6], Grazyna Lieberman[7], James Mayne[8] & Richard Moscicki[8]

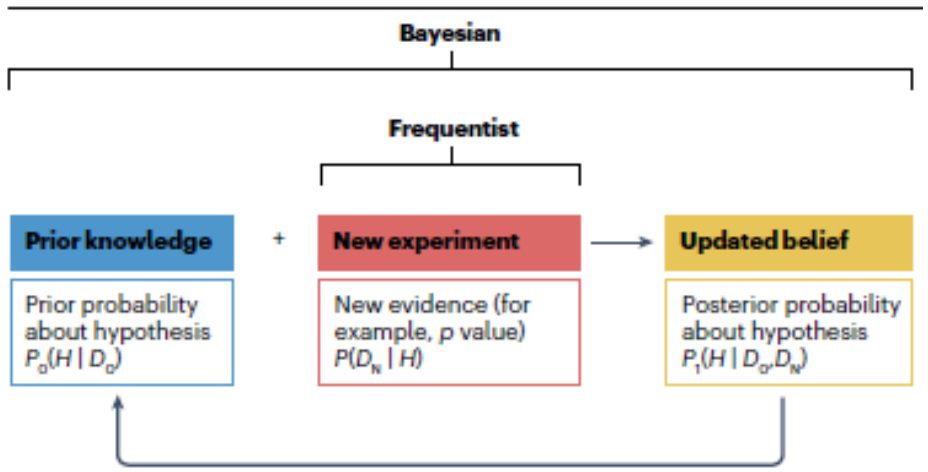

Fig. 1 | Comparison between Bayesian and frequentist approaches. The

Potential Strategies - 5

To reduce patient burden and overall resources

- Adaptive vs. stepwise program design
- Master protocols and "borrowed controls"
- Decentralized trials
- "..coherent approaches to issues across chronic diseases"
  - From Warraich, Marston, Califf NEJM 2024

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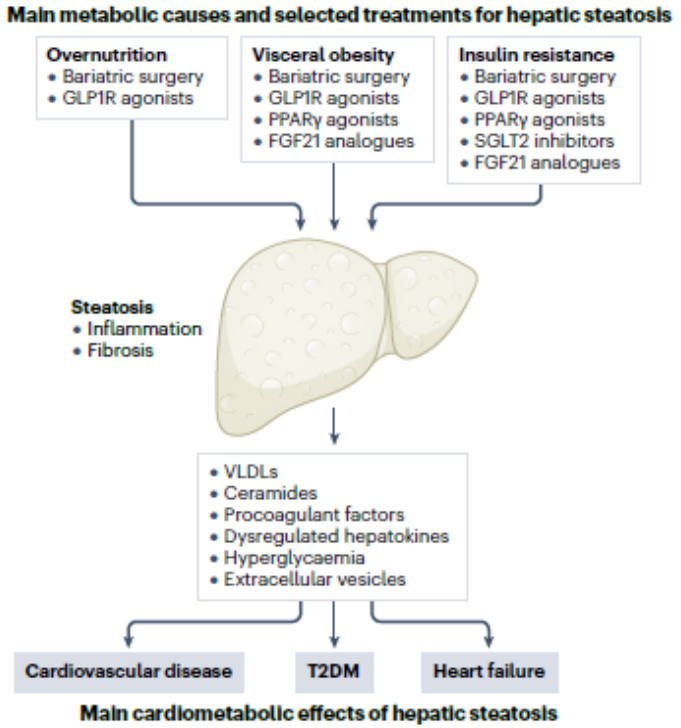

Fig. 1 | Hepatic steatosis. Possible pathogenetic mechanisms, main cardiometabolic consequences and selected pharmacological treatments. FGF21, fibroblast growth factor 21; GLP1R, glucagon-like peptide 1 receptor; PPARγ, peroxisome proliferator-activated receptor-γ; SGLT2, sodium–glucose cotransporter 2; T2DM, type 2 diabetes mellitus; VLDLs, very-low-density lipoproteins.

Stefan, Lonardo & Targher. 2024. Nat Rev Gastro Hep

Non-Invasive Biomarkers Surrogate Endpoints

Questions from (and to) the field

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- Are we obligated to validate the histology endpoint before anything else?
  - Does it have to be demonstrated for each individual program? Each MOA?
- Can we do a meta-analysis across trials (all sponsors) to increase likelihood of clinical events?
  - Done in other disease areas
- Can we simultaneously (or in tandem) propose non-invasive biomarkers *as reasonably likely to predict clinical outcome*, to allow accelerated approval and then be validated against clinical endpoints?

Using data from completed studies

- In HIV, all sponsored studies were included in a meta-analysis to link viral load to clinical outcome

Table 1. Characteristics of studies used for analyzing changes in HIV RNA in response to treatment.

Study	Total (n*)	Regimens	Median baseline CD4 T cells ($\times 10^6$/l)	Median RNA baseline (copies/ml)	Prior drug experience
Analyses showing an association between HIV RNA reductions and decreased clinical progression					
Abbott Study: M94-247 [6]	80	RTV + up to two NRTI	21	263 000	> 9 months
ACTG Studies: 116A, 116B, 117, 175,197, 229, 241, 259 [7,8,11–14]	1000	Many	218	50 000	Mixed
Glaxo-Wellcome Studies: NUCA 3001, 3002; NUCB 3001, 3002, 3007 (CAESAR), 3020 [4,11,15–18]	1581	ZDV + 3TC, others	209	63 000	50% > 6 months ZDV
Pharmacia & Upjohn Studies: 1842 M3331-0017, M3331-0021 [11]		ddI, ZDV, DLV + ddI, DLV + ZDV	230	75 000	50% > 6 months ZDV
Roche Study: NV14256 [11]	940	ddC, SQV, ddC + SQV	170	137 000	> 4 months ZDV
Analyses exploring characteristics of HIV RNA reductions with combination therapy					
Agouron Study: 511 [11]	196	NFV + ZDV + 3TC ZDV + 3TC	288	153 044	Naïve
Boehringer Ingelheim Study: 1046 [19]	100	ZDV + ddI, ZDV + ddI + NVP	376	25 704	Naïve
Merck Studies: 018, 019, 020, 021, 028, 033, 035 [11,20,21]	204†	IDV, IDV + NRTI	215	18 085	Protease and 3TC naïve

*The number of patients listed represents those for which there were both virologic and clinical data and not necessarily the size of the original trial. †Those who achieved a plasma HIV RNA level below the limit of quantification (500 copies/ml). NRTI, Nucleoside reverse transcriptase inhibitors: RTV, ritonavir; DLV, delavirdine; SQV, saquinavir; ZDV, zidovudine; ddI, didanosine; 3TC, lamivudine; ddC, zalcitabine; NFV, nelfinavir; NVP, nevirapine; IDV, indinavir.

AIDS 1999, Vol 13 No 7

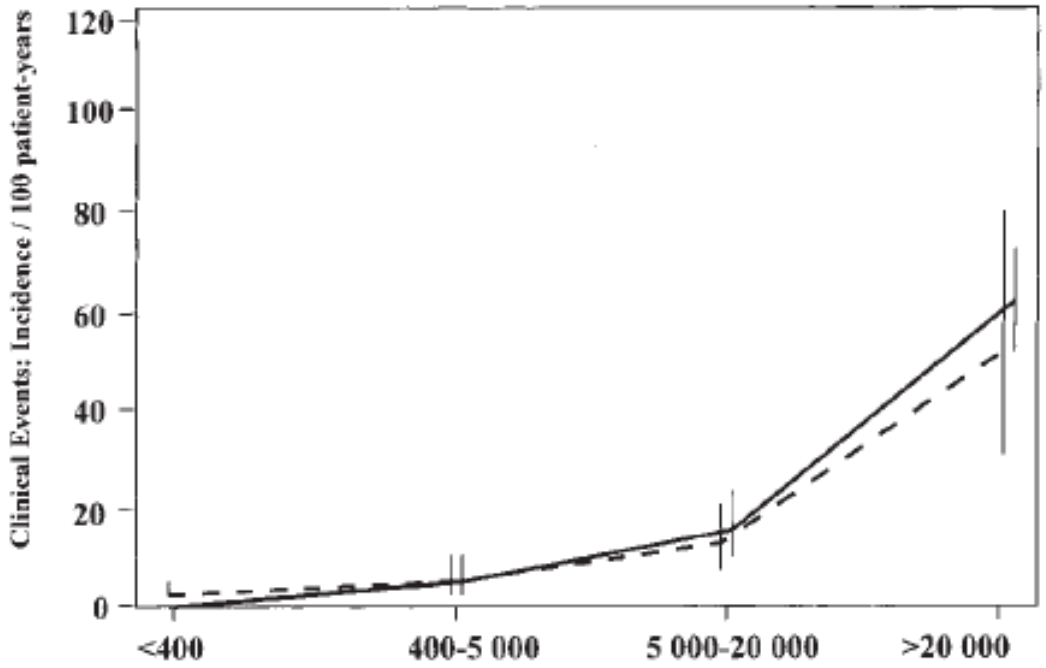

Fig. 1. Incidence of clinical progression to new AIDS event or death (per 100 patient-years) for multiple clinical events per patient. Patients were stratified by median baseline plasma HIV RNA: > 63 000 copies/ml (solid line) and baseline plasma HIV RNA ≤ 63 000 copies/ml (broken line). 95% Confidence intervals are shown as vertical bars.

Table 2. Risk of AIDS disease progression according to duration of virologic response for participants in two delavirdine studies.

Response duration (days)	Hazard ratio	95% CI for hazard ratio
No response	1.000	–
1–29	0.668	(0.428–1.041)
30–57	0.721	(0.409–1.271)
58–113	0.550	(0.320–0.945)
114–141	0.260	(0.128–0.528)
≥ 142	0.286	(0.145–0.564)

CI, Confidence interval.

AIDS 1999, Vol 13 No 7

A word on ethics…

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- Scientific value
- Equipoise
- Use of human and financial resources
- Respect for patients

Take-home message

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- Let's build the broad coalition!

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Thank You

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