CURSO DE AVANCES EN GASTROENTEROLOGÍA
PERSPECTIVAS FUTURAS EN GASTROENTEROLOGÍA
17 - 19 Julio 2024 - Hotel InterContinental, Stgo.
SChGE

Future of research and clinical trials in liver disease

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Disclosures

ORGANIZATION	ORGANIZATION TYPE	NATURE OF INTEREST	TERM ENDS
Akaza Bioscience Ltd.	Biotechnology	Advisory Board	12/03/2021
AgomAb Therapeutics	Biotechnology	Advisory Board	10/26/2021
Ambys Medicines	Biotechnology	Consulting	10/24/2020
Durect Corporation	Pharmaceutical	Consulting	9/22/2021
Generon Shanghai	Biotechnology	Advisory Board	7/25/2020
HepaRegeniX	Biotechnology	Consulting	04/30/2021
Intercept Pharmaceuticals, Inc.	Biopharmaceutical	Advisory Board	09/17/2021
Korro Bio, Inc.	Biotechnology	Consulting	08/19/2023
Mallinckrodt Pharmaceuticals	Pharmaceutical	Advisory Board	10/19/2021
Novartis Pharma AG	Pharmaceutical	Consulting	05/12/2021
Resolution Therapeutics, Ltd.	Biopharmaceutical	Advisory Board	11/20/2022
Seal Rock Therapeutics, Inc.	Biotechnology	Consulting	04/12/2023
Surrozen	Biopharmaceutical	Advisory Board	12/31/2021
US Patent	NOVEL BRD4 INHIBITORS TO TREAT LIVER DISEASE – 2/2021		

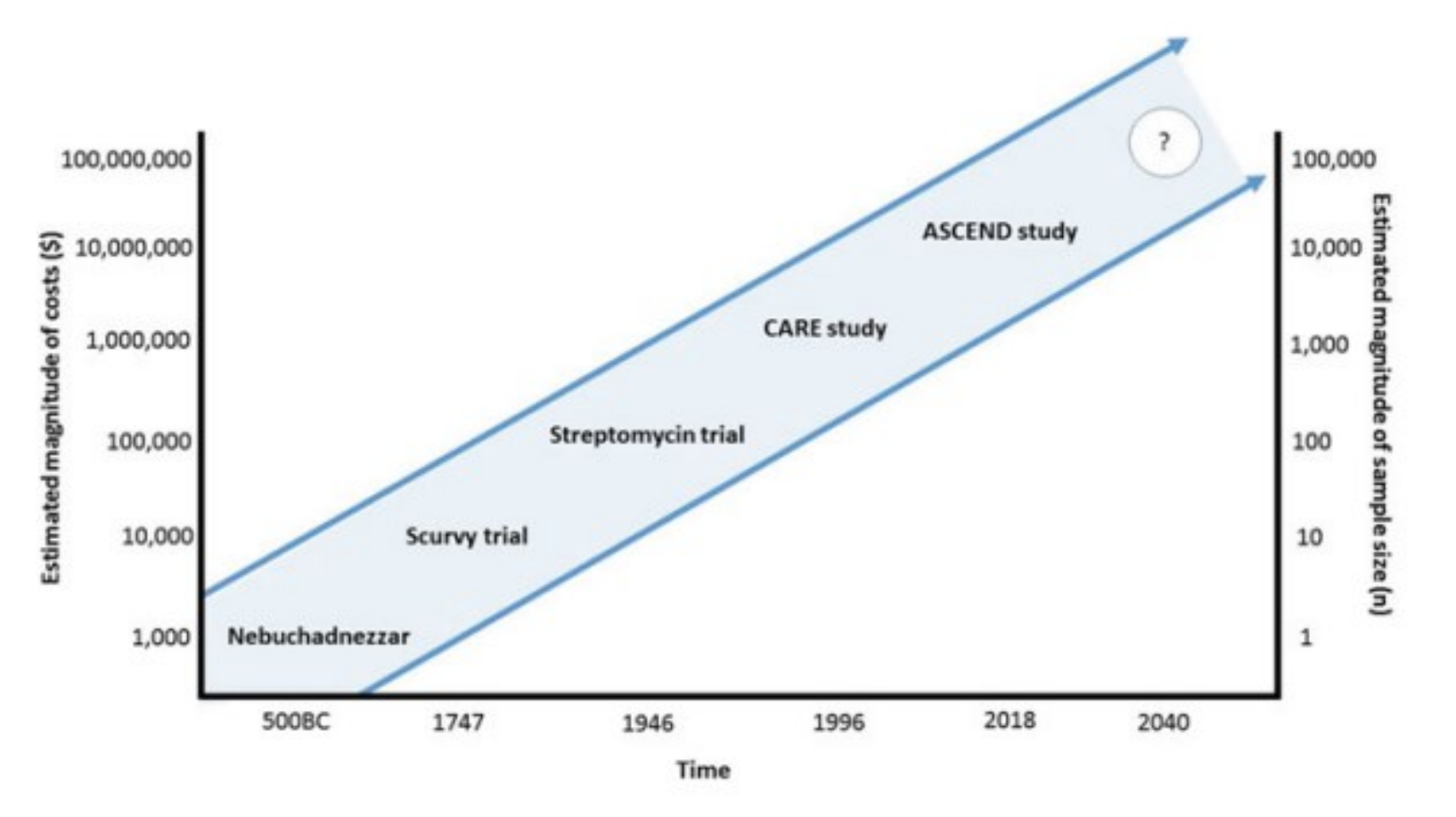
The burning platform…

- Status quo: RCTs are expensive, rarely completed, marginally ethical, and contribute to the Valley of Death for compound development
- The Opportunity: Disruptive technologies and ideas can allow a world without placebo arms and without FTF study visits at crowded AMCs

Forward looking clinical trial concepts

- Burning Platform
- Decentralized clinical trials
- Platform trials
- Real world trials
- AI/synthetic trials
- Point of Care trials
- Phase 1 clinical trials
- Adaptive Trial Designs (slides courtesy of P Kamath)
- Applying concepts to AUD +AH; integrated care

The exponential rise of funds and sample sizes needed to conduct a clinical trial



MD Kruizinga et al *Handb Exp Pharmacol* 2019

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Sir Austin Bradford Hill, the statistician and researcher credited with the invention of modern randomization methods

MD Kruizinga et al *Handb Exp Pharmacol* 2019

Adaptive Design Goal: Reduce Mortality in All Arms

Decentralized clinical trials meet patients where they are

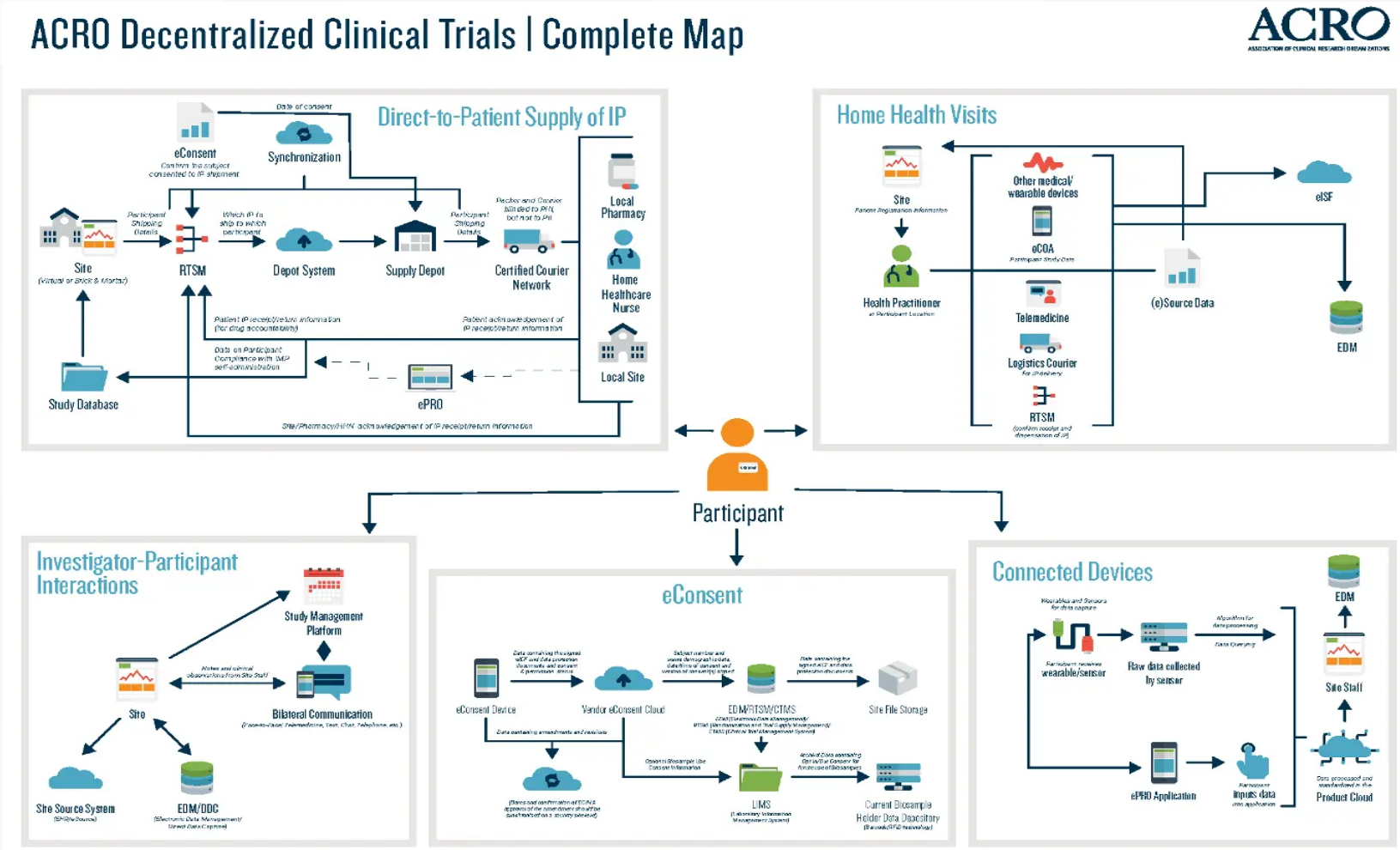
Clinical-trial designs

Fully decentralized ⟷ **Hybrid** ⟷ **Fully centralized**

All trial procedures are conducted virtually, enabled by digital technologies and supply delivery	Less complex trial procedures that don't require in-person visits (eg, vital signs, electrocardiograms) are conducted via telehealthcare, remote data collection, or direct-to-patient supply	Less complex trial procedures that require in-person visits (eg, injections) are conducted via mobile clinicians or alternative sites (eg, mobile clinics, retail sites)	Complex trial procedures (eg, complex screening protocols, cell therapy, magnetic resonance imaging) are conducted via research sites (eg, academic medical centers) or local hospitals	All trial procedures are conducted at a research site (eg, academic medical center)

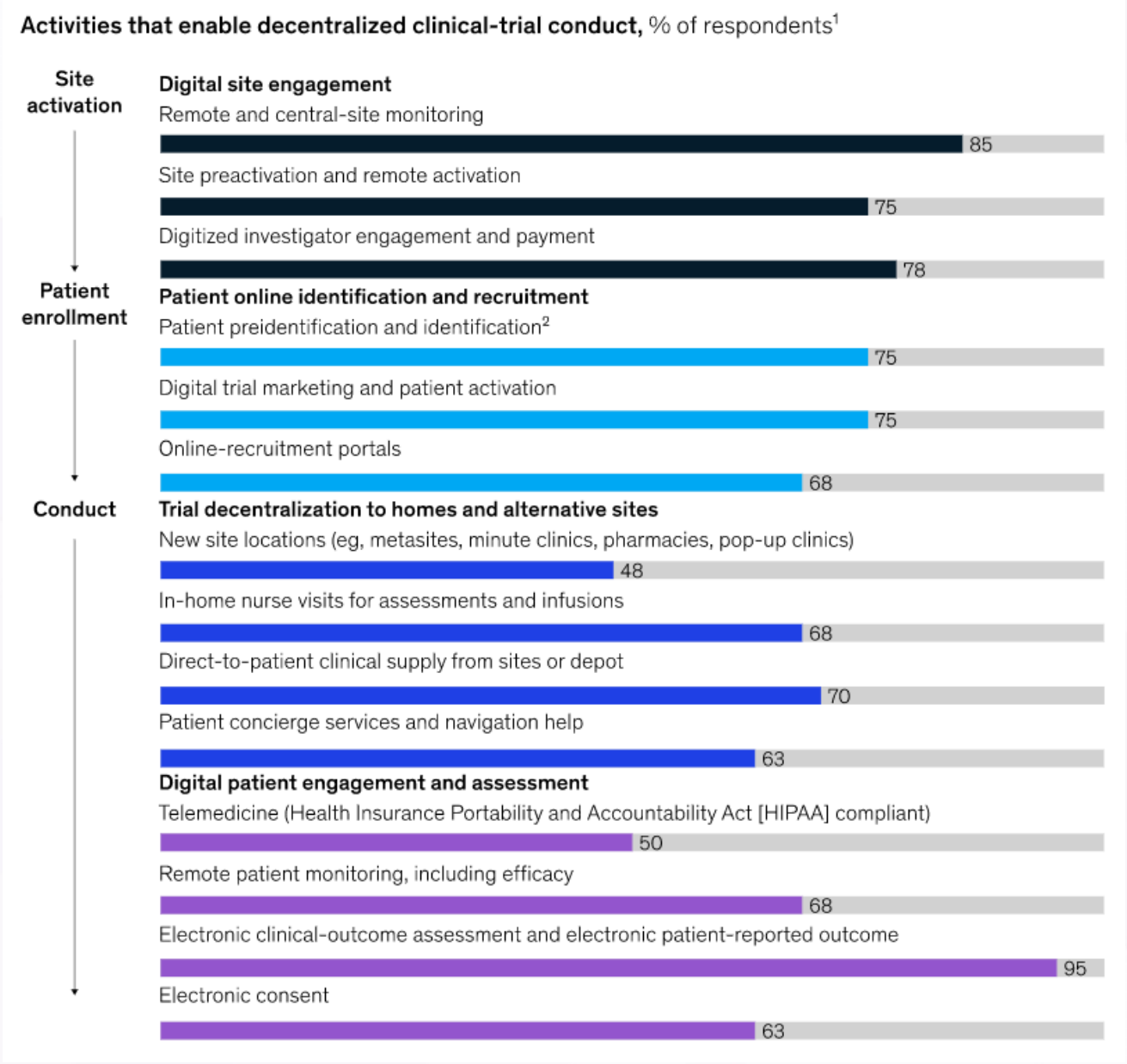
McKinsey & Company

Decentralized clinical trials



ACRO DCT Data Flow Maps

C Bahls *Applied Clin Trials* 2021



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Most clinical trials won't be entirely virtual but will use decentralization elements based on suitability for the end points

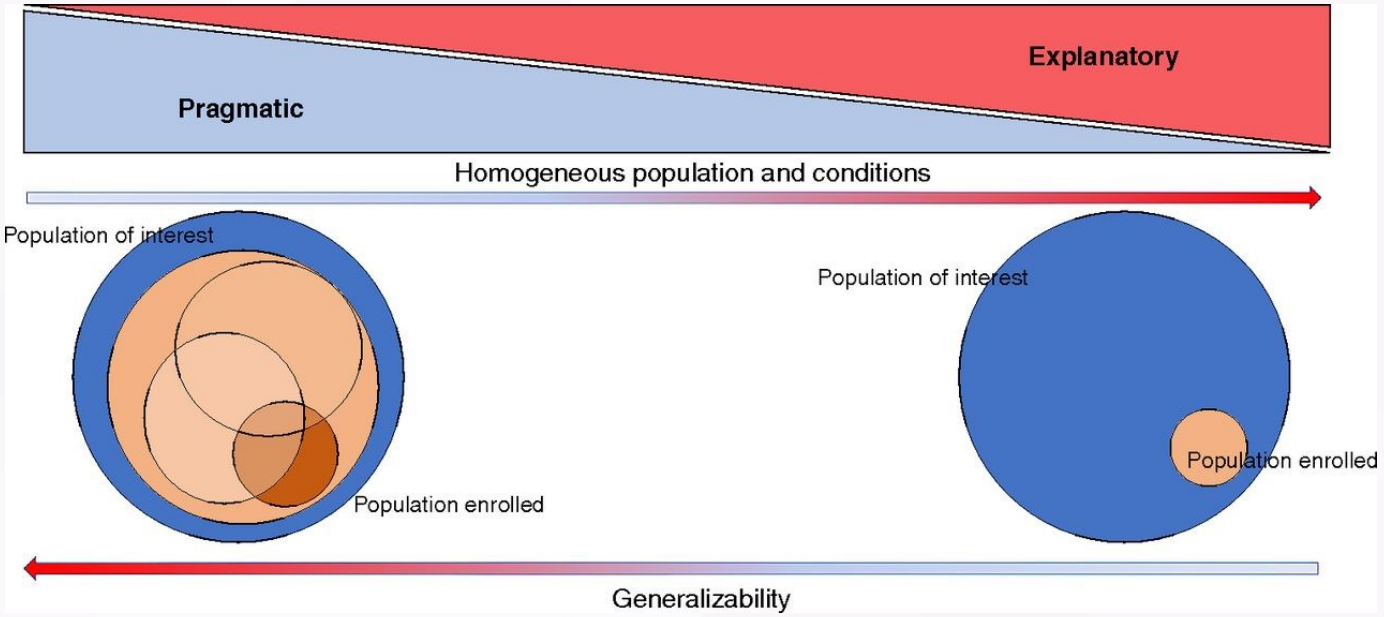
G Agrawal *McKinsey & Co* 2021

Platform Trial Design

- One trial design to answer multiple clinical questions concurrently
- Increased efficiency, reduced cost
- Challenging regulatory and statistical issues

Real-world trials / Pragmatic trials

- Allow enrollment of large numbers of patients within realm of traditional clinical care
- Assess likely impact of intervention in generalizable setting



Matthieu Legrand et al. *JASN* 2022

AI / Synthetic / In Silico trials

- Use of AI to create data sets that simulate real-world data
- Requires large well curated/annotated data sets of natural history of the disease
- Non linear statistical methods (AI) to create simulated match of a placebo cohort.
- Parallels to propensity matching

Point of Care Trials

- Includes many of the above principles
- Utilize EHR data for study purposes
- Utilize wearable and home data for study purposes
- Pragmatic designs for real world experience

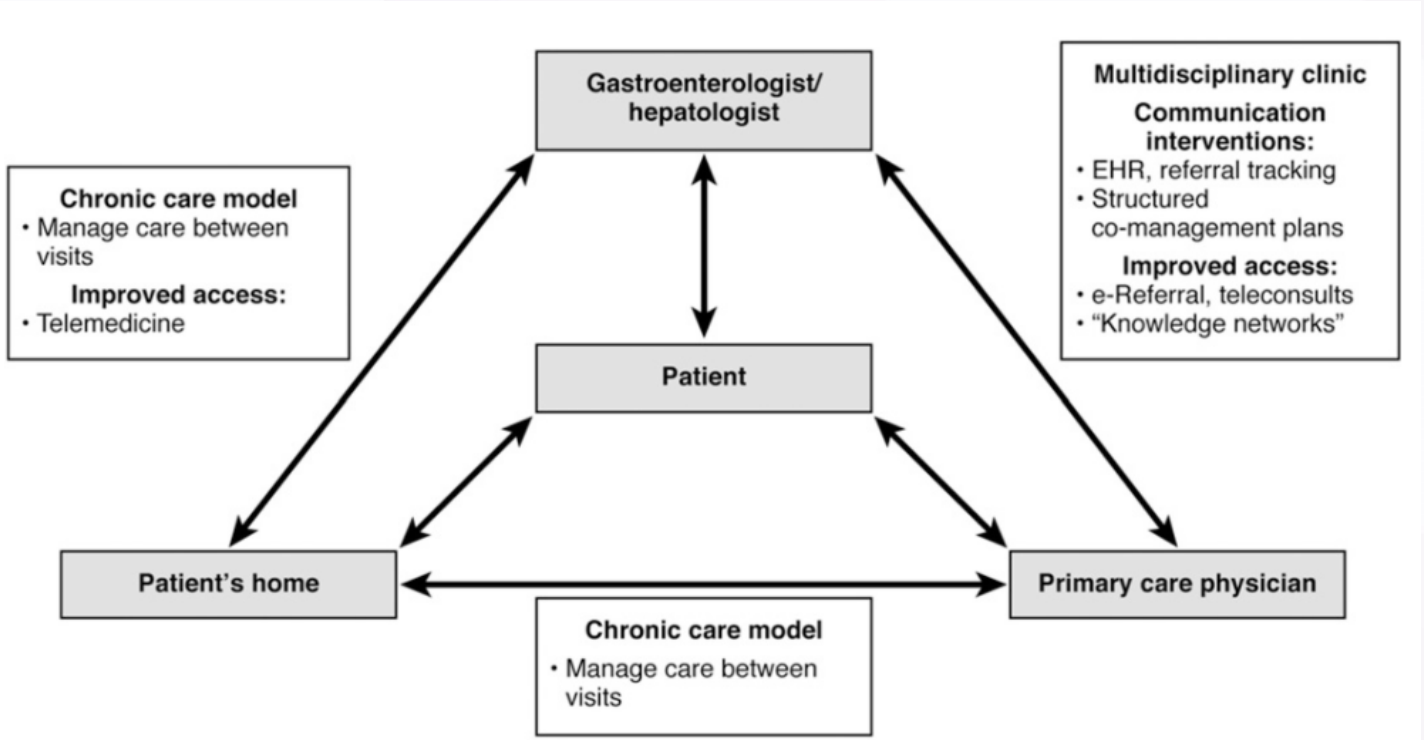
Phase 1 Clinical Trials

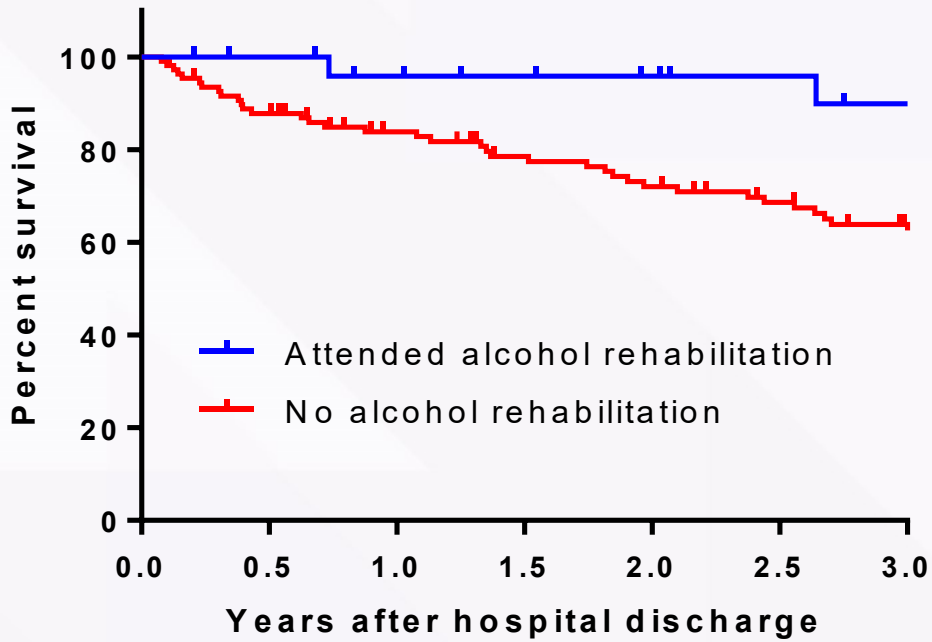
- Traditionally Phase 1 study is performed in healthy volunteers
- Cancer indications introduced Phase 1 studies directly in patients with advanced disease
- AH has same mortality as many cancers
- 3+3 study design introduced in AH (IL22, Durect)
- Dose escalation; disease severity

Adaptive Trial Designs

- Larger proportion of participants assigned to treatment groups performing well
- Reduce participants in treatment groups performing poorly
- Investigate *higher doses* and *longer/shorter duration* and allow for *second intervention* NOT POSSIBLE with non-adaptive designs
- Allow seamless transition of Phase II trials to Phase III

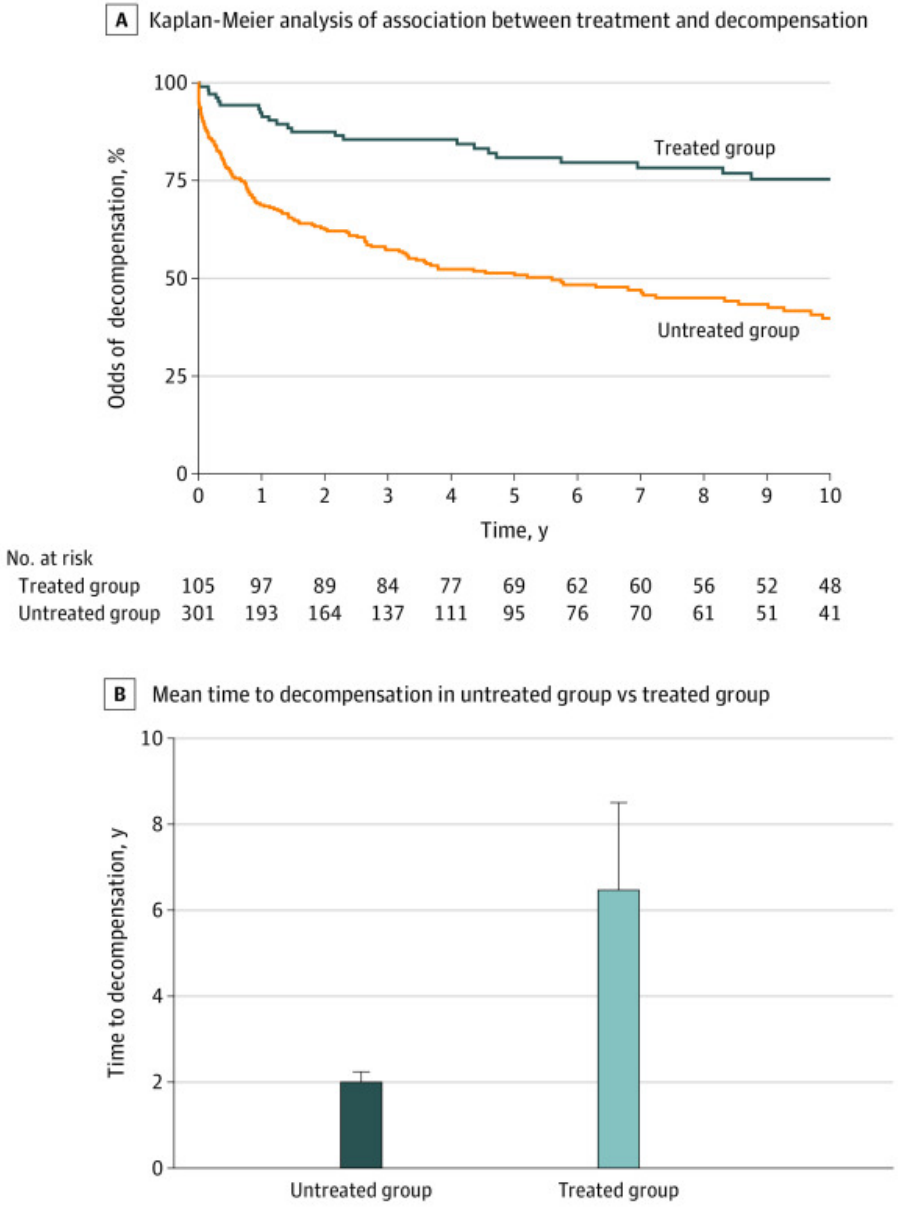
Integrated therapy for ALD/AUD





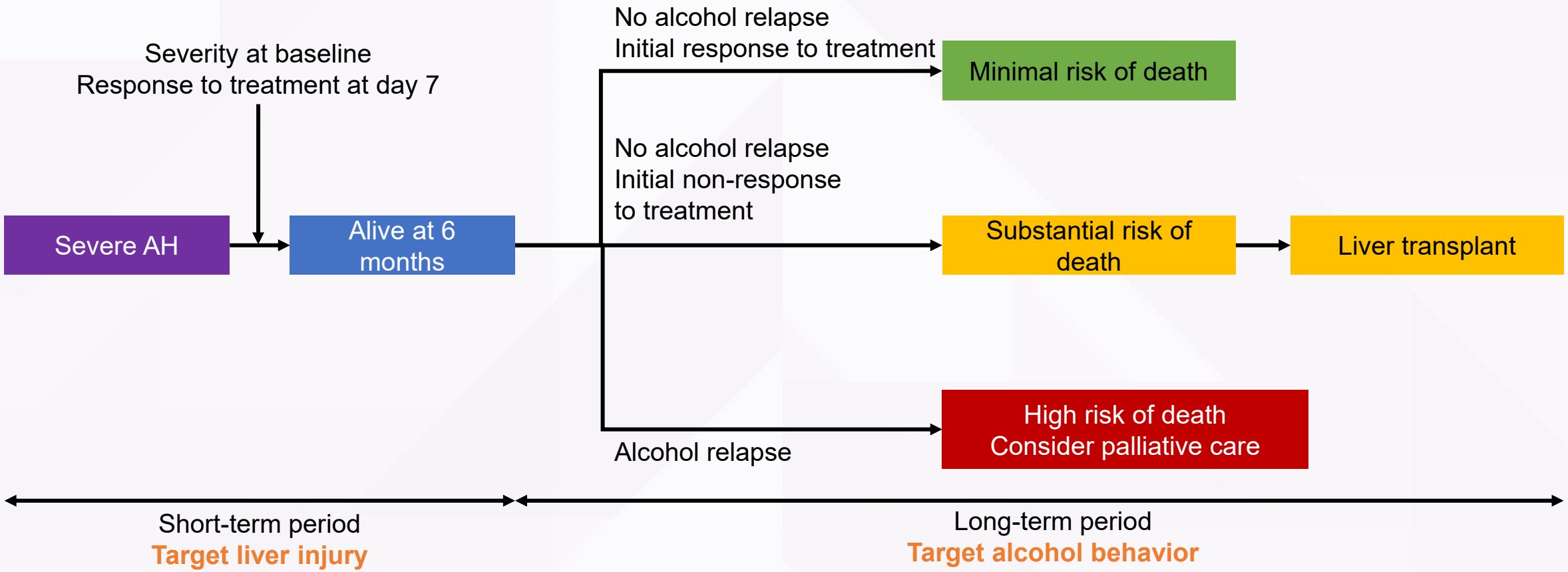
Mellinger JL and Volk ML *Clin Gastroenterol Hepatol* 2013
Peeraphatdit TB et al *Clin Gastroenterol Hepatol* 2020

Association of Medical Addiction Therapy for Alcohol Use Disorder With Odds of Hepatic Decompensation Within 10 Years After Cirrhosis Diagnosis



AGL Vannier et al *JAMA Network Open* 2022

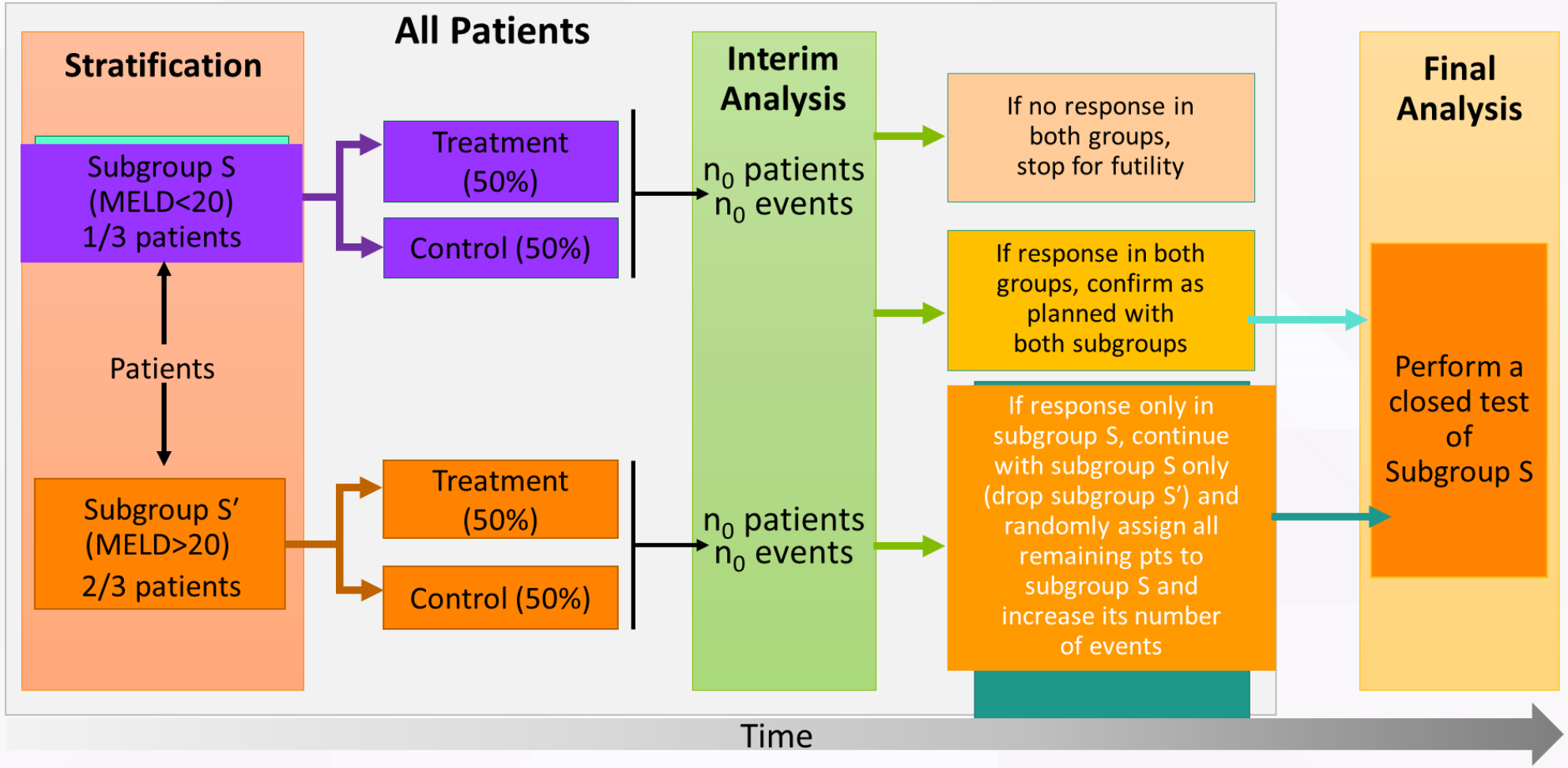
Alcohol Related Hepatitis: Therapeutic Targets



Ideal trial: First phase-Target liver injury and Second phase –Target alcohol behavior

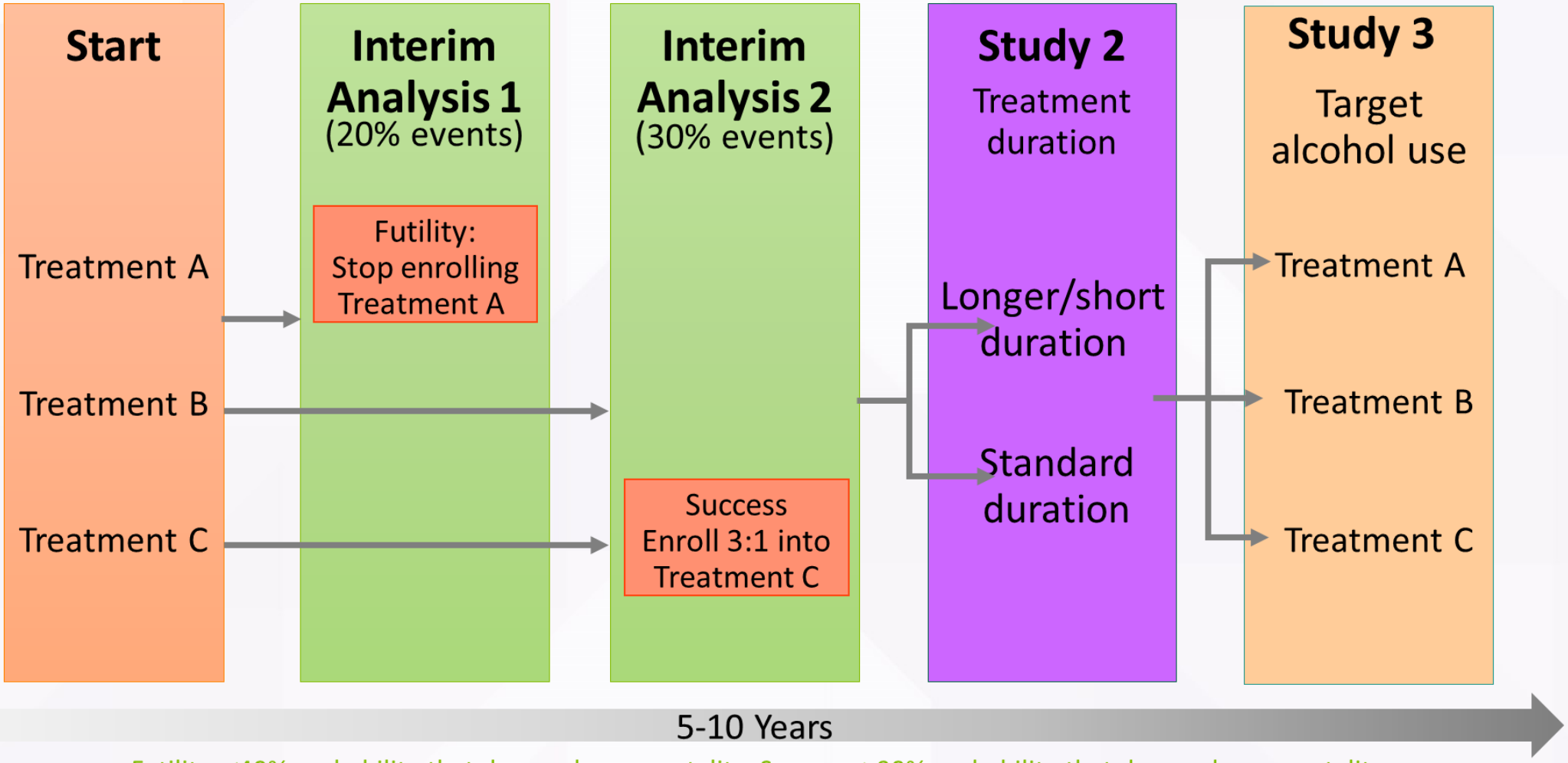
Louvet A et al *Hepatology* 2017

Adaptive Two-Stage Population-Enrichment Study for AUD



Bhatt DL, Mehta C *NEJM* 2016

Bayesian Adaptive Design for 3-Arm Study



Futility: ≤40% probability that drug reduces mortality; Success: ≥90% probability that drug reduces mortality

Adaptive Design Trials: Summary

- Improve efficiency and reduce costs
- Maximize success and data obtained
- Power calculated on study performance
- Accelerate the discovery process
- Advances in adaptive trial design requires acceptance of complex statistical methods
- An adaptive design will not save a poorly planned trial or ineffective treatment

Level Setting

Definitions

DECENTRALIZED CLINICAL TRIAL (DCT)	Some or all of a clinical trial's activities occur at locations other than a traditional clinical trial site
PRAGMATIC CLINICAL TRIAL	Designed to evaluate the effectiveness of interventions in real-life routine practice conditions, whereas explanatory trials aim to test whether an intervention works under optimal situations
REAL WORLD EVIDENCE (RWE)	Clinical evidence on a medical product's safety and efficacy that is generated using real-world data (RWD) resulting from routine healthcare delivery. Sources include EHRs, registries, claims/billing data, PROs, wearables
SYNTHETIC CONTROL ARM	A type of external control arm, in which researchers use historical data to construct a virtual or synthetic control rather than recruiting new patients for a control group
BASKET TRIALS	A type of clinical trial that tests how well a new drug or therapy works in patients who have different types of cancer that all have the same mutation or biomarker
UMBRELLA TRIALS	A type of clinical trial that tests how well new drugs or other substances work in patients who have the same type of cancer but different gene mutations or biomarkers.

Courtesy of Owen Garrick, MD
Dean, Clinical Trials
Mayo Clinic Arizona

Preparing for the Conduct of the Clinical Trials of the Future

HOW SHOULD WE BE PREPARED TO CONDUCT CLINICAL TRIALS IN THE FUTURE?

1. Developing an approach to ensuring real world/truly representative sample sets
2. Leveraging information technology to accelerate cures
3. Should we have a different approach/ methodology to emerging scientific advances?
4. Implementation Science to harness the output of clinical trials for patient care in practice settings of the future

Courtesy of Owen Garrick, MD
Dean, Clinical Trials
Mayo Clinic Arizona

Take-Home Messages

- Given Covid 19 and advances in technology and biostatistics, we have the opportunity to reimagine clinical trials
- Trials in AH should be aimed at targeting liver injury AND alcohol use behavior