A-TANGO Masterclass – Study Design

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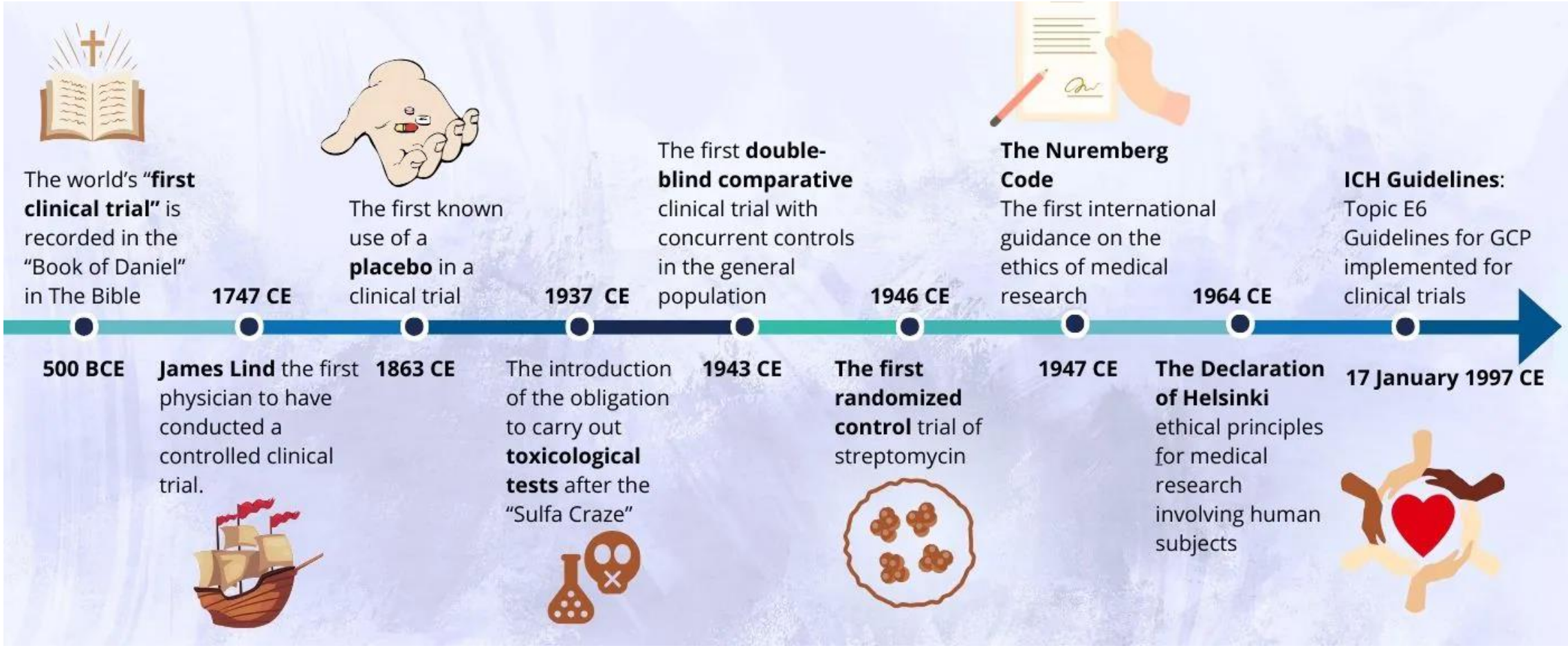
History of clinical trials



https://www.sciencepharma.com/blog/changing-face-of-clinical-trials-history/

Study design - Women's Health Initiative (WHI) - Hormone Replacement Therapy (HRT)

- **Issue**: Early observational studies suggested that HRT reduced cardiovascular disease in postmenopausal women. However, these studies were **not randomized** and had selection bias (healthier women were more likely to take HRT).
- **Consequence**: When a **randomized controlled trial (RCT)** was conducted, it found the opposite—HRT actually increased the risk of heart disease, stroke, and breast cancer.
- **Lesson**: Poor study design in early research led to misleading conclusions, causing confusion and potential harm.

Endpoint - Roche's Avastin for Breast Cancer

- **Issue**: Avastin (bevacizumab) was granted accelerated FDA approval for metastatic breast cancer based on a study that used **progression-free survival (PFS)** as the primary endpoint instead of **overall survival (OS)**.
- **Consequence**: Follow-up RCTs showed no significant improvement in OS, and the drug was eventually **withdrawn** for breast cancer by the FDA in 2011.
- **Lesson**: Choosing the wrong endpoint in study design led to an approval that was later revoked.

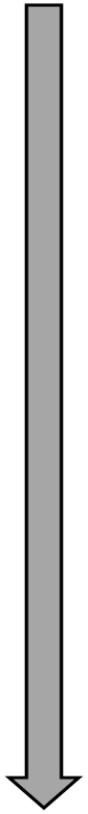
Conduct - Duke University Scandal – Genomic Signatures for Cancer Treatment

- **Issue**: A research team at Duke University developed genomic tests to personalize chemotherapy but relied on **flawed statistical methods and mislabelling of data** in their study design.
- **Consequence**: The trials were **shut down**, and papers were retracted after an independent review found that the results were unreliable.
- **Lesson**: Poor study design and data analysis can lead to wasted resources and ethical concerns.

Study Design – Generating Evidence

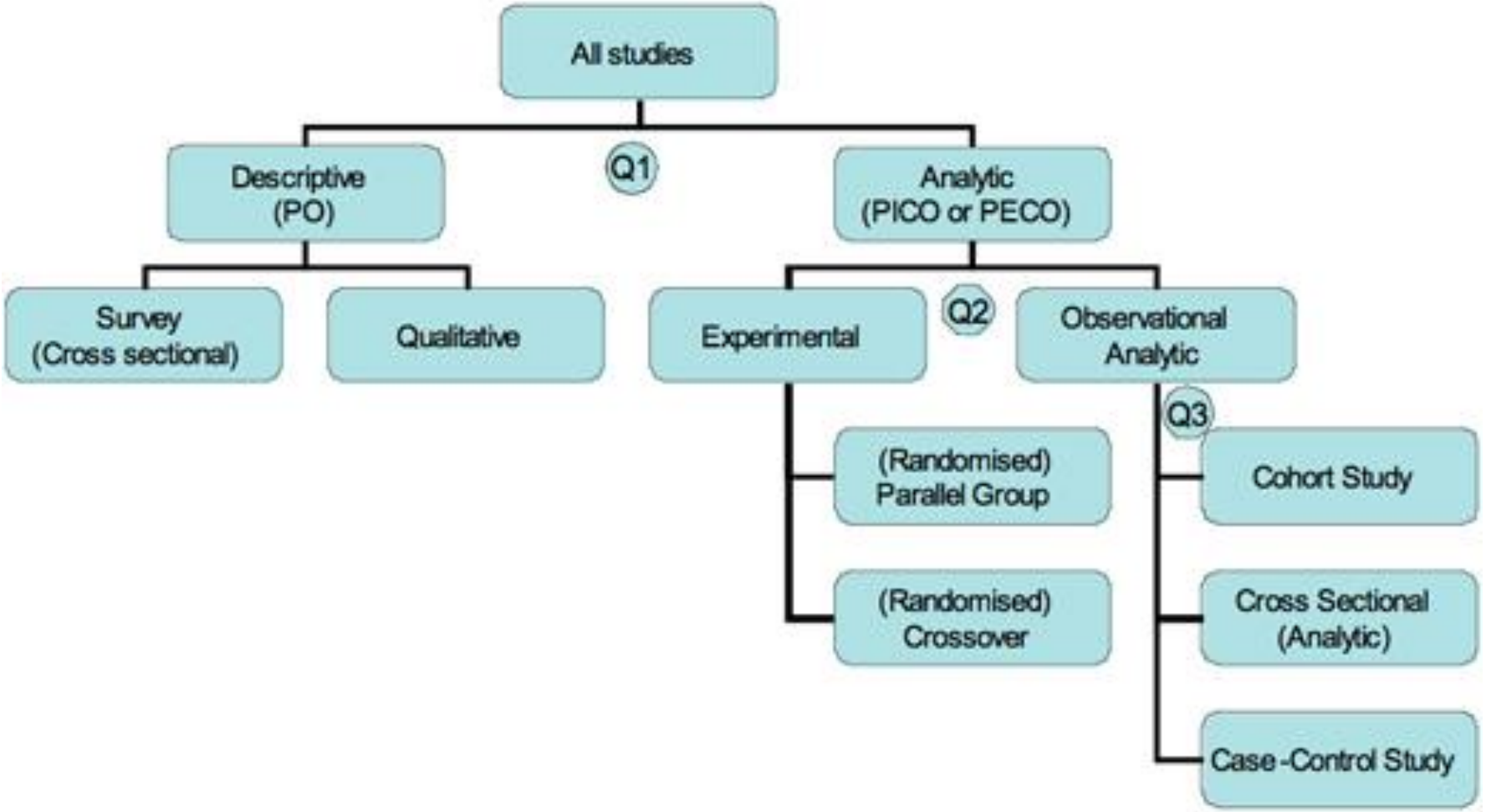
Table 1: The hierarchy of epidemiological study designs

Observational studies		Strength of evidence
Descriptive study designs		
Case report	Single case	
Case series	Collection of similar cases	
Correlational	Population based study - using secondary data	
Cross-sectional (descriptive)	Single sample from larger population- no comparison	
Analytical study designs		
Cross-sectional (analytical)	Single sample from larger population-compares two or more groups in the sample	
Case-control	Compares risk factors between diseased (cases) and non-diseased (controls) groups	
Cohort	Compares outcomes between groups exposed and non-exposed to a risk factor for a disease	
Interventional study		
Clinical trial	Investigator allots the subjects to different groups - intervention versus non-intervention	



Omair A et al. Jounal of Health Specialities 2015

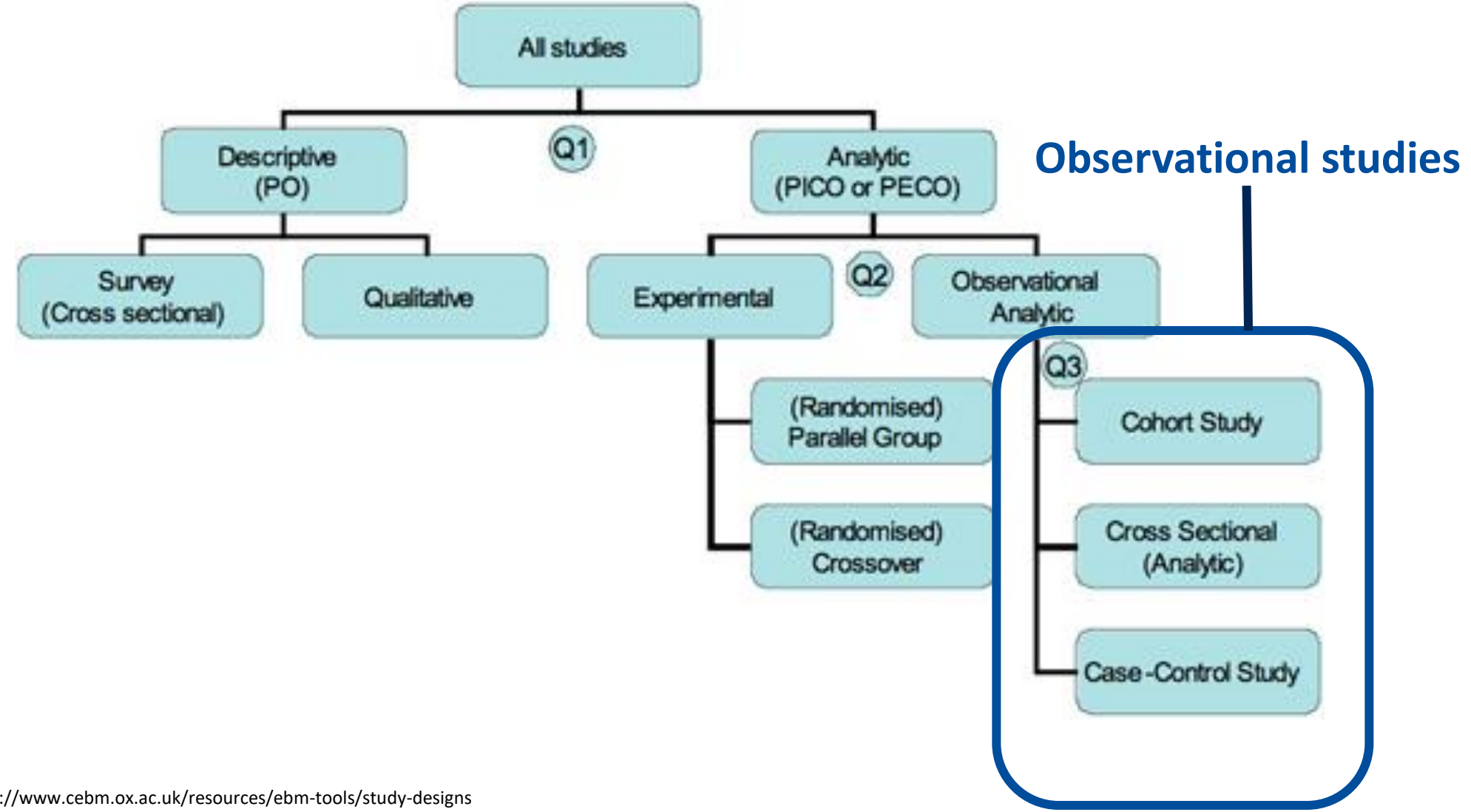
Study design



Observational vs. Interventional Studies

Feature	Observational Study	Interventional Study
Definition	Researchers observe subjects without interference	Researchers actively intervene and control variables.
Purpose	Identify associations between variables.	Establish causal relationships.
Types	Cohort, Case-Control, Cross-Sectional.	Randomized Controlled Trials (RCTs), Non-Randomized Trials.
Control over variables	Minimal control over factors.	High control over exposure/treatment.
Bias & Confounding	Higher risk of bias due to lack of randomization.	Lower risk of bias with proper randomization.
Ethical concerns	Less ethical risk since no intervention is applied.	May have ethical challenges if intervention has risks.
Cost & Time	Usually cheaper and faster.	Often expensive and time-consuming.

Study design



Observational studies

Cross-Sectional Studies (analytical)

- **Definition**: Data collected at a single point in time
- **Pros:** Quick, cost-effective
- **Cons:** Cannot determine causality or temporal relationships

Example of a High-Quality Cross-sectional Study in Cirrhosis"

- ✅ **Study Population:**
  Adults attending primary care clinics for routine checkups.
- ✅ **Exposure Measurement:**
- Self-reported alcohol consumption (frequency, quantity, duration).
- Categorized as: **non-drinker, moderate drinker, heavy drinker**.
- ✅ **Outcome Measurement:**
- Blood tests measuring **ALT (Alanine Aminotransferase) and AST (Aspartate Aminotransferase)** levels.
- Elevated liver enzymes defined as **ALT >40 U/L and/or AST >40 U/L**.
- ✅ **Statistical Analysis:**
- **Prevalence ratios (PR)** calculated using **log-binomial regression**.
- **Comparison of mean liver enzyme levels** across alcohol consumption categories using **ANOVA or t-tests**.
- **Multivariable adjustment** to control for confounders.

Cross-Sectional Studies

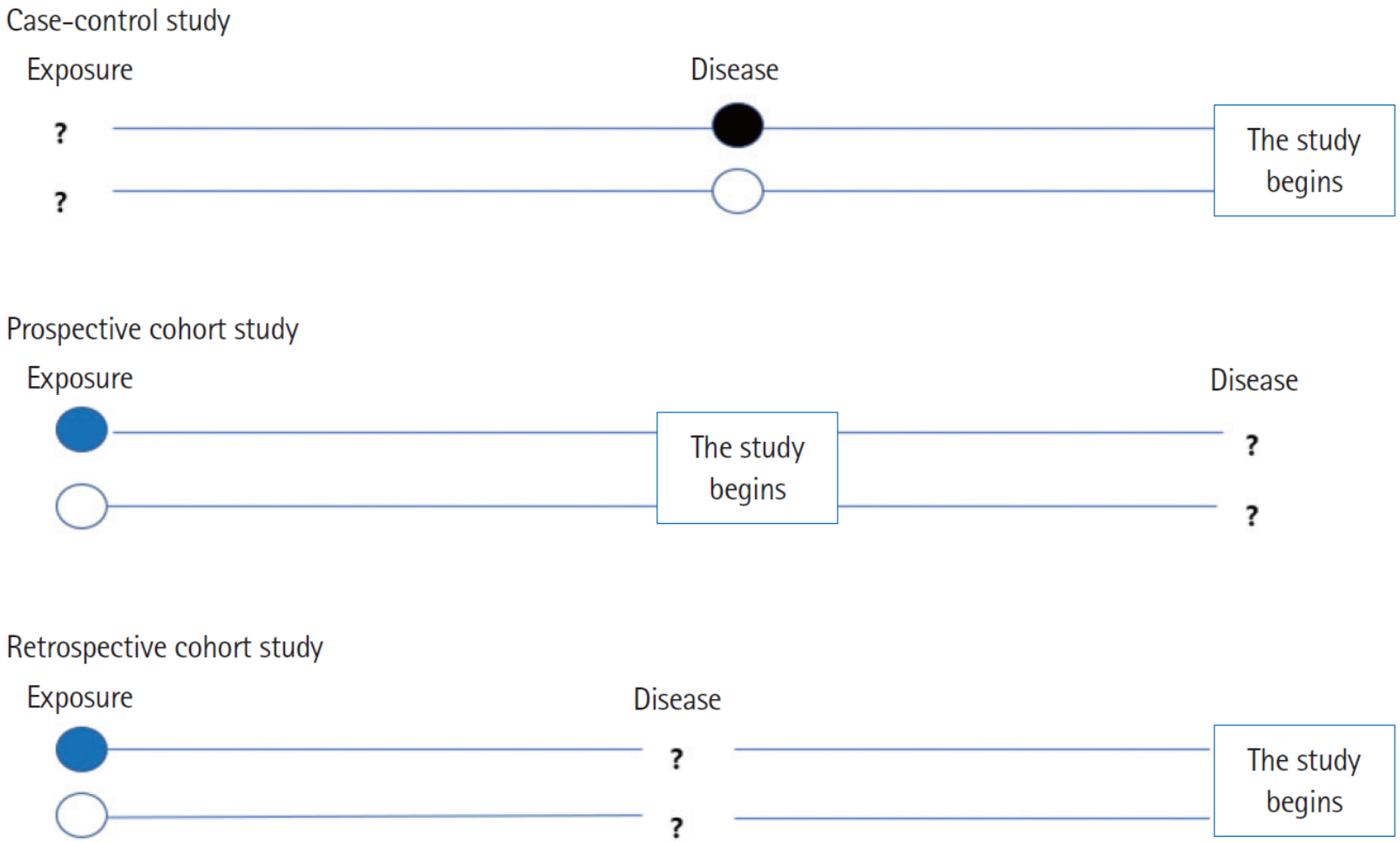
Example: Rathi S et al. J Clin Exp Hepatol 2019

Prevalence of Minimal Hepatic Encephalopathy in Patients With Liver Cirrhosis

Longitudinal observational studies

Feature	Cohort Study	Case-Control Study
Study design	Starts with **exposure**, follows participants over time to see who develops the outcome.	Starts with **outcome** (cases) and looks back to find previous exposures.
Direction of study	**Prospective** (forward in time) or **retrospective**.	**Always retrospective** (looks backward in time).
Grouping	Groups based on **exposure** (e.g., smokers vs. non-smokers).	Groups based on **outcome** (e.g., people with lung cancer vs. people without).
Time Frame	Longitudinal (follows participants over time).	Snapshot of past exposures (does not follow forward in time).
Best for	Studying **incidence** (new cases) and risk factors.	Studying **rare diseases** or outcomes.
Disadvantages	Expensive, time-consuming, potential loss to follow-up.	Prone to **recall bias** (since past exposures are self-reported).

Longitudinal observational studies



Example of a High-Quality Case-Control Study in Cirrhosis

- **Title:**
- *"Association Between Past Alcohol Consumption and the Development of Cirrhosis: A Case-Control Study"*
- **Study Design:**
- ✅ **Cases:** Patients diagnosed with cirrhosis (confirmed via biopsy, imaging, or clinical criteria).
  ✅ **Controls:** Patients without cirrhosis (matched by age, sex, and other relevant factors, but without liver disease).
  ✅ **Exposure Assessment:**
- Past alcohol consumption (self-reported + medical records).
- Viral hepatitis status (HBV, HCV).
- Metabolic risk factors (diabetes, obesity, NAFLD).
  ✅ **Statistical Analysis:** Odds ratios (OR) to measure the association between alcohol intake and cirrhosis risk.

Case-Control Study

Example: Gao X et al. BMC Pregnancy and Childbirth 2021

Maternal and fetal outcomes in patients with liver cirrhosis: a case-control study

Example of a High-Quality Cohort Study in Cirrhosis

- **Title:** Long-Term Outcomes in Patients with Compensated Cirrhosis: A Prospective Cohort Study

Study Design:

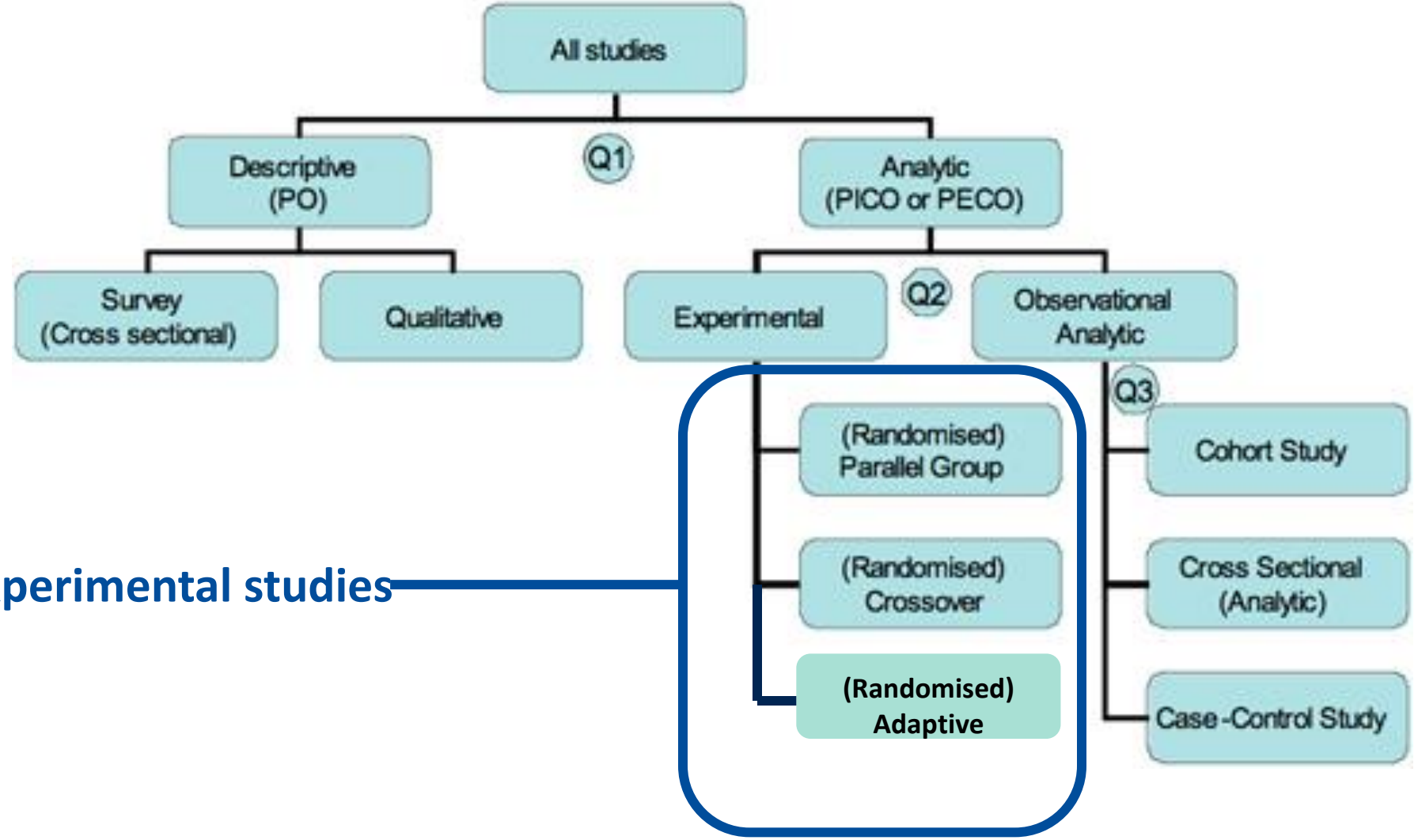
- **Population:** A cohort of 1,500 patients with compensated cirrhosis, prospectively enrolled from multiple tertiary care centers.
- **Exposure:** Patients were stratified based on etiology (e.g., alcohol-related, viral hepatitis, NASH).
- **Follow-up Duration:** 10 years
- **Primary Outcome:** Progression to decompensated cirrhosis (ascites, variceal bleeding, hepatic encephalopathy).
- **Secondary Outcomes:** Liver transplantation, mortality, development of hepatocellular carcinoma.

Cohort Study

Example: Cao Z et al. Lancet Gastroenterol Hepatol 2024

Global prevalence and characteristics of infections and clinical outcomes in hospitalised patients with cirrhosis: a prospective cohort study for the CLEARED Consortium

Study design



Experimental studies

Experimental Studies

Features	Randomised Parallel	Randomised Crossover	Randomised Adaptive
Principals	Participants are randomly assigned to different intervention groups and remain in the same group throughout the study	Participants receive multiple interventions in a sequential manner, with a "washout" period in between to reduce carryover effects.	Uses interim analyses to modify trial aspects (e.g., sample size, randomization ratio, treatment arms) based on accumulated data.
Pros	- Simple design, widely used. - Minimizes carryover effects. - Suitable for long-term outcomes.	- Each participant serves as their own control, reducing variability. - Requires a smaller sample size. - Higher statistical power.	- More flexible and efficient. - Can identify effective treatments faster. - Potentially reduces patient exposure to ineffective treatments
Cons	- Requires a larger sample size. - Inter-individual variability may impact results.	- Not suitable for conditions with permanent effects. - Carryover effects may still exist. - Requires longer study duration due to washout periods	- More complex design and analysis. - Requires continuous monitoring. - Possible risk of operational bias.

Randomized Controlled Trial (RCTs) – Parallel Design

Example: Pose E et al. JAMA 2025

Simvastatin and Rifaximin in Decompensated Cirrhosis – A Randomized Clinical Trial

Randomized Controlled Trial (RCTs) – Crossover Design

Example: Terbah R et al. Hepatology 2024

Continues home terlipressin infusion increases handgrip strength and reduces ascites – A prospective randomized crossover study

Randomized Controlled Trial (RCTs) – Adaptive Design

Example: Pessoa-Amorim G et al. Future Healthcare Journal 2021

Making Trials part of good clinical care: lessons from the RECOVERY trial

Randomized Controlled Trial (RCTs) – Adaptive Design

Example: Horby P et al. NEJM 2020

Dexmethasone in Hospitalized Patients with Covid-19 – Preliminary Report

Endpoints in liver disease and ACLF

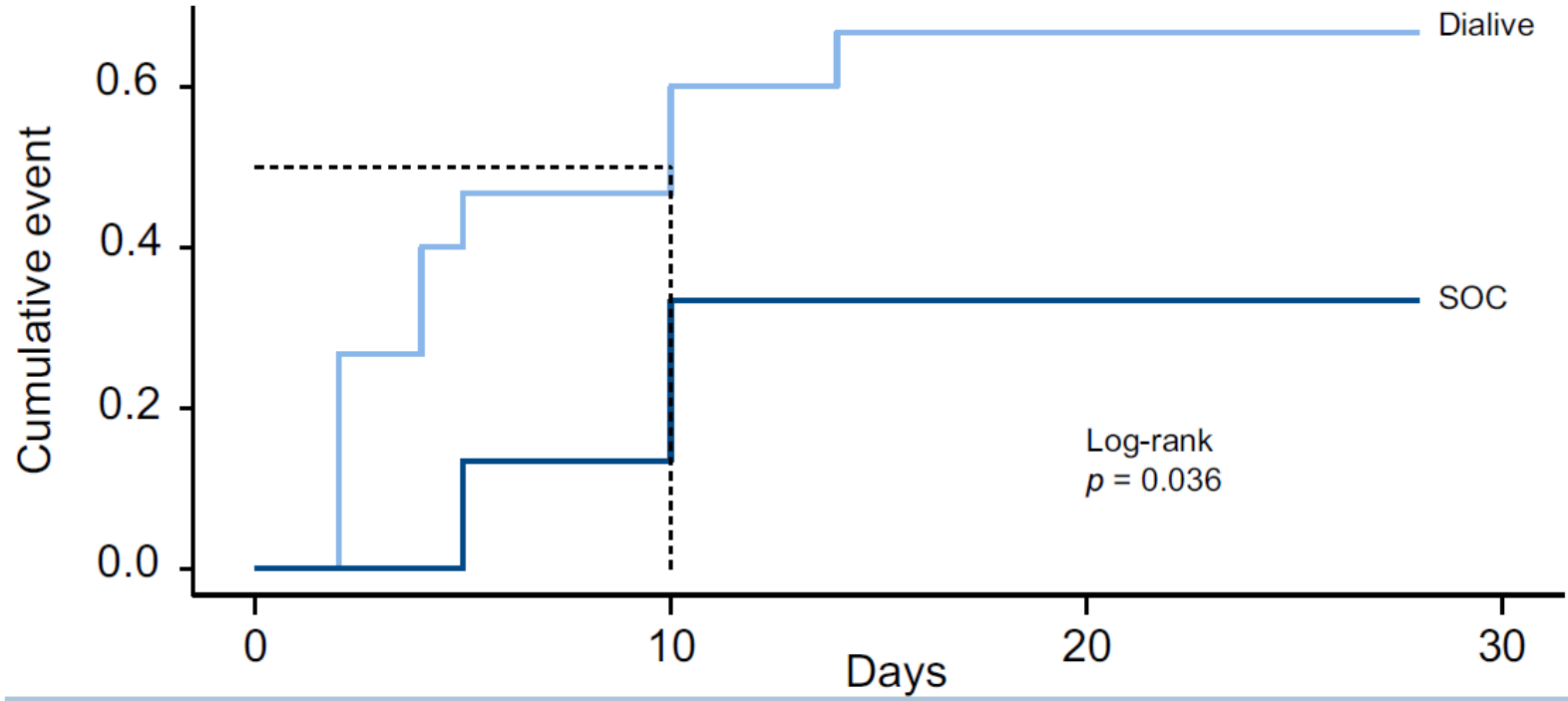
Target population	
Inclusion criteria	• Patients with cirrhosis defined by standard clinical criteria, ultrasonographic findings and/or histology. - Decompensated cirrhosis with CTP score B or C up to 12 points (a subgroup of CTP A patients may have decompensated cirrhosis; in particular those with moderate ascites and preserved hepatic function). • No upper limit for age • Patients on the waiting list for liver transplantation should be included
Exclusion criteria	• Active alcohol consumption expected to preclude correct adherence to study procedures • Patients with a history of significant non-hepatic diseases with impaired short-term prognosis (heart failure NYHA Grade III/IV, COPD GOLD C or above). • Patients with current non-hepatic malignancies including solid tumours and hematologic disorders. • Patients with hepatocellular carcinoma, except for patients with early HCC (BCLC-0 or BCLC-A) or patients with previous history of HCC and absence of recurrence 2 years after treatment. • Patients on antiviral therapy for HCV or those who have received it within the last 12 months. Patients with antiviral therapy for HBV for less than 12 months. • Patients under treatment with corticosteroids for autoimmune hepatitis for less than 6 months. • TIPS insertion within 6 months prior to study inclusion.
Endpoints – phase III trials	
Primary endpoint	• Survival (90-day, 1-year)
Secondary endpoints	• Composite endpoint of complications of cirrhosis • Development of ACLF • Hospital readmissions • Treatment-related adverse events
Endpoints – phase II trials	
Primary endpoint	• Surrogate markers with known association with survival (*i.e.*, changes in CTP or MELD score)
Secondary endpoints	• Biomarkers of disease progression known to correlate with hard clinical endpoints (*i.e.*, cytokines, oxidized albumin, NGAL or other biomarkers). • Treatment-related adverse events

Endpoints in liver disease and ACLF

Target population	
Inclusion criteria	• Use the most updated international definition for ACLF, according to the recommendations of the main international scientific societies
Exclusion criteria	• Patients with ACLF with 4 or more organ failures. • Comorbidities or clinical conditions that modify only the long-term prognosis may not be relevant in the setting of ACLF and, thus, patients with these conditions should not be excluded
Endpoints	
Primary endpoint	• Short-term survival (in-hospital and 28-day)
Secondary endpoints	• Changes in ACLF stage (worsening or improvement) • Treatment-related adverse events

ACLF Resolution – Clinical endpoint with prognostic relevance

Cumulative incidence – ACLF resolution



N° at risk				
Dialive	15 (0)	8 (9)	5 (10)	0 (10)
SOC	15 (0)	13 (5)	10 (5)	0 (5)

ACLF Resolution – Clinical endpoint with prognostic relevance

Initial Grade	Final Grade			
	No ACLF (n = 165)	ACLF-1 (n = 70)	ACLF-2 (n = 59)	ACLF-3 (n = 94)
ACLF-1 (%)				
Prevalence (n = 202)	110 (54.5)	49 (24.3)	18 (8.9)	25 (12.4)
28-day tx-free mortality (n = 190)	7/104 (6.7)	10/47 (21.3)	8/15 (53.3)	21/24 (87.5)
90-day tx-free mortality (n = 172)	19/95 (20.0)	17/41 (41.5)	10/13 (76.9)	23/23 (100)
ACLF-2 (%)				
Prevalence (n = 136)	47 (34.6)	19 (14.0)	35 (25.7)	35 (25.7)
28-day tx-free mortality (n = 118)	1/42 (2.4)	2/17 (11.8)	8/27 (29.6)	29/32 (90.63)
90-day tx-free mortality (n = 110)	5/39 (12.8)	5/16 (31.3)	18/23 (78.3)	32/32 (100)
ACLF-3 (%)				
Prevalence (n = 50)	8 (16.0)	2 (4.0)	6 (12)	34 (68)
28-day tx-free mortality (n = 45)	1/8 (12.5)	0/2 (0.0)	4/6 (66.7)	28/29 (96.6)
90-day tx-free mortality (n = 45)	1/8 (12.5)	1/2 (50.0)	4/6 (66.7)	28/29 (96.6)

FDA requirements for clinical endpoints

- 1. Clinical Meaningfulness
- 2. Validity & Reliability
- 3. Regulatory Acceptability
- 4. Sensitivity & Specificity
- 5. Types of Acceptable Endpoints
- 6. Statistical Considerations
- 7. Patient-Reported Outcomes (if applicable)
- 8. Consistency Across Studies
- 9. Ethical Considerations
- 10. FDA Engagement

Summary

- There are multiple study designs and the choice for or against a design results from the research question, ethics, resources and future plans for research translation, drug approval
- Observational trials are relevant for disease characterization and factors that impact on the disease phenotype
- Randomized trials are strong in identifying causal relationship
- Endpoints in cirrhosis and ACLF may include survival and the organ recovery or the disease course.
- The choice of endpoints impacts significantly on the regulatory approval for new drugs