Potential trial designs and suitable study populations

EMA stakeholder interaction on the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH)

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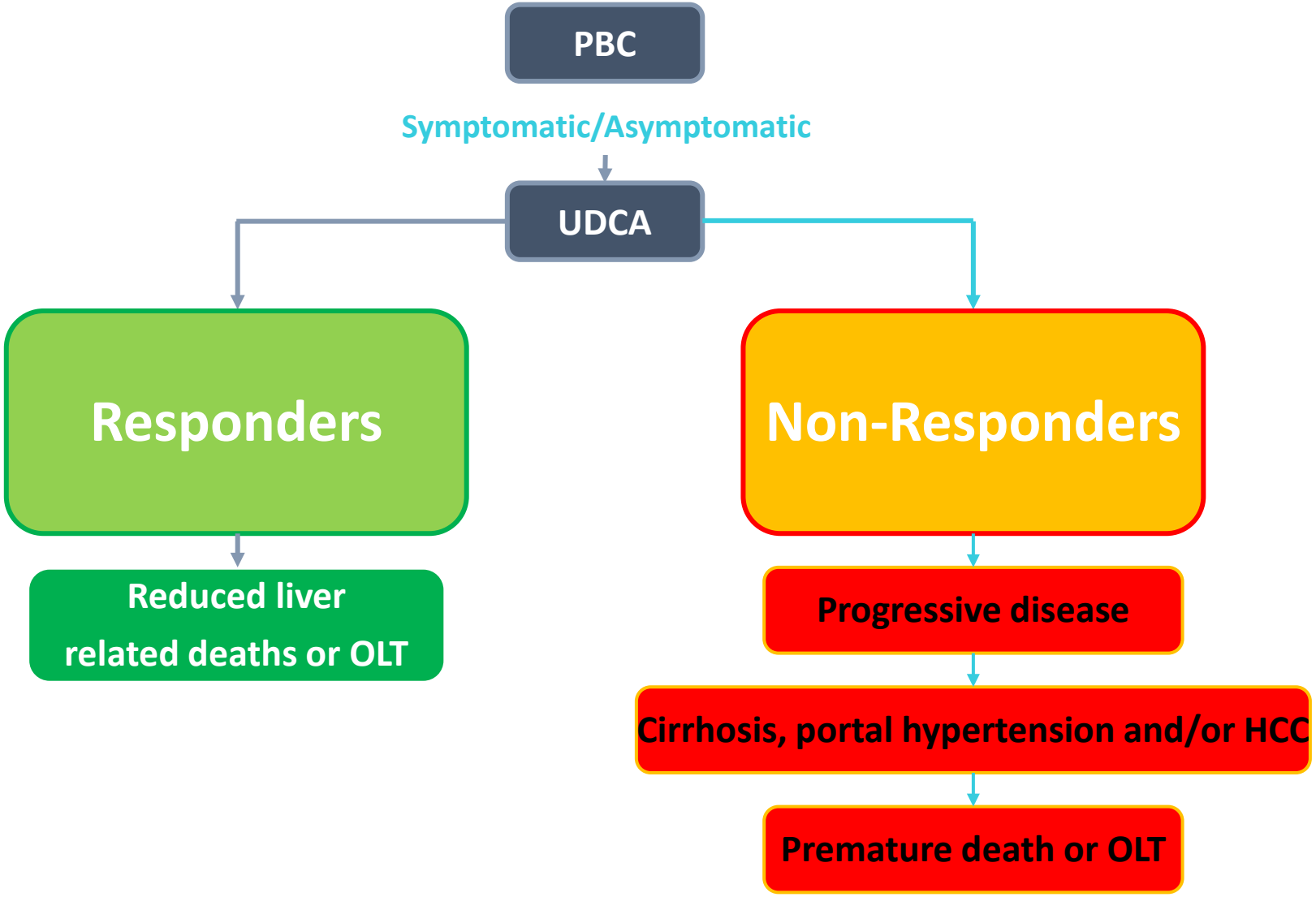
TORONTO CENTRE FOR LIVER DISEASE

Selection of study population



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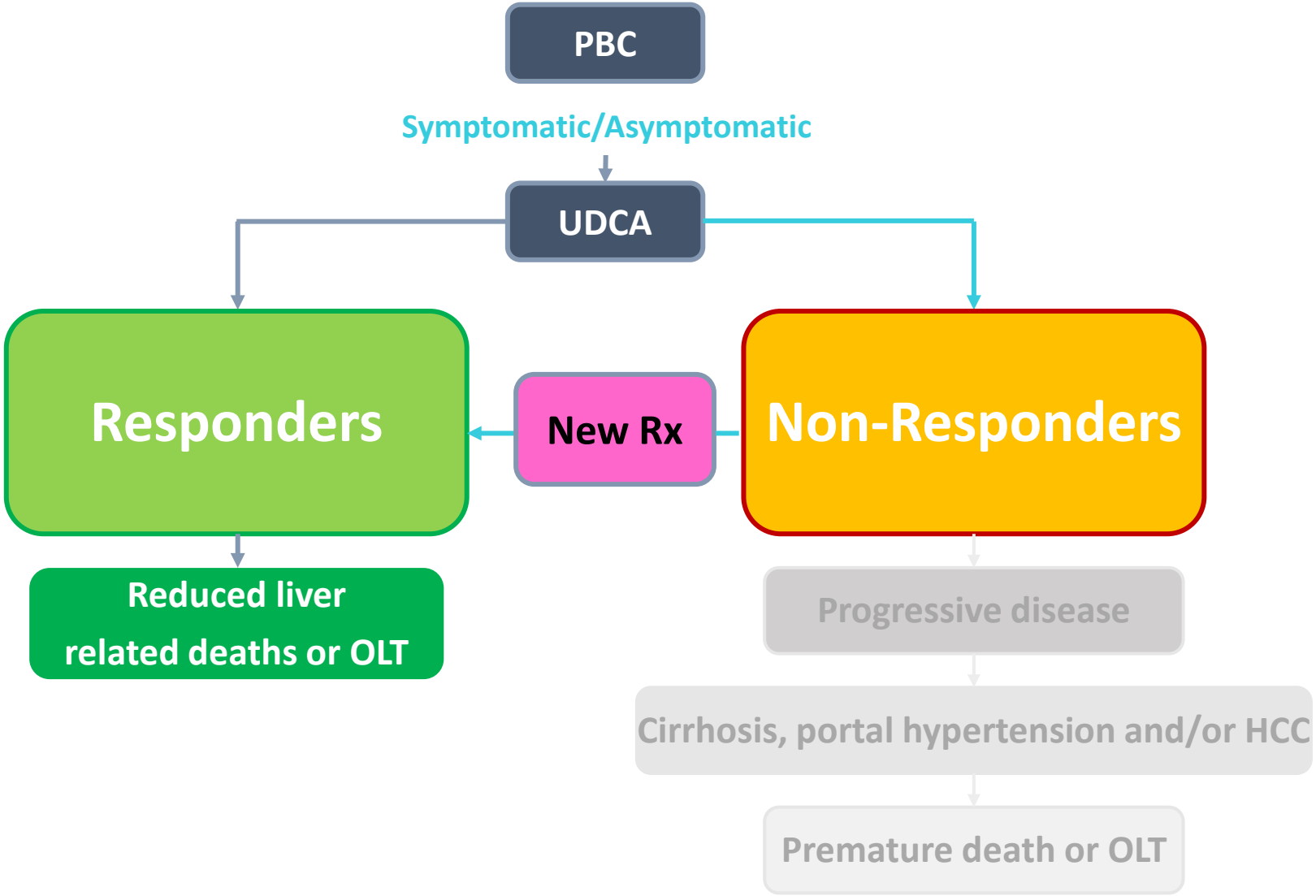
New Treatment (Rx) if insufficient response to UDCA



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Inclusion criteria often related to response criteria

Duration: 1 year

POISE[1] – trial

Inclusion: ALP>1.67 OR abnormal bilirubin, but bilirubin < 3xULN

Response: ALP<=1.67 AND min. 15 % reduction compared to baseline AND normal bilirubin

BEZURSO[2] - trial

Inclusion: Non-responder according to Paris I

Response: normal bilirubin, normal ALP, AST, ALT, albumin and PT

[1]*Nevens et al ; NEJM 2016;* [2]*Corpechot at al; NEJM 2018*

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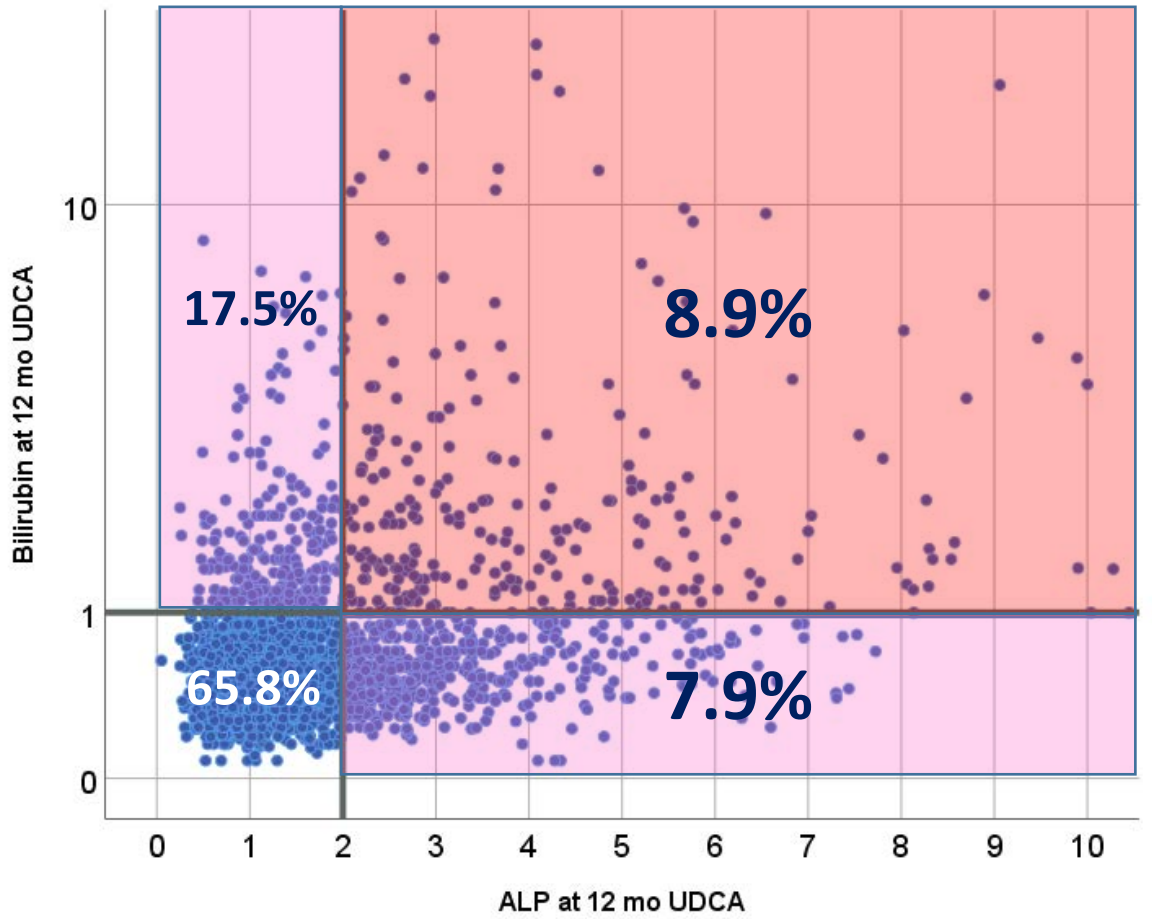
Study population: high risk

EMA advocates a study population:

- at highest risk for progression

→ in urgent need of new treatment

- risk population after min 1 year of UDCA:
  - ALP >2 xULN ? AND ?
  - abnormal bilirubin
- additional selection may depend on
  - AST, albumin, GGT, Mayo risk



Hansen, Global PBC dec 2018

Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH); 2018; Prentice, Stat in Med; 1989

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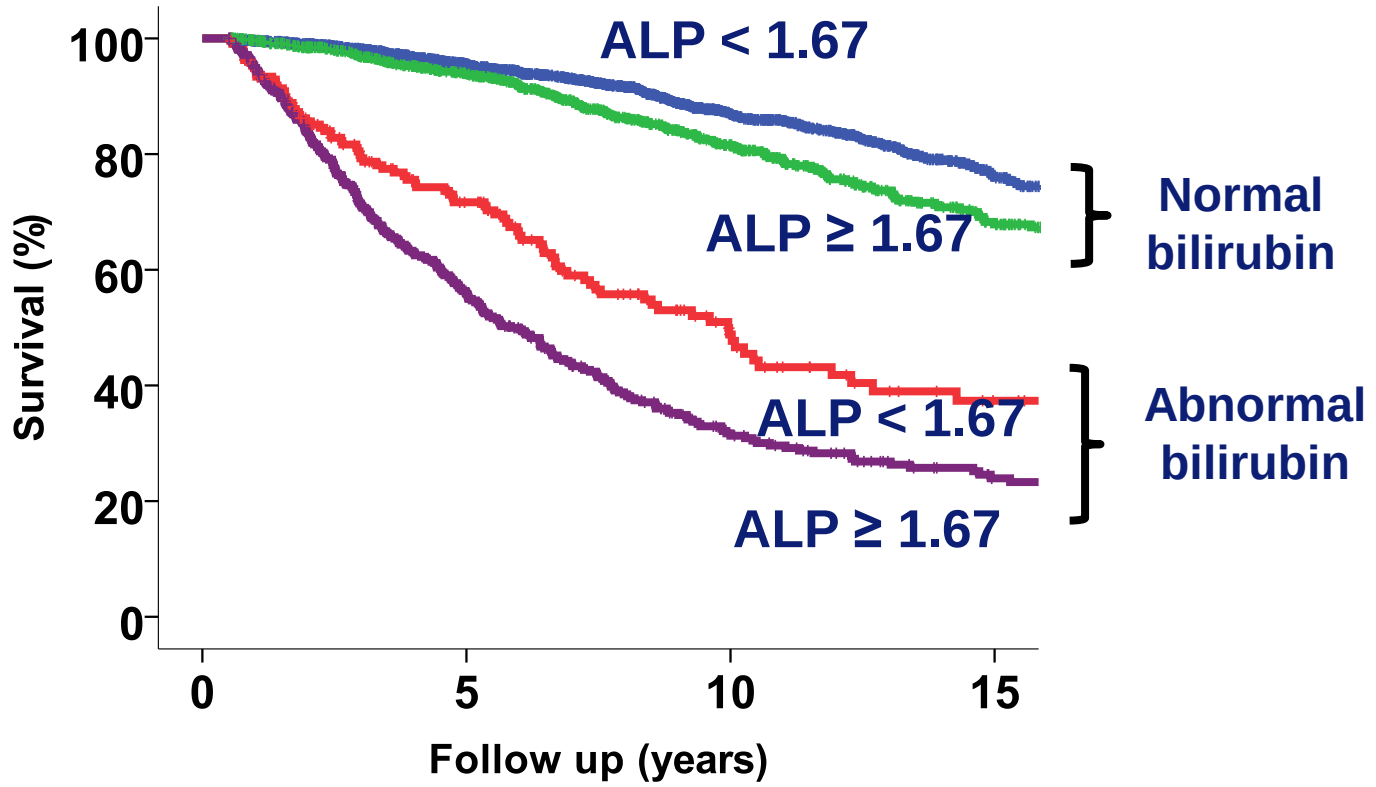
Suitable study populatin

Selection of an appropriate study population is critical to:

- Ethical acceptability
- Minimize bias confounders
- Numbers of subjects
- Speed of enrollment
- Interpretation and extrapolation of data
- Acceptance by physicians and regulatory authorities

Study population: at risk



Lammers et al, Gastroenterology 2014

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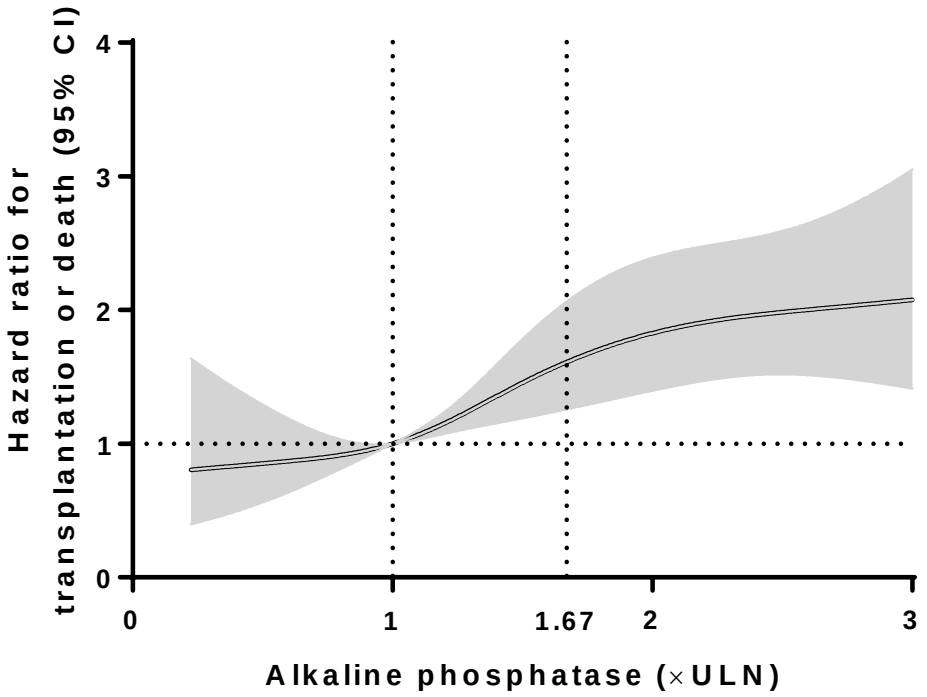
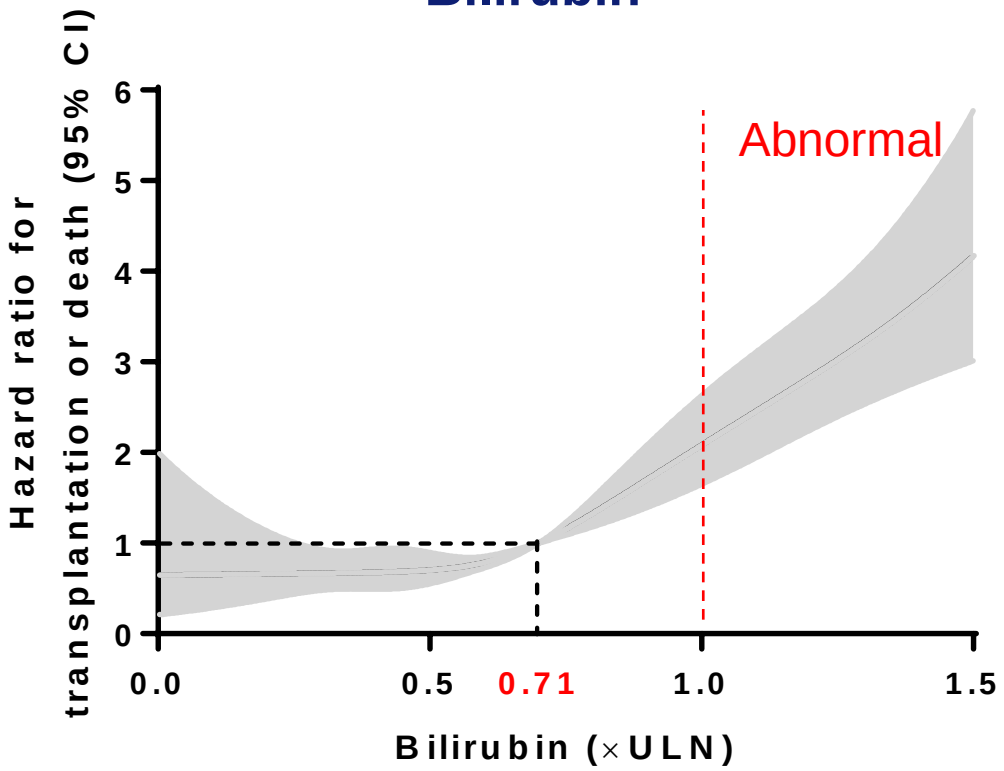
Zooming in on ALP below 2 and normal bilirubin

Alkaline phosphatase (ALP)



ALP: lower is better

Bilirubin



Bilirubin: > 0.6 - 0.7 at higher risk

Murillo et al., AASLD 2017; Murillo et al., AASLD 2018

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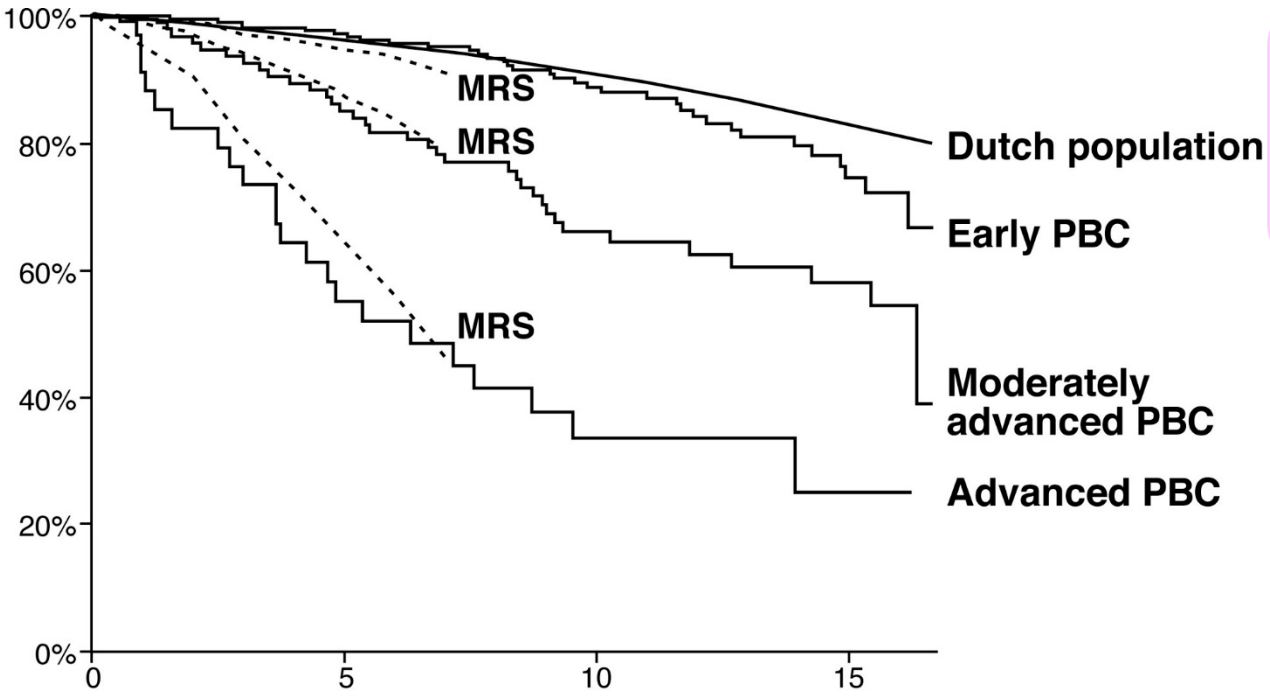
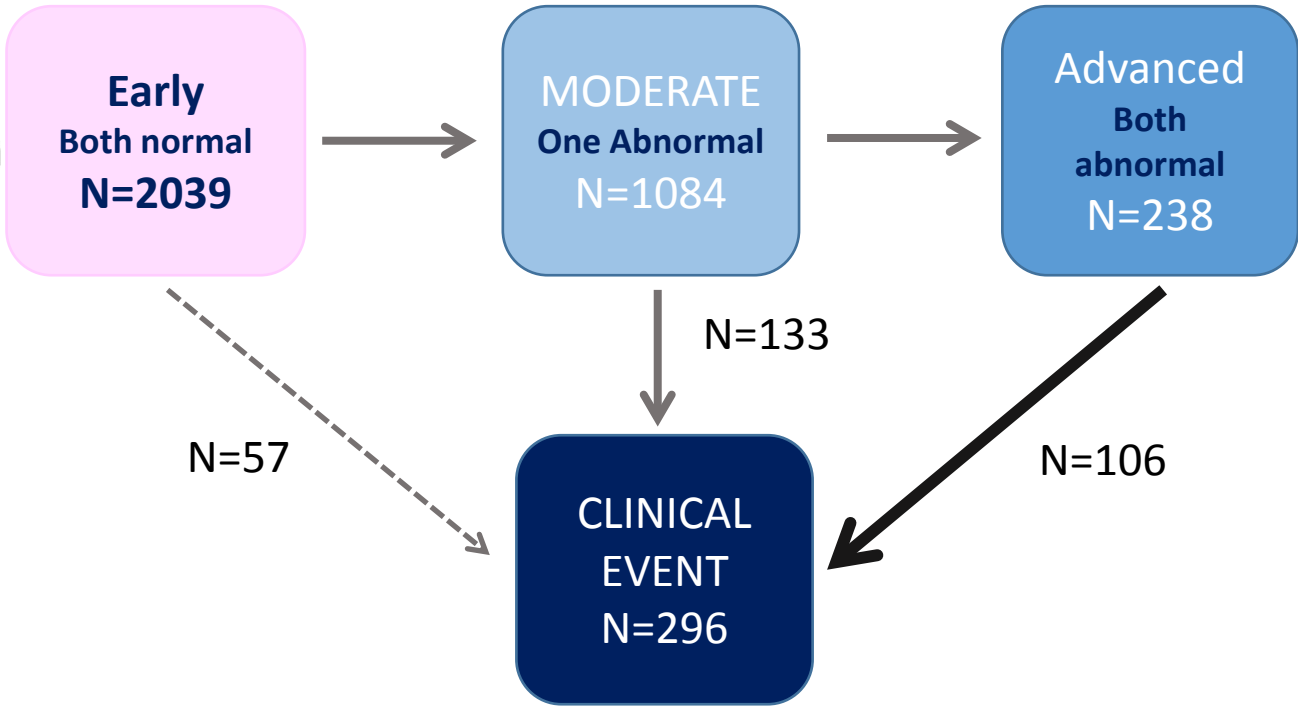
Rotterdam Disease Stage: Bilirubin & albumin





[1]*Kuiper et al; Gastroenterology 2009; Hansen 2017 APASL*

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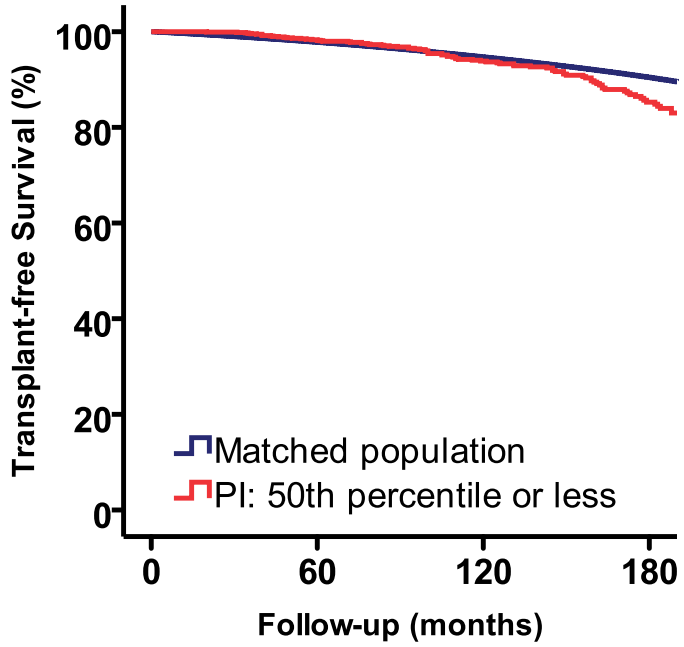
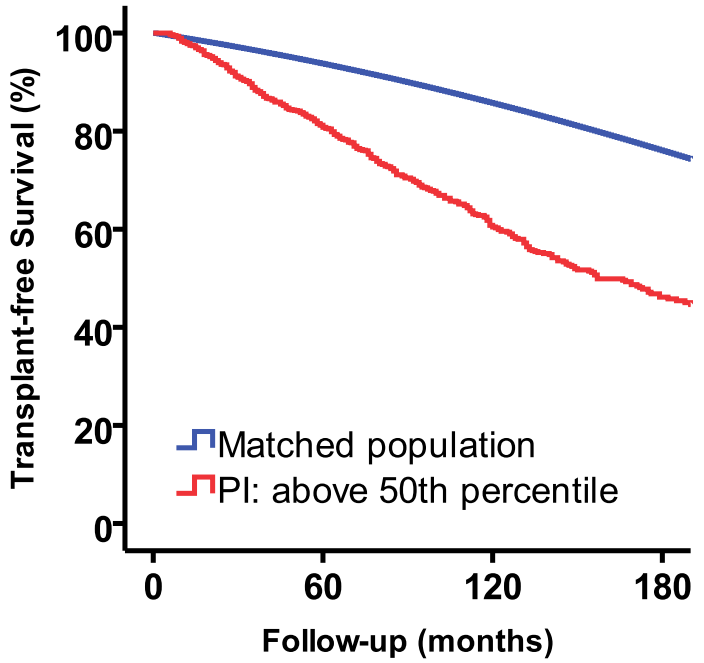
Use of Globe score or other risk scores to select study population





HR globe score > threshold = 4.5
C-stat = 0.82

These patients could potentially benefit of additional therapies

0 **50th percentile** **100**

Lammers et al., Gastroenterology 2015

http://globalpbc.com/globe

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Discussion: selection of high risk population

PROS

- In urgent need
- Balance of cost benefit?
- ….

CONS

- May be to late
  - Treatment not efficient in high risk group
- Other population need to wait
- Extrapolation of results questionable
- Ethical aspects
- ….

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Recycle and Reuse data and knowledge

Huge databanks are part of the solution - **Especially these are powerful:**

- For rare diseases and events are distant in time
- To gain knowledge of the natural history / standard of care
- To understand differences in disease stage, patient characteristics, geographical differences
- To study outcomes
- To study biomarkers
- To support the search for potential surrogate endpoints
- To use for design of new studies (power analysis, selection of patients)
- **To use as potential historical controls**

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Design of phase 3 and 4 studies

- Phase 3
  - Two/3 arm study (active arm (add on) versus control arm (UDCA))
  - intermediate endpoint

- Phase 4 confirmatory study
  - two arm study: active versus control
  - true endpoint = liver transplantation or death, decompensation, MELD>14
  - Power calculation – min 8-15 years follow-up n>500 patients – event driven

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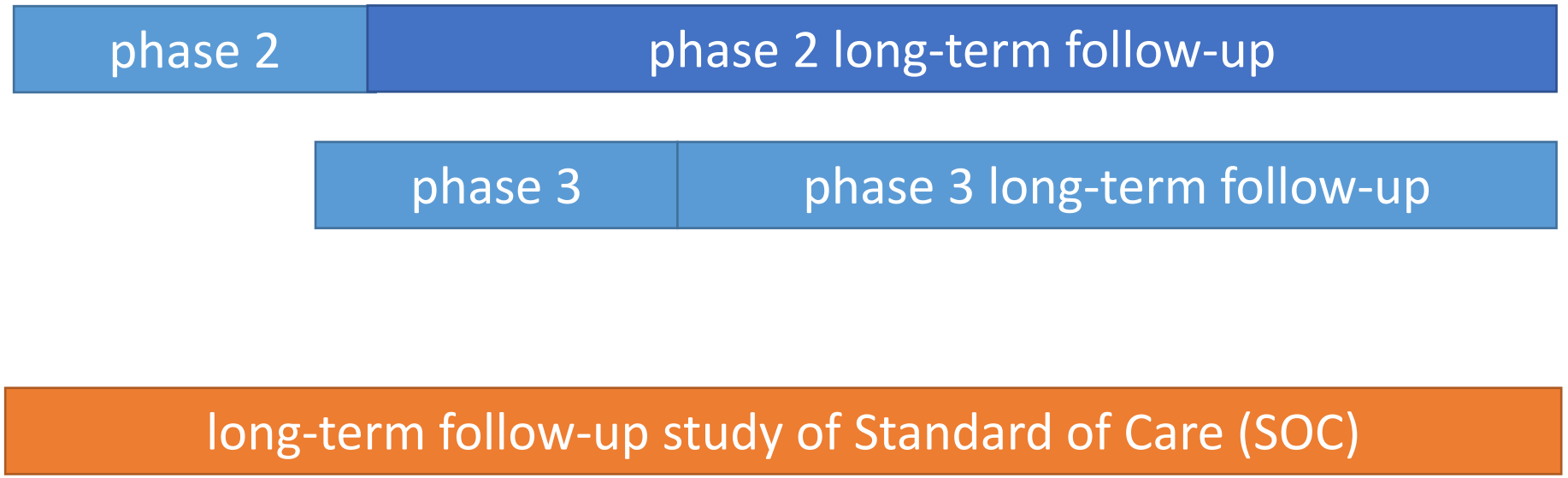
Design phase 4 confirmatory study using a (historical) matched control arm



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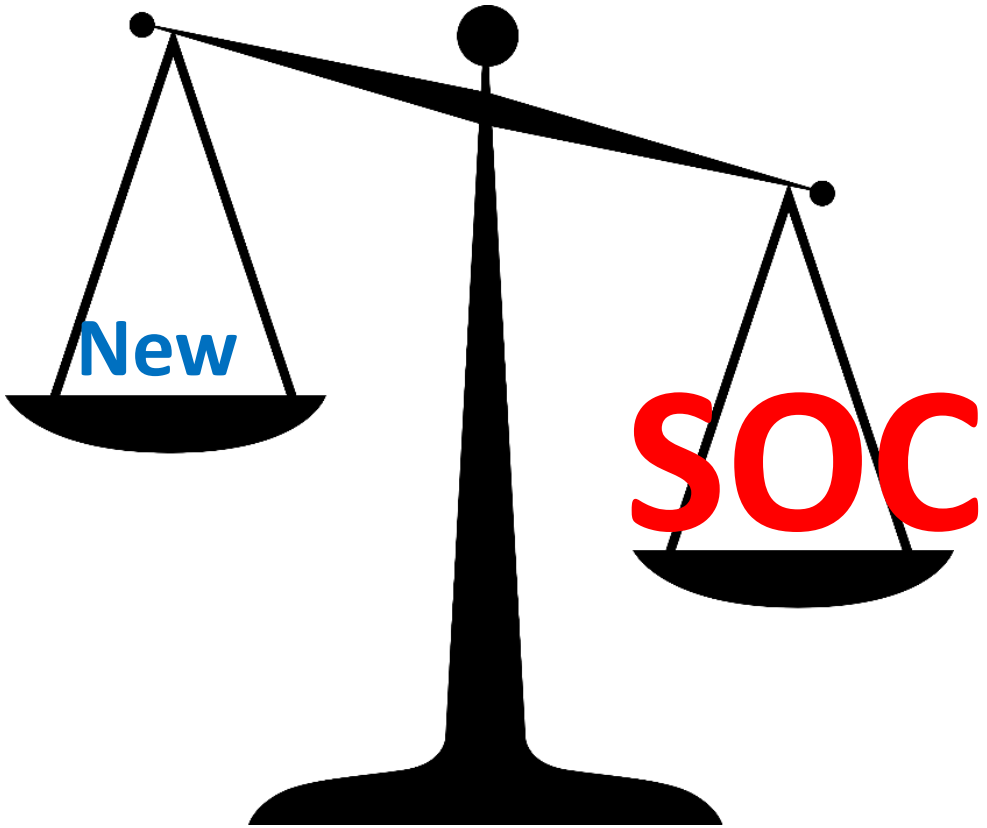
Design Phase 4 confirmatory study using a matched control arm



Pros

- reuse of gained knowledge
- reuse of data

  = recycling data and knowledge
- reduction of study-time
  - to clinical endpoint
  - to assess **benefit or harm**
  - to approval for the patients

Cons

- selection bias
- heterogeneity
- quality bias

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Design phase 4 confirmatory study using a matched control arm

Consider if disease is rare and/or chronic = clinical endpoint is far away

How to solve Cons

- selection bias
  ➔ Use incl/excl criteria
- heterogeneity
  ➔ use weights (IPTW) to stabilize differences
- quality bias
  ➔ minimize bias, install quality control

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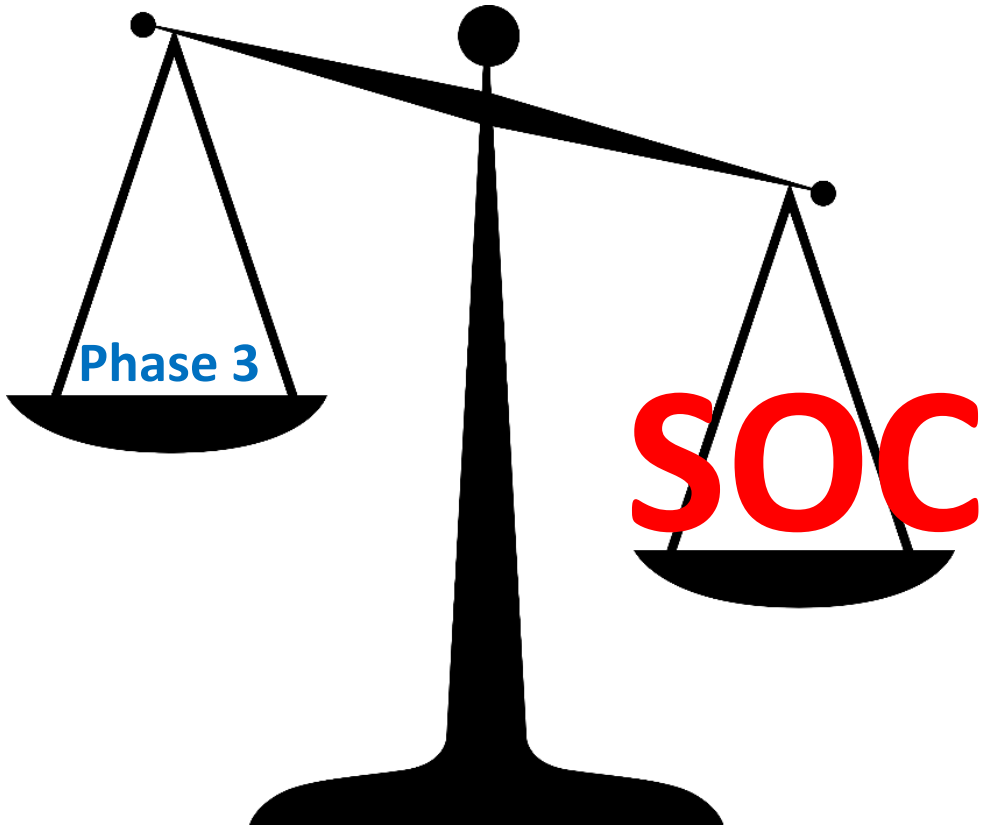
An example



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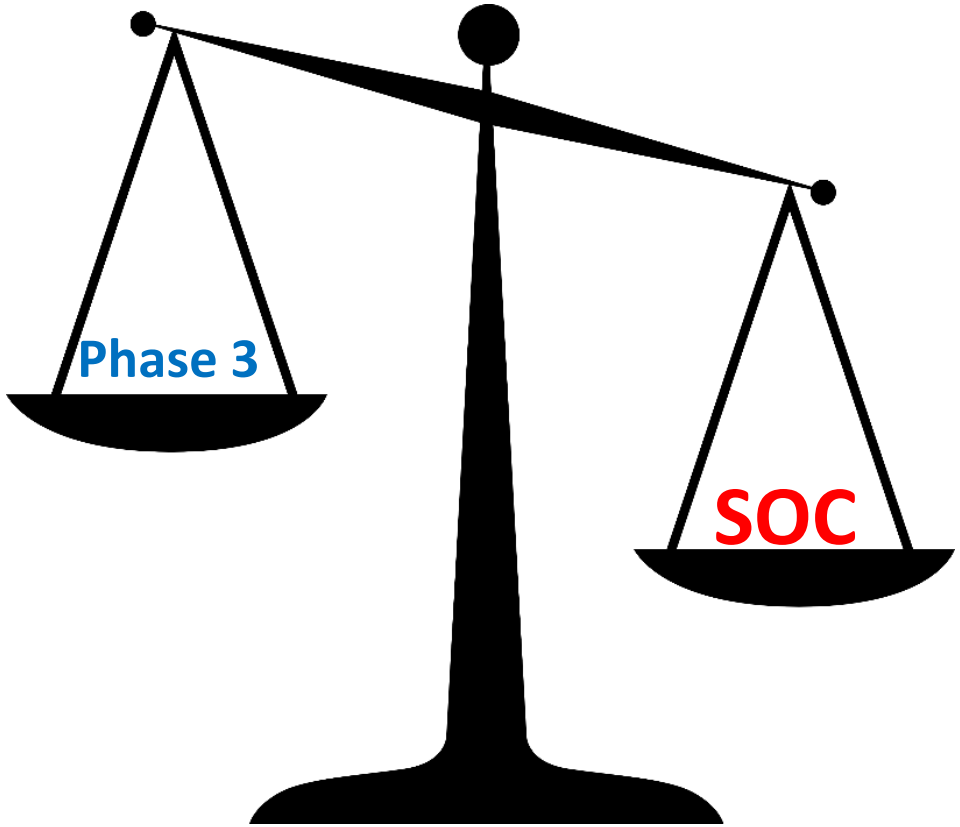
Selection

In the control cohort apply

Selection criteria phase 3

- ALP>1.67xULN or bilirubin>1xULN
- Bilirubin<threshold xULN
- UDCA min 12 months or untreated

- Of all visits fulfilling above first visit selected
- diagnosed after 1990 to control for
  - population differences
  - UDCA dosage differences
  - Changes in treatment of decompensation
  - Listing for liver transplantation



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Comparison Phase 3 and Selection

	Phase 3 n=137	Selection n=361	p
Sex %Female	83.9%	92.5%	0.007
Age, yr (mean,SD)	58.8 (11.9)	54.9 (12.2)	0.002
UDCA %	97.8%	94.2%	0.10
Duration UDCA(yr) (mean, SD)	3.6 (3.4)	3.9 (3.7)	0.001

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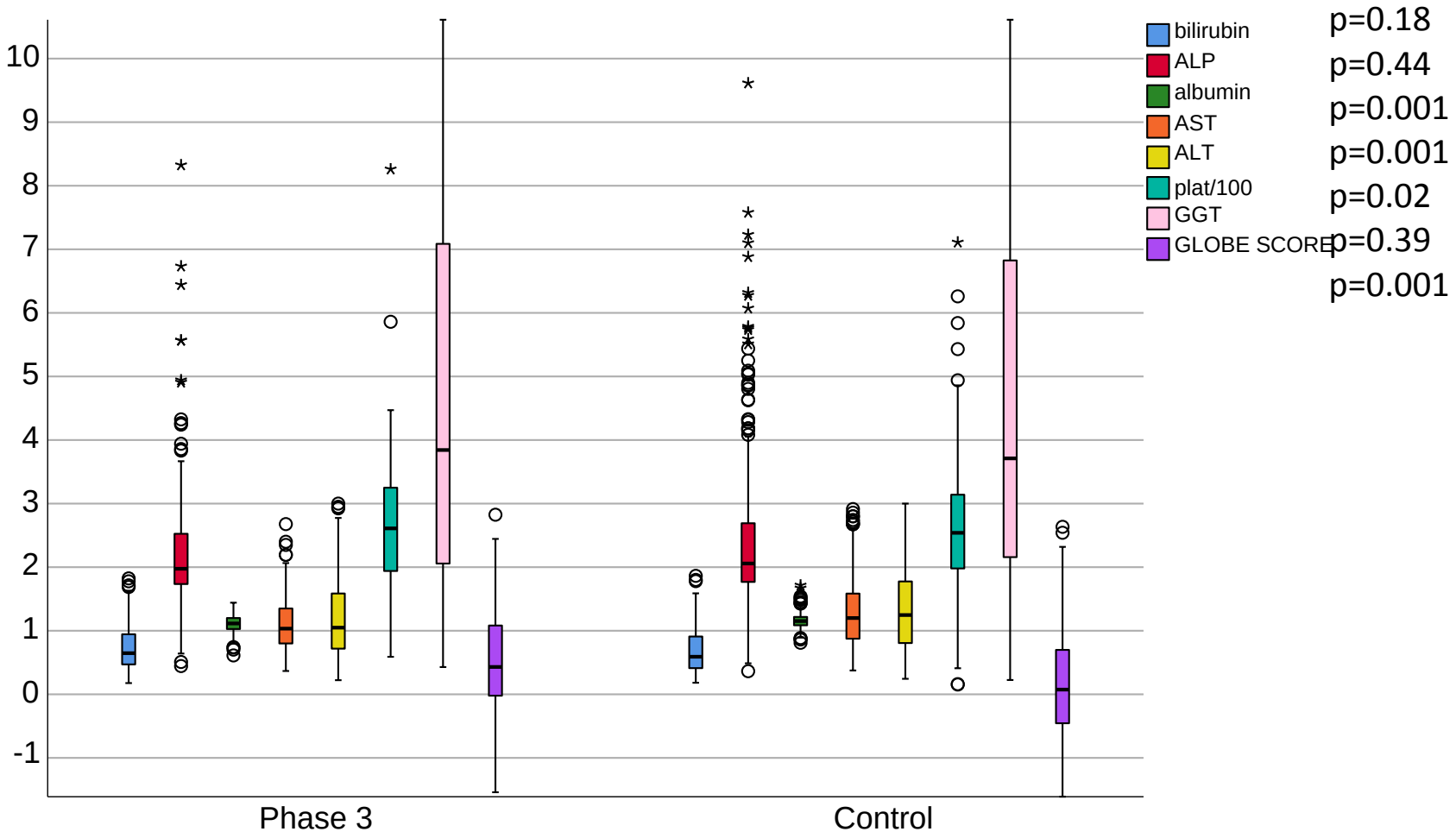
Comparison Phase 3 and Selection



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Comparison Phase 3 and Global Selection IPTW weighted analysis

	Phase 2 n=135 sum of weights	Global n=361 sum of weights	p
Sex %Female	90.4%	88.7%	0.75
Age, yr (mean,SD)	55.8 (11.8)	56.4 (12.7)	0.63
UDCA	94.1%	95.2%	0.65
Duration UDCA(yr) (mean, SD)	3.8 (3.7)	3.8 (3.6)	0.98

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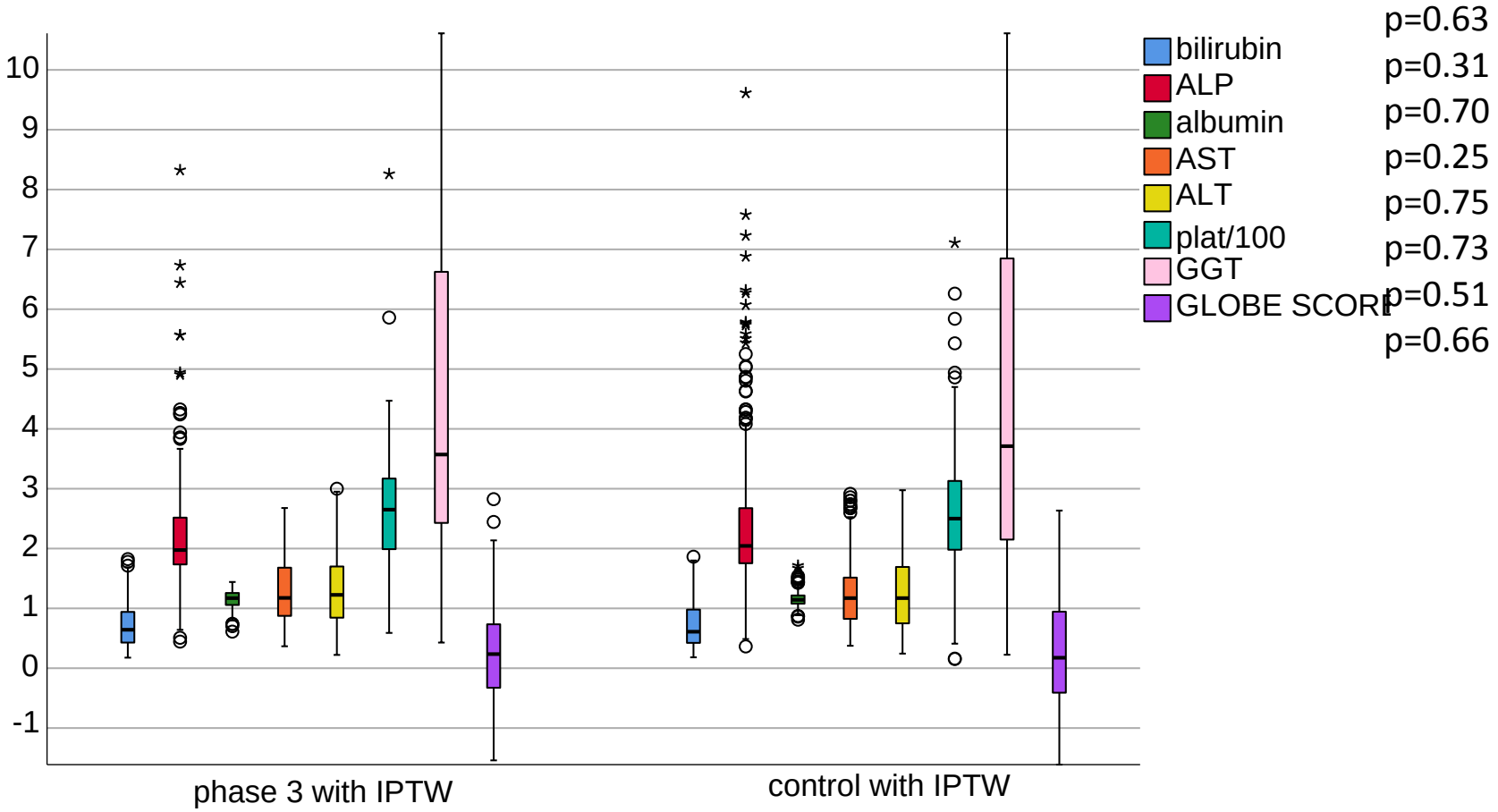
Comparison Phase 2 and Global Selection

IPTW weighted analysis



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Design phase 4 confirmatory study using a matched control arm

Consider if disease is rare and/or chronic = clinical endpoint is far away

How to solve Cons

- ✓ selection bias
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  ➔ minimize bias, install quality control

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Quality control

- SOP which includes:
  - Site visits: at site data inspection/capture
  - REDCAP data collection – safe tracking and storing
  - Queries automatically generated
  - Lab-test provided with units and Upper/Lower Limit of Normal
- All clinical endpoints (decompensation, HCC, liver transplantation, death and cause of death) reassessed by board of experts

Inclusion of other SOC-databases:

- Prospective data collection in parallel with phase 3

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Comments and discussion

- In case of rare/chronic disease reuse/recycle of historical database is feasible
- Selection bias can be avoided
- Heterogeneity can be avoided with use of IPTW weights to mimic a RCT
- Quality control rules must be applied and standardized
- Consider prospective SOC/registry cohort to run in parallel

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