

Applying the proposed Liver Forum strata to suggest clinical trial design and endpoints

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Disclosures

- **Consulting**

- Madrigal
- Zydus
- GSK
- Merck
- Altimmune
- Foresite

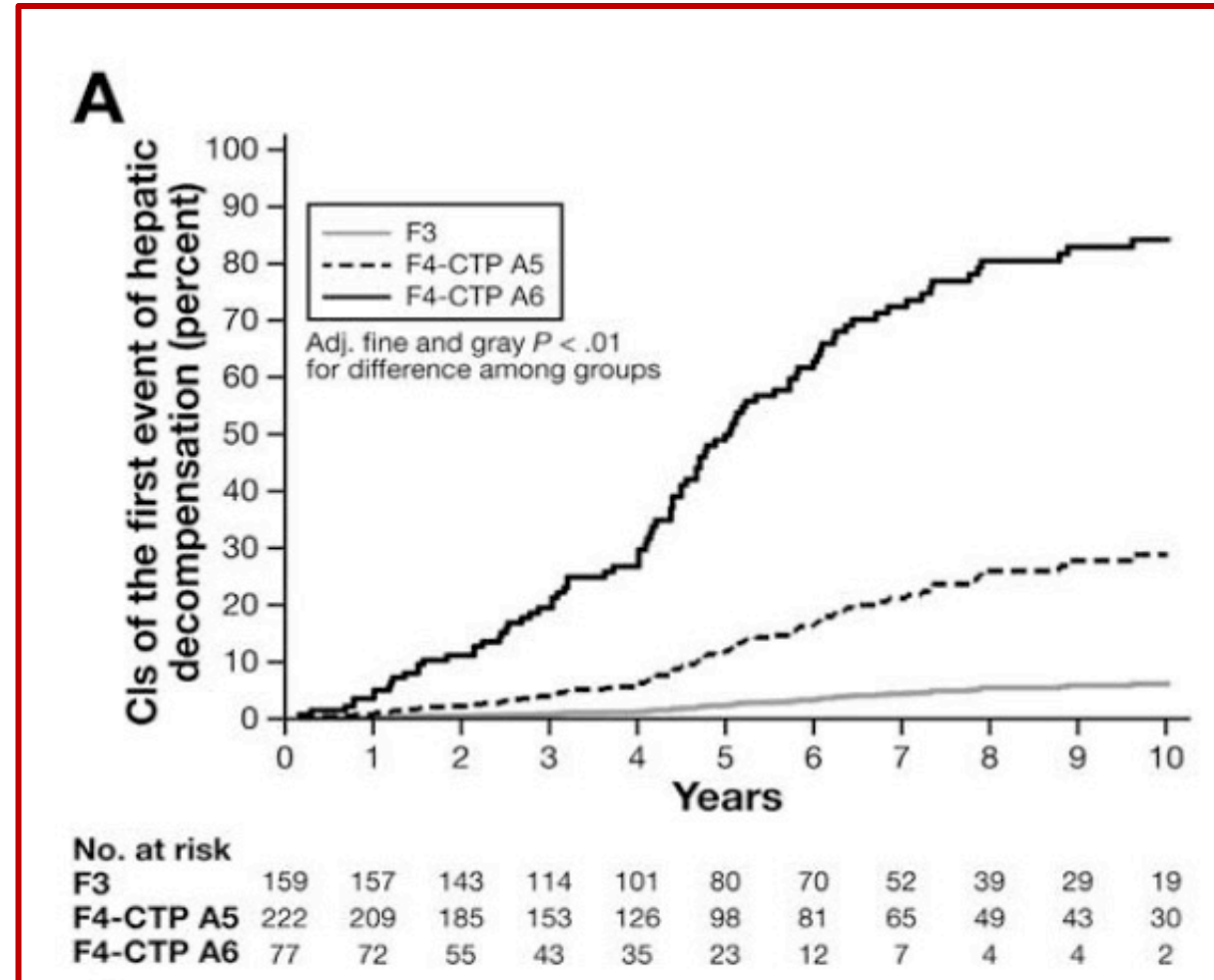
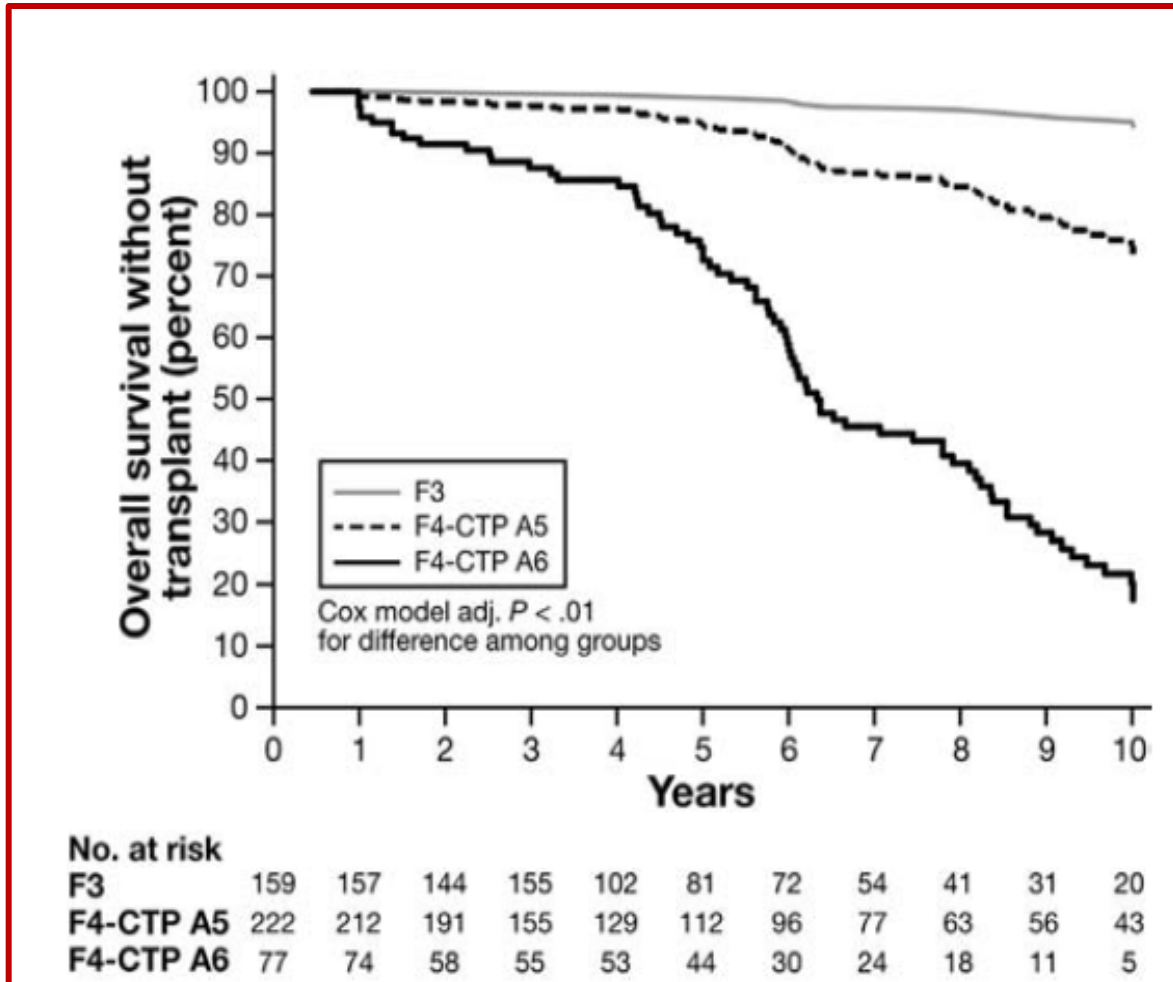
- **Research support**

- DSM
- Exact Sciences

- **Speaking**

- None

Child's A5 vs A6 NASH cirrhosis has different natural history



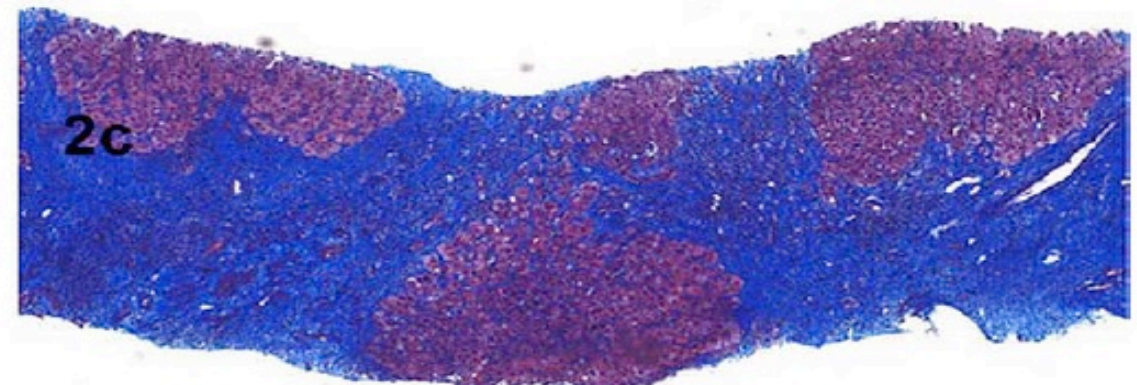
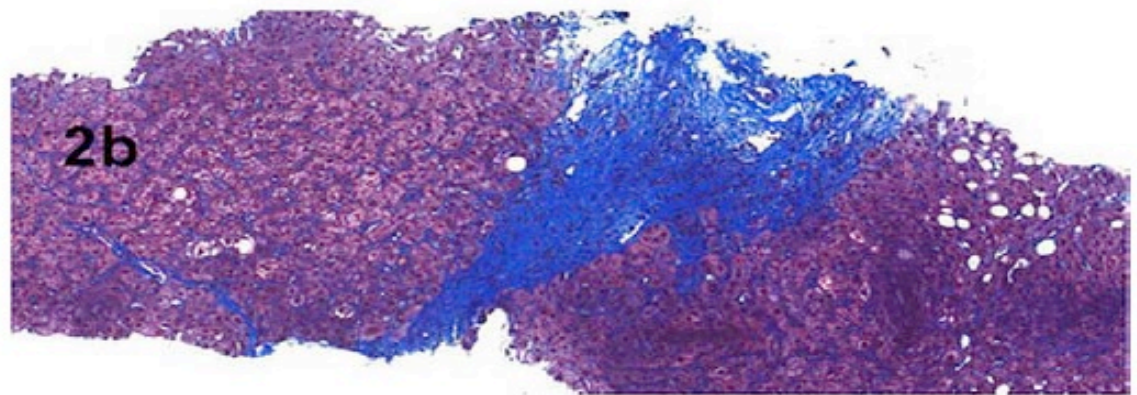
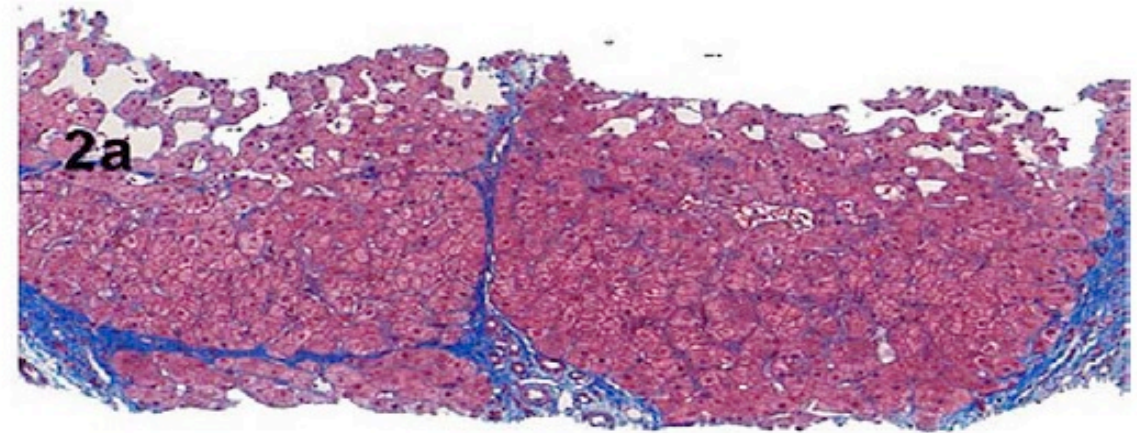
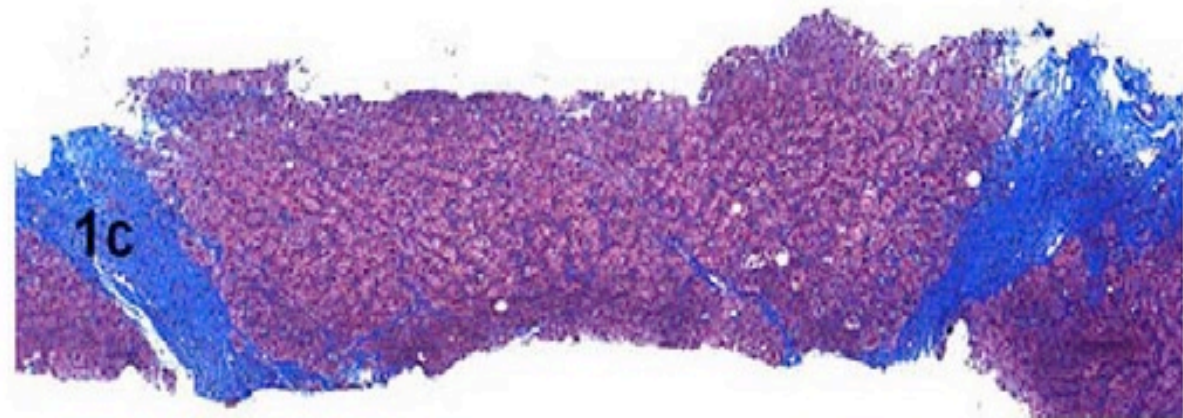
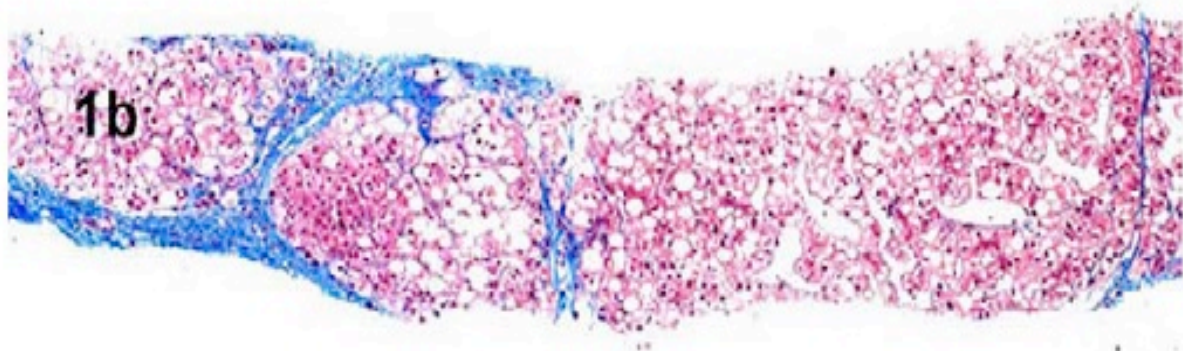
Histological-hemodynamic correlation in cirrhosis—a histological classification of the severity of cirrhosis

Satish Nagula¹, Dhanpat Jain³, Roberto J. Groszmann^{1,2}, Guadalupe Garcia-Tsao^{1,2,*}

- 43 patients with cirrhosis (HCV, Alcohol) with paired liver histology and HVPG
- Nodule size and septal thickness were independently correlated with HPVG
- Histological subclassification of cirrhosis
 - Subgroup A: Large nodules & thin septa
 - Subgroup B: Mixed nodules & medium septa
 - Subgroup C: Small nodules & thick septa

Table 1
Histological parameters and grading scale

Histological parameter	Range	Scale
Fibrosis		
Sinusoidal	0–3	0, 1 (mild), 2 (moderate), 3 (severe)
Septal Thickness ^a	0–3	0, 1 (thin), 2 (medium), 3 (thick)
Nodularity		
Small nodules		Nodule size is comparable to width of needle biopsy specimen
Mixed nodules		Presence of both small and large nodules ^b
Large nodules		Nodule size larger than biopsy width
Portal tracts lost	0–4	0, 1 (1–25%), 2 (26–50%), 3 (51–75%), 4 (76–100%)
Central veins lost	0–4	0, 1 (1–25%), 2 (26–50%), 3 (51–75%), 4 (76–100%)
Inflammation		
Lobular	0–3	0, 1 (mild), 2 (moderate), 3 (severe)
Interface	0–3	0, 1 (mild), 2 (moderate), 3 (severe)
Steatosis	0–4	0, 1 (1–25%), 2 (26–50%), 3 (51–75%), 4 (76–100%)
Iron	0–4	0, 1 (visible at 250× magnification), 2 (100×), 3 (25×), 4 (10×)



Important factors which characterize the spectrum of compensated NASH cirrhosis

- Hot vs cold cirrhosis
- Child's A vs B
- CSPH
- Hepatic & extrahepatic shunting
- Synthetic function
- Histology – septa thickness and nodule size
- Drug metabolizing enzymes & transporter function
- Hepatic & extra-hepatic safety

NASH Cirrhosis Working Group Planning Call: February 2022

Cirrhosis Strata and Guidance from Stakeholders for Risk Stratification and Enrollment in NASH Cirrhosis Trials

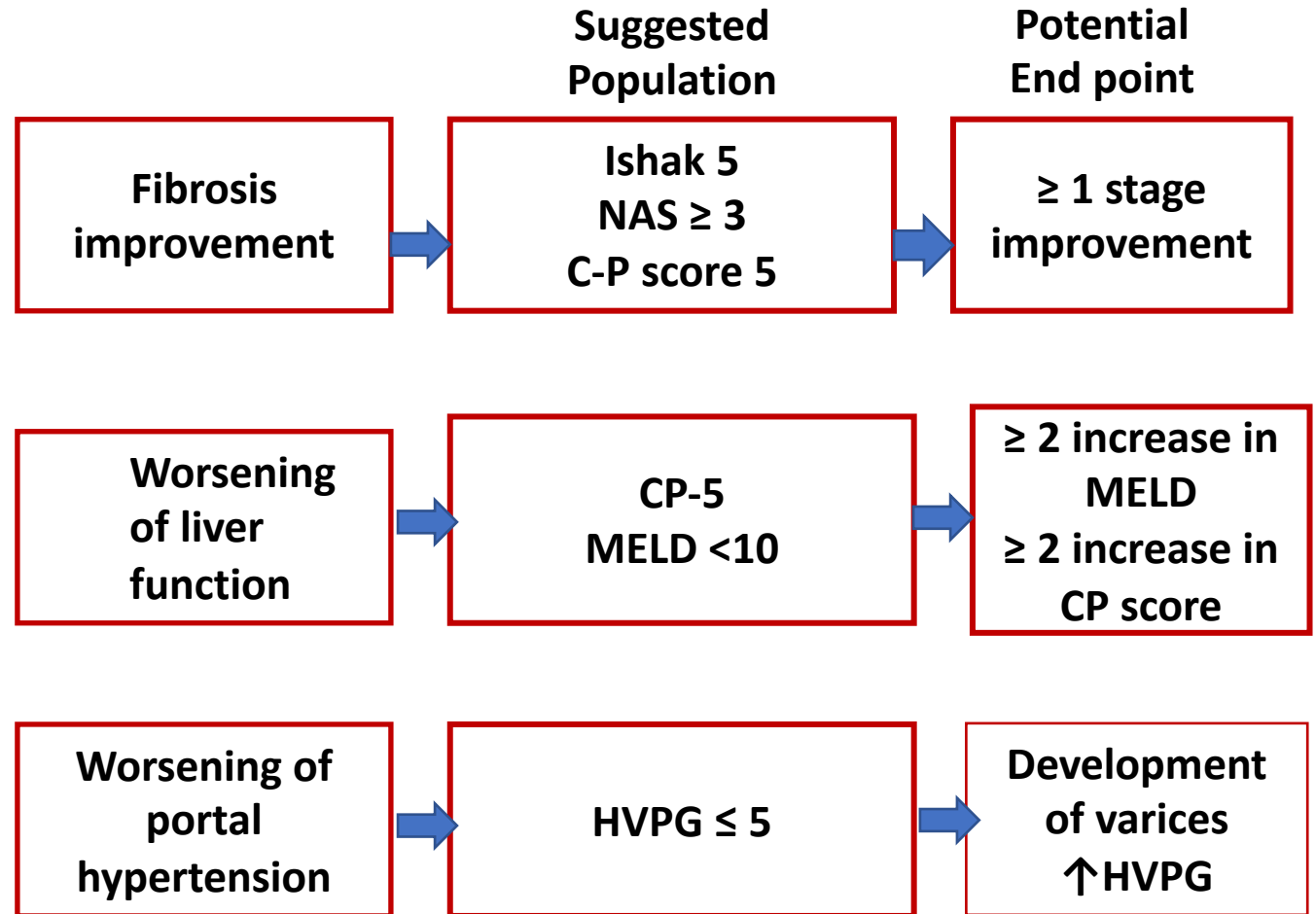
Table: Liver related measurements in NASH cirrhosis Trials

	Stratum A	Stratum B	Stratum C
High Evidence Tier			
Portal pressure related measurements			
HVPG (mm Hg) ^{&}	~ 5	6-10	> 10
Varices	Absent	Absent	Present e*
Ascites	Absent	Absent	Seen on Imaging only or recompensated
Hepatic encephalopathy	Absent	Absent	Absent-Minimal and recompensated
Platelets count (10 ⁹ /L)**	≥ 150,000	<150,000	<150,000
Child-Pugh Score	CTP-5	CTP-5	CTP-6
Histology Related Measures			
?Ishak Fibrosis stage	5	5-6	6
NAS score	≥3 or 4	≥3 or 4	None (cryptogenic)
Function related measurements			
MELD	<10	10-12	>12*
Albumin (gm/dl)	> 3.5	2.8-3.5	≤2.8
Bilirubin (mg/dl)	< 1.3 mg/dL	1.3-2 mg/dL	>2 mg/dL
INR	<1.2	>1.2	>1.2

Compensated cirrhosis – Stratum A

STRATUM A	
HVPG	≤ 5
Varices	Absent
Ascites	Absent
HE	Absent
Platelet Count	≥ 150k
C-P	5
Ishak Fibrosis Stage	5
NAS	≥ 3 or 4
MELD	<10
Albumin	>3.5
Bilirubin	<1.3
INR	<1.2

→ **Sub Part H**



Strata B & C – Likely too late for fibrosis improvement & for conditional approval

	STRATUM B	STRATUM C
HVPG	6-10	>10
Varices	Absent	Present
Ascites	Absent	On imaging
HE	Absent	MHE
Platelet Count	<150 K	<150K
C-P	5	6
Ishak Fibrosis Stage	6	6
NAS	≥3 or 4	< 3
MELD	10-12	>12
Albumin	2.8-3.5	<2.8
Bilirubin	1.3-2	>2 mg/dL
INR	>1.2	>1.2



Targeting

- Microbiome
- Cell injury
- Senescence
- Inflammation
- Fibrosis
- Significant weight loss
- Statins

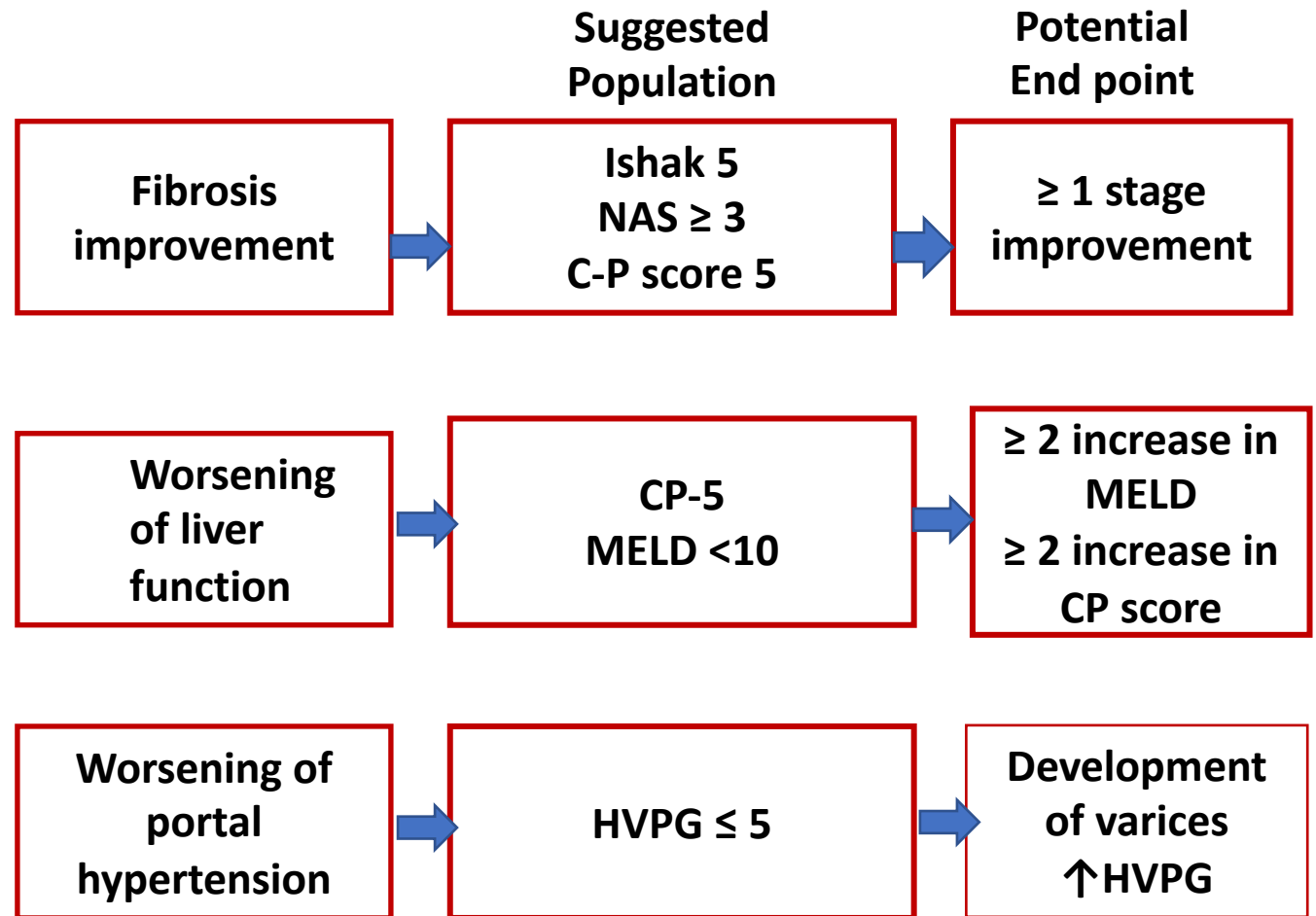
Prevention of
clinical
complications

- Variceal bleeding
- Rx requiring ascites or HE
- HCC
- MELD >15
- Death

Compensated cirrhosis – Stratum B/C

STRATUM A	
HVPG	≤ 5
Varices	Absent
Ascites	Absent
HE	Absent
Platelet Count	≥ 150k
C-P	5
Ishak Fibrosis Stage	5
NAS	≥ 3 or 4
MELD	<10
Albumin	>3.5
Bilirubin	<1.3
INR	<1.2

→ **Sub Part H**



Summary

- Subclassifying compensated cirrhosis is critical because there are distinct strata with important multidimensional differences
- Stratum A patients can be approached via fibrosis improvement or clinical surrogates for a conditional approval as clinical outcomes in this Stratum will take longer
- Stratum C (with some mixture of Stratum B) patients are in urgent need of an intervention and can be approached for prevention of clinical outcomes and for full approval.
- Criteria listed for Strata A through C will need to be tweaked further