Worldwide Clinical Trials

Infographic

Beyond MASH: Expecting the Unexpected in Hepatology

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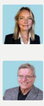

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While established indications like Hepatitis B and C benefit from well-defined disease criteria, proven endpoints, and mature regulatory frameworks, newer and evolving conditions such as metabolic dysfunction-associated steatohepatitis (MASH) and alcoholic hepatitis (AH) present unique challenges. These include shifting disease definitions, complex biomarker-driven endpoints, and heterogeneous patient populations. To succeed, liver disease programs require bespoke trial design and operational strategies tailored to each indication's complexity and maturity. Achieving this level of customization is only possible with a strategic CRO partner that brings:

- Deep hepatology-specific expertise
- Insight into evolving regulatory sentiment
- Proven capability in high-acuity trial operations

Such partnerships ensure that both well-established indications and emerging therapeutic areas are addressed with rigor, flexibility, and innovation.

FDA-Approved Indications

- **Cholestatic Pruritus in Alagille Syndrome (ALGS)**
- **Hepatic Encephalopathy (HE)**
- **Hepatitis B (HBV)**
- **Hepatitis C (HCV)**
- **Hepatorenal Syndrome**
- **Primary Biliary Cholangitis (PBC)**
- **Metabolic Liver Disease (MASH, formerly NASH)**

To Be Determined...

- Acute-on-Chronic Liver Failure (ACLF)
- Alcoholic(-associated) Hepatitis (AH/AAH)
- Autoimmune Hepatitis (AIH)
- Cirrhosis/Fibrosis (± MASH)
- Drug-Induced Liver Injury
- Metabolic Dysfunction Alcohol-Related Liver Disease (MetALD)
- Portal Hypertension
- Prevention of Hepatocellular Carcinoma (HCC)
- Primary Sclerosing Cholangitis

Emerging Trend in Development

- **New diagnostic taxonomy** for MASLD, MASH, and MetALD all require stricter eligibility criteria, alcohol-use characterization, and biomarker stratification
- Growing reliance on **surrogate endpoints** (i.e., histology, MRI-PDFF, non-invasive biomarkers, and composite endpoints) may be used for **accelerated approvals**
- Novel treatment modalities (i.e., cell/gene therapy or RNA)
- Complimentary and physiologically adjacent mechanisms (i.e., metabolism, immune modulation, and microbiome)

Risk to Drug Development

- Regardless of external consensus (i.e., societies and clinicians), many **new (sub) populations are yet to be endorsed** by FDA
- Narrow etiologic or stage-specific indications **(F2/F3 vs. F1/0 or F4/cirrhosis)** may restrain labeling of approved therapies
- Broad or ambiguous labels face access barriers **without strong subgroup data**. Payers and providers are more likely to implement therapy with clear risk-benefit in pre-specified groups
- **Confirmatory burden** with time-sensitive post-marketing outcome studies poses a risk and challenge in heterogenous liver disease populations, even if product obtained accelerated approval in narrow population
- **Complex liver-related PK/PD and heightened safety scrutiny** (e.g., drug-induced liver injury, immunogenicity, and long-term follow-up requirements)
- Targeting indirect and interconnect pathway(s) **increases biological and clinical uncertainty** with risks of overlapping or counteracting effects
- Heightened regulatory expectations for **mechanistic justification, biomarker validation, and clear attribution of liver-specific benefit**

Integrated Design & Operations in Liver Disease

Regulatory Positioning

- Programs require **iterative regulatory strategy, such as pre-IND/End-of-Phase (EOP) alignment** and modeling of 'labelable' populations
- **Strategic program discussion/portfolio review** should provide indication comparison, endpoint justification, and structured FDA-facing documents tailored to evolving taxonomy

Worldwide's regulatory experts bring deep, hands-on experience with both FDA and EMA, providing strategic guidance to navigate complex requirements and accelerate the most efficient path to approval.

Precise Populations

- Overlapping phenotypes (e.g., MetALD) require nuanced inclusion/exclusion criteria incorporating alcohol use biomarkers (i.e., PEth, CDT), metabolic markers, imaging, and genetic testing, if applicable.
- Trial design must **avoid or account for mixed disease etiology** with a priori statistical frameworks.
- Collaboration between study design and operations teams to develop **phenotyping workflows** across diverse sites to ensure regulatory-grade consistency.
- PI, site staff, and CRAs receive comprehensive, targeted training designed to ensure precise patient identification and optimal enrollment – reinforcing accuracy at every step to protect study integrity and accelerate timelines.

Recruitment & Retention

- Tailored pre-screening and retention strategies **combat high screen failure and dropout risk** due to common comorbid psychosocial burdens.
- Liver disease trials benefit from **site feasibility algorithms** focused on transplant centers, high volume hepatology networks, and emergency department-based enrollment for acute presentations.

Our highly experienced trial teams craft tailored recruitment and retention strategies, such as prescreening approaches to reduce screen failure rates, integrated digital outreach, peer-to-peer engagement, and patient- and site-level programs. This combination ensures sustained participation and maximizes the opportunity for trial success. For example, our proactive strategy and interdisciplinary experience with rare disease resulted in **>96% retention in a contemporaneous Primary Sclerosing Cholangitis study.**

Endpoint Complexity & Variability

- Histology-based endpoints require **central reading, standardization, and safety oversight**.
- Non-invasive imaging phenotypes (i.e., MRI-PDFF) demand **calibrated instrumentation, quality control pipelines, credentialed operators, and timely access to imaging facilities.**
- Alcohol-associated diseases may require **event-driven endpoints**, mortality monitoring, and high-acuity site capabilities.

Working in seamless partnership with sponsors, sites, and vendors, Worldwide's team proactively safeguards study endpoints, leveraging rigorous oversight, risk mitigation strategies, and real-time collaboration to ensure data integrity and regulatory compliance.

Safety Monitoring

- Hepatology carries inherent risks (i.e., drug-induced liver injury, acute decompensation, infection, and renal dysfunction)
- Specialized medical monitoring, DSMB coordination, rapid serious adverse event adjudication, and **hepatology-specific safety algorithms with attention to drug-induced liver injury** are required

Worldwide's Medical Monitors bring combined expertise in hepatology, gastroenterology, and endocrinology, ensuring meticulous safety reviews, rapid accessibility, and clear, timely reporting. Their deep understanding of liver disease complexities drives proactive oversight and precision in every trial.