Pitfalls & Best Practices: Clinical Trial Design in MASH

Presented by Worldwide Clinical Trials

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Introduction

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading liver disease worldwide, with an estimated global prevalence of 30% in adults.
- Experts predict the MASLD global prevalence may reach more than 50% by 2040.
- Prevalence varies substantially by world region due to genetic and socioeconomic factors.
- Metabolic dysfunction-associated steatohepatitis (MASH) is often difficult to diagnosis, research, and treat.
- Although intermediate and surrogate endpoints are desired in clinical research, histological assessments and long-term outcomes are crucial to regulatory approval.
- Existing and emerging treatments for conditions closely linked to MASH (e.g., GLP-1 agonists) are beneficial yet confound the development of targeted therapy.

What's in a Name? NASH Is Now MASH

- Existing "non-alcoholic" terminology (e.g., NAFLD, NASH) has been described as exclusionary and potentially stigmatizing.
- A broader emphasis on metabolism acknowledges the diverse etiology of the disease.
- Previous diagnostic standards often excluded patients from clinical research.
- Updated criteria require at least one of five select cardiometabolic factors.
- These changes widen the eligible patient populations, emphasizing overlap with other metabolic conditions (e.g., type 2 diabetes and obesity).

MASH Clinical Trial Landscape

Table 1: Planned and ongoing industry-sponsored MASH trials.

Phase	Total	Ongoing	Planned	Enrollment (pts)	Treatment (mo)	Sites
I	86	44	42	54 (14-250)	1.17 (0.2-12)	1 (1-18)
I/II	8	5	3	95 (48-180)	6.74 (3-13.68)	3 (1-9)
II	81	50	31	112 (9-672)	7 (3-43.39)	30 (1-264)
II/III	1	1	0	357	18	156
III	31	16	15	781 (80-10,000)	12 (1.5-56)	56 (1-523)
IV	26	15	11	148 (38-1,500)	9 (0.03-48)	1 (1-40)

Data accessed via Citeline TrialTrove on 17 July 2024. Search criteria were (1) Medical Subject Headings (MeSH) Term = "Non-alcoholic steatohepatitis", (2) trial status = "ongoing" or "planned", and (3) sponsor = industry. Enrollment and Treatment Duration combine actual with planned. Values shown as median with (range).

Objectives

- Worldwide Clinical Trials examined case studies and engaged scientific, medical, and operations staff in guided discussion to (1) identify common pitfalls and (2) recommend best practices in MASH clinical program development.

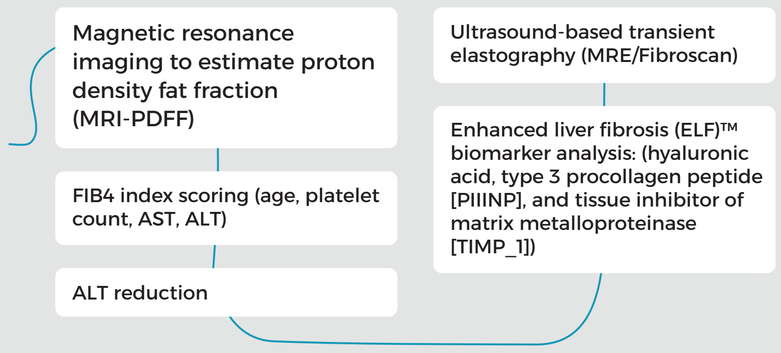
Methods

- Medical monitors, subject matter experts, business developers, project managers, and translational scientists joined a series of guided semi-structured interviews to identify common pitfalls and best practices for interventional MASH study designs.

Results

- Trial design challenges centered on selecting and recruiting homogenous patient populations despite unknown etiology, manifestation, and progression.
- On- and off-label medications (e.g., GLP-1 agonists) render placebo-controlled studies less attractive for patient recruitment and retention in developed markets.

- Best practices acknowledge differences in the duration of studies (e.g., steatosis vs. fibrosis resolution) to capture clinically meaningful changes in sensitive endpoints and patient-reported outcomes (PRO) across phenotypes.
- Invasive biopsies may be replaced in early phase research with surrogate endpoints, such as:



EMA: Evolving Regulatory Guidance

The EMA released a reflection paper on regulatory requirements for medical products for NASH, scheduled to become effective on 1 October 2024.

Key Program Design Takeaways

What patient population should we target?

Programs should include F2-4 patients. Endpoints and outcomes may vary depending on disease stage.

Should we plan for a single or multi-study Phase III program?

Either. If a multi-study approach is taken, each study should examine different stages of fibrosis.

Is a biopsy still required?

Yes, for enrollment and efficacy confirmation. Though a sponsor should consider a biomarker and imaging-based algorithm for patient recruitment and/or management.

Are intermediate endpoints acceptable?

Yes. However, they are only acceptable if (1) an unmet need is still present, (2) a positive benefit-risk ratio can be concluded, and (3) the sponsor is positioned to provide comprehensive data post-marketing.

What are the primary intermediate endpoints?

For non-cirrhotic NASH (F2-3), two composite endpoints are suggested as co-primary endpoints:

- NASH resolution and any grade of steatosis, along with the following: no ballooning, minimal (grade 1) lobular inflammation, and no worsening fibrosis.
- Improvement of fibrosis by at least one stage without any worsening of NASH.

What are the long-term efficacy endpoints?

For non-cirrhotic NASH, assess long-term efficacy with a single composite endpoint with any of the following: all cause death, decompensation of liver disease (with a complete listing), (histology) diagnosis of (progression to) liver disease, or MELD >= 15.