Worldwide Clinical Trials

Guide

Mastering MASH

A Guide for Innovative Approaches to Clinical Trials & Patient-Centered Care

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Updating Our Arsenal: MASH Trials & the Patient Journey

Metabolic dysfunction-associated steatohepatitis (MASH) and metabolic dysfunction-associated steatotic liver disease (MASLD) are complex conditions, and successful clinical research and patient care require a broad understanding of the patient's experience and a holistic approach to trial design. With close ties to metabolic syndrome, cardiovascular kidney and metabolic (CKM), type 2 diabetes (T2D), and obesity, the high comorbidity rates require careful care coordination. Additionally, MASH is a silent disease that often goes undetected until it reaches advanced stages, complicating interventional treatments. Current and future MASH research must consider the patient's entire medical journey and employ innovative trial designs and patient-centric strategies to enhance treatment efficacy and patient outcomes.

This guide explores the essential elements of MASH/MASLD trial design, from the importance of early and continuous patient engagement to the incorporation of multidisciplinary teams. We also discuss the critical role of patient education and support in managing the disease and improving the overall patient retention and success of clinical trials.

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More Than MASH: A Multifaceted Condition That Warrants Comprehensive Care

Patients with MASH are likely managing multiple health conditions simultaneously, necessitating a comprehensive approach to their care. Collectively, these factors underscore the need to balance various medical appointments and address a range of healthcare needs. Understanding the interconnected nature of these conditions allows for more effective treatment plans from a multidisciplinary, holistic approach and better patient outcomes. The global prevalence of MASH further emphasizes the need for holistic care, as early, multidisciplinary intervention can reduce associated complications, including cirrhosis or liver transplant.

In the big picture, MASH and the associated comorbidities speak to the importance of educating on lifestyle changes as a part of the study to help encourage better results from the interventional therapeutic and healthier patient outcomes.

Utilizing the Patient Voice & Perspective to Inform Trial Design

The patient and caregiver perspectives are paramount in designing clinical trials for MASH. It is essential to involve patient advocacy groups (PAGs) to provide extra support and ensure that trials hear the patient's voice, highlighting the importance of early and continuous PAG engagement. Patient advocacy groups are crucial in enhancing healthcare by influencing research trials. These organizations advocate for increased medical research funding and strive for policy changes that benefit individuals with specific conditions. Additionally, they ensure that clinical trials are designed with a patient-first approach, reflecting patient needs and experiences. These groups' primary mission is to improve healthcare quality and expand access to services, thereby shaping clinical research protocols to align with patient perspectives and promoting outcomes that truly benefit patients. Early dialogue creates an atmosphere where patient perspectives can seamlessly integrate into trial design, study objectives, and meaningful primary or secondary endpoints. Maintaining ongoing PAG communication facilitates trust while keeping patient groups informed

Patient Education Considerations

- Weight management focused on portion control and meal preparation education, enhancing patient understanding of portion sizing, emphasizing the immediate and long-term benefits of portion control and a healthier diet.
- Providing suggested dietary modifications with examples and approachable recipes the patient may start incorporating into their lifestyle.
- Educating avoidance of alcohol consumption entirely as it is an influential factor in liver disease progression, leading to advanced fibrosis and cirrhosis.
- Physical activity and exercise programs tailored to the individual and their physical capabilities; track progress, possibly through wearable technology, and monitor and positively reinforce work through objective data.
- Consider adding therapy resources for patients, as they are frequently comorbid with depression, anxiety, and eating disorders and may not be seeking active treatment.
- Curate a library of educational resources with 24/7 digital accessibility to support diet, exercise, and mental health.

and actively involved in support of the trial. Co-creating educational materials with PAGs helps explain the trial to patients in sensical and meaningful language and improves recruitment efforts.

Additionally, PAGs who co-create educational materials are more likely to advertise these trials to their members. In addition, establishing feedback mechanisms between the sponsor and PAG reinforces the trusting and partnership-oriented approach to community health and clinical trials. Depending on the trial design, this can also foster mid-trial modifications to enhance the study's relevance and optimize patient trial adherence. All these factors require transparency, including open communication about trial participation's potential benefits and risks. Open communication allows PAGs to recommend respecting patient autonomy, prioritizing welfare, and reducing patient burden.

In MASH/MASLD trials, the patient burden often includes frequent assessments, invasive procedures, and long-term follow-up. The increased burden makes eConsent and ePRO welcomed components of the protocol design, incorporating an eDiary to monitor study data, including caloric intake reduction, exercise, and protocol adherence. Additionally, covering transportation costs and compensating for potential lost wages from missed workdays can alleviate some of the patient's financial stress. Leveraging technology, such as digital pill caps and syringe dispensers, can help patients adhere to medication schedules and improve overall treatment compliance. Studies can further demonstrate patient centricity through adequate equipment tailored to individual body types and attending to simple components like adequate seat sizing in treatment facilities and ramps to accommodate potential mobility issues.

Trial considerations extend beyond physical burden to emotional support, from verbiage in patient-facing materials to site setup. Patients within the MASH/MASLD population frequently experience comorbid conditions such as obesity and mental health concerns, such as depression, anxiety, and sometimes substance use disorders; it is essential to use language that is devoid of any judgment. Perhaps equally important is the patient-first language that fosters patient humanization, de-stigmatizing MASLD/ MASH.

Multi-Disciplinary Staff Are Required for a Multifaceted Disease

A multidisciplinary team approach is essential for addressing the complex nature of MASH. It is important to involve specialists from various backgrounds, including those from sponsor CROs and vendors, to ensure comprehensive care. Cross-training CRO staff to be competent in MASH and general metabolic conditions enhances safety solutions and avoids needing individual staff for each cardiovascular, metabolic, and inflammatory disease indication. Cross-training also enables staff to understand the patient journey better and improves informed consent form language and safety measures. As many patients are on various medications, having a base knowledge of common medications, side effects, and associated risks facilitates a smoothly run trial and high-quality patient care. Such staff better understand the potential complications, increasing trial efficiency by anticipating and avoiding issues before they arise. From a logistics standpoint, cross-trained staff also reduces the total staff required on-site to ensure a safe patient experience; instead of requiring separate teams of specialized staff, one unified team can confidently provide complete trial support.

With a thorough understanding of the complete patient journey, cross-trained staff can propose more meaningful retention strategies.

Planning and Logistics for Biopsy Collection, Adjudication, & Management

Biopsy remains the primary endpoint metric expected by the FDA and EMA for MASH/MASLD trials and serves as the gold standard for diagnostics. Adhering to the best biopsy collection and adjudication practices is required for accurate results. All biopsies require a central read following a defined process to ensure a robust confirmation of the MASH diagnosis and to characterize early signs of efficacy in the MASH patient population. The central reading process utilizes three independent pathologists and employs the mode/median method. In this process, digitized stained slide images are read in parallel by three independent pathologists, blinded to the treatment group and sequence of sampling.

Though not directly paired, end-of-treatment biopsies are shuffled with screening biopsies to blind the sampling sequence. For all biopsy reads, including screening/baseline and end-of-treatment, the fibrosis score and each component of the NAFLD Activity Score (NAS), including hepatocyte ballooning, lobular inflammation, and steatosis, require agreement from at least two of the three pathologists to constitute a consensus score, known as the mode.

When fibrosis scores do not have the agreement of at least two pathologists, all three pathologists resolve the scoring through a joint consensus meeting. The median

constitutes the consensus score for each NAS component without the agreement of at least two pathologists. If the median cannot be calculated, a joint consensus meeting involving all three pathologists resolves the scoring.

The results of a biopsy can vary widely, highlighting the importance of proper collection to ensure sufficient tissue samples without fragmentation. Proper management of biopsy samples, including pre- and post-treatment collection time points, is critical for the study's success. Emerging AI-based tools often assist in adjudication, providing additional accuracy and efficiency.

To ensure an on-time database lock, it is essential to carefully plan the timing of each patient's first and last biopsy collection. The sheer sample volume takes significant time to read through, bottlenecked by the review speed, conducted by only two blinded reviewers. Without careful planning, a delay in readouts can, in turn, significantly impact both ends of the study: patient screening and final endpoint screening. This highlights the influential role of effective biopsy management, especially during large Phase III studies, potentially enrolling 2,000 patients and a possible range of 4,000-6,000 biopsy samples to process by the end of the study.

Emerging Potential for Biopsy Screening & Endpoint Alternatives

Though biopsy remains required for diagnosis and as a primary endpoint, both the EMA and FDA are exploring alternative endpoints to liver biopsy; however, these alternatives are still subject to rigorous validation before they become acceptable non- or minimally invasive endpoint metrics (Figure 1). Integrating biomarkers and imaging methods into trial designs as composite endpoints or in combination with histological data will help shift toward broader regulatory acceptance in the future.

GLP-1 Therapy Impact on Protocol Ethics & Study Participation

Recruiting patients for MASH clinical trials presents unique challenges, as many patients are asymptomatic until significant liver damage has occurred. Often, patients discover they have MASH while seeking treatment for related conditions such as T2D or obesity. These patients may already be participating in other clinical trials for these comorbidities, complicating their participation in MASH studies. Ethical considerations arise when patients are on medications, particularly GLP-1 therapies, which may interfere with study protocols. Many MASH protocols require patients to cease GLP-1 therapy or to maintain a stable dose over an extended period, which is often not feasible. Therefore, ensuring ethical patient treatment and considering the impact of their current medications is vital for successful recruitment and trial integrity. Beginning and maintaining a stable dose of GLP-1 medications for an extended period is a known challenge for this class of drugs. Adherence to GLP-1 regimen ranges from 30 – 45% at the one-year mark. Ensuring patients have the medical and emotional support needed to stay on medications for MASH/MASLD protocols cannot be underestimated from the study due to medication changes. In addition, an obese patient may have MASH but be hesitant to get screened; however, the ideal goal is early diagnosis before advanced fibrosis. The complications around interfering

Retention Benefits from a Cross-Trained Staff

- Cross-trained staff facilitate flexible clinic visit scheduling, stemming from understanding the other medical appointments and approved treatments the patient may require during the study.
- Staff that understand the patients' multifaceted medical needs can inherently provide a more patient-centric environment.
- Cross-trained staff contribute to protocol design and can minimize the trial's invasive components wherever possible.
- The staff will understand how to provide lifestyle support to patients and can incorporate this into their clinic interactions and other communication.
- The staff can answer questions regarding the trial and comorbidities, creating a positive atmosphere and encouraging better patient retention.

Minimally-Invasive Surrogate Endpoints Under Regulatory Consideration.

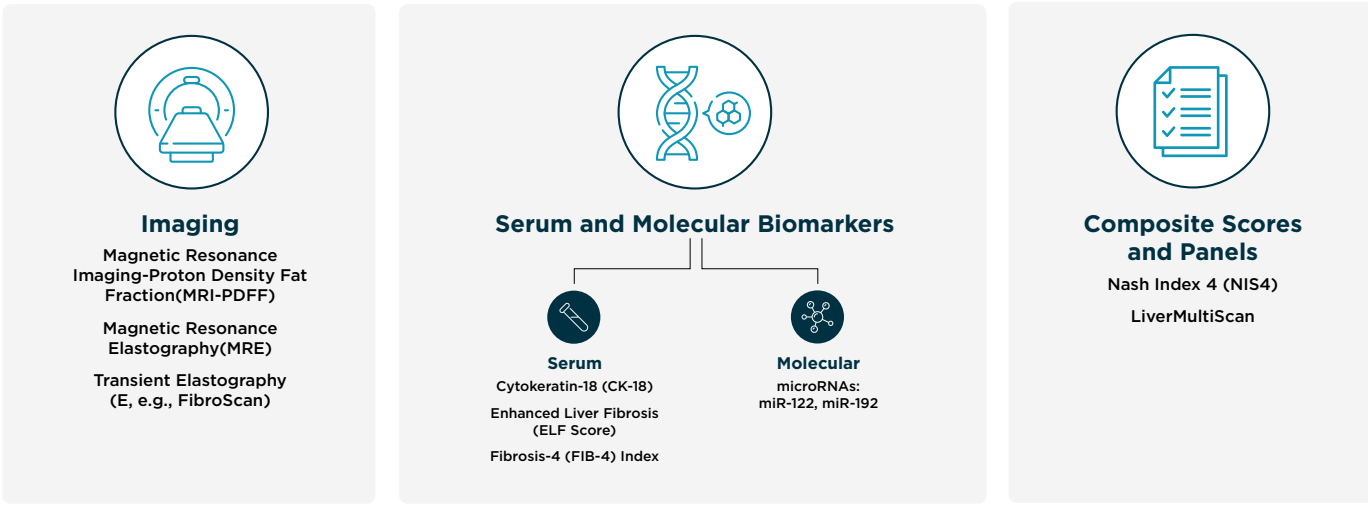

Figure 1. Minimally invasive surrogate endpoint alternatives to liver biopsy. *The FDA and EMA are becoming more open to clinical endpoints besides the gold standard liver biopsy. The required multiple liver biopsies present a significant barrier to patient participation; sometimes, patients are subjected to as many as three to demonstrate treatment efficacy. However, these metrics require substantial and rigorous validation before gaining official regulatory approval to serve as diagnostic tools or primary endpoints.*

medications further emphasize the importance of designing a trial that stands out in the crowded arena of MASH studies and a decreased population of willing patients.

Standing Out in a Competitive Arena & Untapped Site Utility

Differentiating your MASH clinical trial in the patient's eye involves addressing the values and priorities of PAGs and providing meaningful patient incentives. Utilizing groups like EmVenio and Apex to achieve more expansive patient screening can enhance recruitment efforts. Emphasizing previous experience and success in MASH trial conduct and providing additional education for lifestyle changes to patients and caregivers can also attract patients.

Increasing patient diversity by including sites in Latin America and the Asia-Pacific (APAC) region offers unique insights and broadens the study population. Latin America has a high volume of MASH patients, with many sites already equipped for MASH studies. APAC presents an opportunity for advanced patient stratification due to its high proportion of lean MASH diagnoses. Utilizing untapped sites with access to advanced capabilities like MRI and involving sites experienced in related comorbidities can further enhance the study.

Both within the U.S. and globally, consider sites running obesity or T2D studies that are already familiar with the patient population, even if not specifically in MASH. If they are performing well in their other studies, they are worth consideration, and site feasibility should be relatively streamlined compared with an entirely naïve site. When considering untapped sites, emphasize the sites having access to various specialists.

The Future of MASH Research

As our understanding of MASH and MASLD continues progressing, we must adjust our approach to clinical trials and patient care accordingly. The associated comorbidities, including metabolic syndrome, CKM, T2D, and obesity, require innovative trial designs with a holistic, patient-centric approach. By integrating patient voices, multidisciplinary teams, and advanced technologies, we can enhance the efficacy of trials and improve patient outcomes. With regulatory agencies beginning to explore non-invasive alternatives to liver biopsy as endpoints, the landscape of MASH/MASLD research is poised for significant advancement. However, sustained progress requires continued collaboration with PAGs, careful design considerations around comorbidities and medications, and strategic site selection to ensure optimal trial visibility.

Contact Worldwide today and discuss with our experts how to position your MASH/MASLD study for success.

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