Maintaining Patient Safety and Data Integrity of NASH Clinical Trials During the SARS-CoV-2 Pandemic

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Potential COI:

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Introduction

Coronavirus disease 2019 (COVID-19), the illness caused by the SARS-CoV-2 virus, has spread rapidly throughout the world (1) overwhelming healthcare systems. Fever and cough are the dominant symptoms with 15% of patients developing severe illness especially in the elderly and those with concurrent illnesses. Quarantine, shelter in place, and social distancing strategies have been instituted, restricting people from going out for all but essential services. The prevalence of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), have steadily increased and now affect approximately 25% of the global population. Therefore, the overlap between the COVID-19 and NASH pandemics is inevitable. Given that there are no FDA-approved therapies for NASH, numerous trials are being conducted. Unfortunately, the COVID-19 pandemic has disrupted every aspect of NASH clinical trials from patient recruitment, to administration of the investigational products (IP) and safety monitoring, to data integrity. In this commentary, we will discuss the rationale for the continuation of NASH clinical trials during the COVID-19 pandemic and
provide several strategies to mitigate the effects of the pandemic on continuity and veracity of data being collected.

The Rationale for NASH Clinical Trial Continuation During the SARS-COV-2 Pandemic

Over the past five years, the number of clinical trials investigating NASH therapeutic agents has exponentially increased. Some of these agents have already shown great promise to improve NASH and/or improve NASH related fibrosis.

For patients in NASH clinical trials and other stakeholders (CROs, Sponsors, research sites) engaged in NASH drug development, the paths to ensure patient safety and data integrity during this time of pandemic are complex. Nevertheless, it is of utmost importance that we continue NASH clinical trials for several reasons. First, large amounts of resources have already been dedicated to the NASH drug development process, with an estimated cost in the hundreds of millions of dollars, and of labor and risk (2). Secondly, medications in many of these clinical trials have the potential to benefit millions of people with NASH and fibrosis long after the coronavirus pandemic has ended. Finally, we have an ethical obligation to adequately care for patients who are potentially benefiting from these investigational drugs as well as monitor their safety.

The Risk for Severe COVID-19 in NAFLD Patients

The SARS-CoV-2 binds to target cells through angiotensin-converting enzyme 2 which occurs abundantly on liver and biliary epithelial cells making the liver a potential target for infection (3). In fact, elevation in liver enzymes in hospitalized patients with COVID-19 is common (4) although it is difficult to differentiate whether increases in liver enzymes are due to SARS-CoV-2 infection itself, its complications, or a drug-induced liver injury (DILI).

The link between NASH-associated co-morbidities such as type 2 diabetes and obesity and severe COVID-19 has been established (5, 6). A summary report of a large cohort of patients with COVID-19 from the Chinese Center for Disease Control and Prevention reported a case fatality rate of 7.3% in diabetics compared to of 2.3% in the general population (7).
However, less data are available on NAFLD/NASH as an independent risk factor for COVID-19 progression. A recent study evaluated 202 consecutive patients with confirmed COVID-19 and information relating NAFLD status based on the hepatic steatosis index or liver ultrasonography (8). Liver injury was observed in 101 (50%) and 152 (75.2%) patients on admission and during hospitalization respectively. Almost all liver injury was mild with a hepatocellular pattern (elevation in ALT). Compared with non-NAFLD subjects, patients with NAFLD had higher risk of disease progression to severe COVID-19 [6.6% (5/126) vs 44.7% (34/76) p<0.0001] and longer viral shedding time.

**Strategies for clinical trial sites during COVID-19 pandemic**

Research centers are making changes to their clinical trial programs, while pharmaceutical companies are deciding how—or whether—trials should continue. To that end, the FDA released a new Guidance documents on the conduct of clinical trials during the COVID-19 pandemic (9). Strategies for clinical trial sites to ensure compliance, data integrity and mitigate infectious disease risk during these unprecedented times are critical (Table 1). These strategies vary based on research procedure to be performed, clinical trial risk/benefit, COVID-19 community disease prevalence, and patient comorbidities.

**Trial Start Up: Prescreening and Screening Activities**

Prescreening used to identify patients may be able to be done remotely and most records are digital with staff contacting potential participants by email or telephone. Given that many patients have limited time outside of the house, this may be an ideal time for robust prescreening activities as patients can be more easily reached. This can ensure that once quarantine measures have been removed, clinical trial programs are able to restart without significant delay.

Screening for NASH clinical trials require an in-office visit for physical exam assessment, electrocardiograms (EKGs) and laboratory data. Often, visits to other healthcare institutions for radiology tests and/or liver biopsy are needed. It is imperative to take into consideration local COVID-19 disease prevalence and the patients’ comorbidities before proceeding as additional
healthcare visits may put the patient at increased risk for infection with SARS-COV-2. In particular, patients with type 2 diabetes and those with cardiovascular disease have been shown to have higher mortality rates if they develop symptomatic SARS-COV-2 infection (7). If sites do elect to continue with screening, they should ensure that imaging or biopsy sites are open to research procedures and that they implement steps to decrease risk of SARS-CoV-2 transmission for patients and research personnel who may need to be on site to ship tissue samples out for processing and central reading of histology. Sites may consider testing for SARS-CoV-2 within 72 hours prior to bringing patients in for a liver biopsy as a mitigation strategy to decrease the risk for staff and other patients. This can ensure patients’ safety and vendor understanding of the importance of continuing with select research procedures. Another concern about continuing in clinical trials at this time, is the probability that patients may be receiving a placebo, which puts them at potential risk of infection due to additional healthcare visits with no clear in regards to their underlying liver disease. Conversely, the risk of each therapeutic agent to predisposing patients to infection with SARS-COV-2 should also be addressed with each sponsor based on mechanism of the investigational agent. If additional risk is noted, amendments to the protocol should be expedited and relayed to patients expeditiously.

**Managing Patients Who Are Already Enrolled in Clinical Trials**

For patients currently enrolled in NASH clinical trials and receiving IP, it is imperative that the safety of the patient is given the highest priority. Frequent communication with the patient is important to ensure prevention or appropriate management of untoward adverse events. DILI remains a major concern for drug developers and investigators in NASH trials and differentiating elevation of liver tests from DILI versus COVID-19 poses a significant challenge. Patients presenting with elevated ALT and AST along with gastrointestinal symptoms during a trial should be tested for SARS-CoV-2 infection. Furthermore, if a patient develops severe COVID-19 that requires hospital admission, the IP should be placed on hold until deemed safe by the investigator and the study team.

Scheduled study visits themselves may be done in office, by telehealth, or home visits (10). Telehealth research visits should be conducted using HIPAA compliant audio and/or video. Clear documentation of method of visit and how data were obtained is critical (i.e., vitals – patient
reported). In office, extra attention should be given to ensuring a clean clinic space to minimize disease transmission. Where possible consider providing masks for patients and staff. Patients with symptoms of COVID-19 and/or fever should be counseled to not come into the clinic and can be seen through telehealth. Patients with confirmed COVID-19 will need to remain quarantined for at least 14 days after symptoms have resolved.

Study questionnaires can be mailed to the patient and returned by mail, or if not feasible, read to the patient on the phone. Study laboratory tests could be collected by mobile phlebotomy using study specific kits, which will allow for collection of biomarkers that are critical in NASH trials. If this is not possible, a local laboratory can be used for safety laboratory tests alone.

**Safety and Efficacy Assessment**

Data integrity, particularly as it pertains to critical safety and efficacy endpoint analysis is also paramount. Special importance should be placed on collecting laboratory tests or other procedures (e.g. EKG’s) required to assess a patient for imminent safety concerns, either in office visits, through home visits or at a local laboratory. Safety assessments for non-urgent issues- i.e. DEXA scan for bone mineral density, should be considered for deferral until after pandemic restrictions have been lifted.

The risks and benefits of completing study related procedures not directly linked to ensuring patient safety should be adjudicated individually. Priority should be given to completing procedures related to the primary endpoint of the study and then major secondary endpoints (i.e. liver biopsies, MRI/MRE/PDFF, biomarkers). If these cannot be done safely, the sponsor and/or medical monitor should be contacted, and alternate plans made. This may include deferring endpoint measurement until they are safe to complete and potentially continuing the IP until that endpoint can be measured.

With clinical study monitors restricted from travel, remote electronic monitoring offers an alternative to traditional onsite monitoring practices. Research sites may elect to share information with monitors via paper mail, email, enabling direct access to the electronic medical records, or remote monitoring systems. Flexibility in institutional review board (IRB) policies is of utmost importance to support clinical trials in this extraordinary pandemic. Protocol modifications are
expected to occur frequently requiring expedited reviews. Considerations should be given to revising specific protocol deviation definitions especially when they pertain to performing certain tests within a tight time frame that may not be feasible for logistical reasons due to COVID-19.

In conclusion, there is scientific and ethical evidence for the need to continue ongoing NAFLD/NASH trials. However, NAFLD patients have higher risk of progressive COVID-19 requiring mitigation strategies.
Table 1. Strategies to mitigate the effects of the COVID-19 pandemic on NASH clinical trials

- Delay the opening of new clinical trials.
- Robust prescreening activities: patients can be more easily reached (phone/ email) due to quarantine.
- For ongoing trials, add pre-visit questionnaires to exclude patients with COVID-19 symptoms and those who have been exposed to COVID-19.
- Consider testing for SARS-CoV-2 within 72 hours prior to bringing patients in for a liver biopsy.
- Decrease or delay protocol mandated in-person study visits and allow wider visit windows.
- Try to replace in-person study visits with phone calls, home visits, or telemedicine visits.
- Allow blood draws at commercial laboratory when appropriate.
- Ship the investigational product to the patients directly if allowed by state laws.
- Working remotely for data managers and study coordinators.
- Preserve both scientific validity of results and safety of patients/ trial personnel by implementing decision sharing and maintaining communications with the trial sponsors.
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