

OPINION PAPER

Developing Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Noncirrhotic Nonalcoholic Steatohepatitis (NASH) Liver Fibrosis

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Nonalcoholic steatohepatitis (NASH) can progress to cirrhosis and liver failure and is associated with an increase incidence of liver cancer. Currently, there are no approved therapies for treatment of NASH fibrosis. During evaluation of a new drug application, it can be challenging to differentiate between progression of liver disease and potential drug-induced liver injury (DILI) in subjects with NASH fibrosis and DILI. Therefore, clinical trials for treatment of NASH fibrosis require standardized disease-specific metadata to adequately support evaluation of efficacy and safety, including potentially DILI assessment. To improve reviewability and quality of data submission, it is helpful for all stakeholders to understand specifications needed for subject level data submission to the FDA. Development of technical specifications requires a multidisciplinary approach. This report describes the rationale, process and methods used in developing Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Noncirrhotic Nonalcoholic Steatohepatitis (NASH). The recommendations outlined in the NASH technical specifications pertain to submission of the sponsor's tabulated and analysis data sets in a standardized manner based on CDISC standards to improve reviewability. These specifications also provide an opportunity for dialogue between the sponsor and regulatory agency to discuss issues related to trial design or conduct that may affect the content of these data sets. These specifications are intended to support the draft guidance for industry *Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment* (NASH Guidance) and reflect the data standards and processes described in the FDA *Study Data Technical Conformance Guide* and the *FDA Data Standards Catalog*.

Keywords: Study Data Technical Specification; Regulatory; FDA data Standards; Nonalcoholic Steatohepatitis clinical trial data sets

Background

Disease Background

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide. The worldwide prevalence NAFLD in the adult population has been estimated to be 25–30%.^{1,2} NAFLD includes a wide spectrum of liver manifestations ranging from macrovesicular steatosis, steatohepatitis, advanced fibrosis, and cirrhosis. Only a subgroup of patients with NAFLD will progress to nonalcoholic steatohepatitis (NASH) and subsequent cirrhosis.^{1,3} The exact underlying etiology of NASH is unknown but risk factors for developing this condition

include obesity, type 2 diabetes mellitus, dyslipidemia and “metabolic syndrome”.^{4,5} Patients with NASH have increased overall mortality related to cardiovascular disease and liver-related mortality rate.⁵ Currently, FDA has not approved any therapies for treatment of NASH fibrosis. Clinical trials evaluating various agents targeting insulin sensitization, lipid metabolism, oxidative stress, fibrosis, inflammation, and the intestinal microbiota for the treatment of NASH fibrosis are in development.

The Division of Hepatology and Nutrition (DHN) serves as the clinical review division in the Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER) for review of drug products for treatment of liver fibrosis due to NASH. In December 2018, FDA issued a draft guidance outlining recommendations for clinical development of drugs intended for treatment of noncirrhotic NASH with liver fibrosis (Noncirrhotic NASH Guidance).⁶ The 2018 draft guidance acknowledges that subjects with NASH fibrosis have unique challenges (e.g., underlying hepatic dysfunction) during drug development. Furthermore, evaluation of potential drug-induced liver injury (DILI) in this population is challenging because it is unclear whether

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patients with underlying liver disease are at increased risk for DILI and it can be difficult to differentiate between progression of liver disease and DILI.^{7,8}

Standardized Data and Technical Specifications

Data standards play a pivotal role in analysis of subject level data during regulatory review of a marketing application. Following standards and terminologies in the FDA Data Standard Catalog and the FDA Study Data Technical Conformance Guide³ will allow regulators to analyze and interpret data in an efficient and consistent manner.^{9,10} Currently, FDA supports and requires (under section 745A(a) of the FD&C Act) data submission using the Clinical Data Interchange Standards Consortium (CDISC) data exchange and terminology standards for clinical and non-clinical submissions. The required standards for submission to the FDA are located on the FDA Data Standards Catalog.⁹

There can be great variability in clinical trial design (e.g., safety and efficacy endpoints, adjudication processes) depending on the proposed therapeutic indication for marketing application. Therefore, regulatory guidance related to data submission for individual therapeutic indications can reduce sponsor burden and potential delays in regulatory review by potentially reducing the need for subsequent information requests. FDA guidances are documents that explain the agency's interpretation of, or policy on, a regulatory issue. Although FDA guidances are not legally binding, they provide recommendations on how stakeholders can reach their regulatory goal. Technical Specifications are issued as FDA guidances, which are intended to address existing practices or minor changes in FDA's interpretation or policy.

In general, FDA Technical Specifications documents contain data submission guidance to support recommendations already provided in a clinical guidance. These guidances represent the clinical review divisions' current thinking in their respective therapeutic area. Technical Specifications provide recommendations on how to submit standardized study data using required CDISC standards. They can also highlight opportunities for dialogue between the sponsor and clinical review division. While current CDISC standards allow for significant flexibility, this potentially leads to variability in data submissions. The goal of a technical specification is to create a data structure roadmap for sponsors to ensure that complete clinical trial data is submitted in an organized fashion conducive to a thorough and efficient regulatory review of safety and efficacy.

Data Challenges to Support Efficacy and Safety in NASH Clinical Trials

Designing a data structure for submitting data to support efficacy and safety in clinical trials intended to support marketing application for treatment of patients with noncirrhotic NASH fibrosis is challenging due to therapeutic area specific data considerations related to safety and efficacy endpoints, including the number and variety of biomarkers reported and evaluation of potential DILI in patients with underlying liver disease.

Histopathological evaluation of liver biopsy is of critical importance to support efficacy and safety for these drug development programs because the surrogate endpoints currently acceptable to FDA to support approval for this indication under the accelerated approval pathway (21 CFR Subpart H)¹¹ are biopsy-based. Data submitted will need to support assessment of biopsy specimen adequacy, inter and intra-observer variability, and adjudication of histopathological interpretation.

In addition to standard laboratory parameters, sponsors may wish to include serum and imaging biomarkers potentially relevant to understanding NASH, liver fibrosis, or DILI such as ELF, FIB-4, and MELD score. While serum and imaging-based biomarkers are currently not accepted by FDA to support primary efficacy assessments in trials intending to support a marketing application for treatment of NASH, they can be used to assess efficacy in early phase trials and as exploratory or secondary endpoints to provide supportive evidence. It is therefore important for these data points to be submitted consistently for a more comprehensive and efficient regulatory review.

Evaluation of potential DILI is a complex and challenging process in patients without underlying liver disease. The challenge becomes magnified when study subjects have underlying liver disease and may have abnormal baseline liver biochemistry that fluctuates throughout the clinical trial. When potential cases of DILI are identified during review of marketing applications, it is recognized that submitted data related to DILI evaluation is frequently incomplete (i.e., missing lab parameters), inconsistent across data sets, or does not provide a clear indication of work-up and patient outcome. Therefore, technical specification related guidance is needed to facilitate data submission to allow for regulatory assessment of potential DILI.

Developing the NASH Technical Specifications

Given the identified need for guidance regarding data submission in the NASH therapeutic area, the Biomedical Informatics and Regulatory Review Science (BIRRS) team within the Office of Drug Evaluation Science (ODES), Office of New Drugs (OND), Center for Drug Evaluation (CDER) was tasked with developing a technical specification, i.e., Noncirrhotic NASH Technical Specifications,¹² to address this need and to provide guidance on data submission that aligns with the draft Noncirrhotic NASH Guidance.

The process of developing the technical specification required a cross-functional, multidisciplinary approach with expertise from clinical reviewers, statisticians, data standards experts, etc. As background research, the BIRRS team analyzed previously submitted data sets from relevant clinical trials and conducted interviews with members from the multidisciplinary review team to identify data-related barriers to allow a thorough and efficient review of applications. This analysis uncovered key data-related deficiencies such as missing data, non-standardized data, and poor data structures. Additionally, the team worked with multidisciplinary subject matter experts (SMEs) to identify a list of the safety and efficacy end points relevant in NASH clinical trials and ascertained

data elements required to facilitate regulatory review. The endpoints are each accounted for in different parameters within the Analysis Data Model (ADaM) data sets while the individual biomarkers required to evaluate the endpoints are organized within the Study Data Tabulation Model (SDTM) domains.

For efficiency, a decision was made to focus the content of the Noncirrhotic NASH Technical Specifications on recommendations pertaining to data elements unique to NASH clinical development. In addition to recommendations based on the FDA Study Data Technical Conformance Guide, and existing CDISC data standards and controlled terminology, the technical specification also proposed new strategies where no current modeling exists. For example, specific recommendations were provided on inclusion of the Microscopic Findings (MI) domain to house liver biopsy data required for efficacy determination. While controlled terminology exists for reporting the NAFLD Activity Score (NAS) on liver biopsy, each component of the NAS (Steatosis, Lobular Inflammation, Hepatocellular Ballooning) is not captured. Based on feedback from the clinical review division, the NASH technical specifications recommended a new data submission strategy that included reporting of individual components of the NAS. Specific recommendations were also made on how to capture data from multiple histopathologist evaluators to allow for assessment of inter and intra-observer variability given that was also a concern for the regulatory reviewers. Other proposed data submission strategies included recommendations related to pathology specimen adequacy, reporting of non-invasive serum and imaging biomarkers relevant to understanding NASH, fibrosis, or DILI and creation of supplemental or custom domains, such as the Adjudication Domain to store information for adjudicated events, when more granular details may be required.

Where the recommendations in the SDTM Implementation Guide provided direction on sorting data into specific domains, the ADaM Implementation Guide focuses on the derivation of parameters (rows), variables (columns), and datasets to support the endpoint analysis.^{13,14} Derived parameters assess the extent to which a subject has met an endpoint. An example parameter might be "Improvement of Fibrosis Stage with No Worsening of NASH" if the study uses this as an endpoint. These parameters help identify which subjects met the prespecified endpoints during regulatory review.

The different types of variables used in the ADaM data sets include: Flag Variables (ending in --FL), Baseline Variables (ending in --BL, derived in the Subject-Level Analysis Data Set (ADSL) and carried through to other data sets), and Category Variables (ending in --CAT). All these variable types are used ubiquitously in ADaM. Each serves a different purpose and has a different set of rules. Flag Variables are binary (Y/N) and are used to determine if record meets certain criteria. In some cases, the variable may allow for Y/<null> and in other cases it may allow for Y/N/<null>. For example, DIABFL (Diabetes Flag) was recommended to flag subjects with baseline history of diabetes to allow for regulators to conduct a subgroup

analysis in diabetics. The variable DILIFL (Potential DILI Event Flag) could be used to identify subjects with potential DILI. Baseline variables are used to establish the value of a given parameter prior to treatment. These variables are needed to assess changes in a patient's measurements, such as labs, vitals, biopsy, etc., after the start of treatment. They are typically derived from the SDTM domains, stored in the ADSL data set, and carried onward to other analysis data sets as needed. In NASH clinical trials, baseline liver biochemistries and biopsy characteristics are important variables in evaluation of efficacy and safety. Category variables are used to classify records into one of multiple mutually exclusive groups. For example, potential confounding concomitant medications such as lipid-lowering agents could be placed in categories of "No Concomitant Use", "Prior and Concomitant Use", "New Concomitant Use". These variables are used by the review teams to conduct a thorough, efficient, and data-driven review of a NASH clinical trial.

Of particular interest to the regulatory review team was how data submission can facilitate evaluation of potential DILI in drug development programs that enroll patients with underlying liver disease. The team adopted a similar approach and proposed strategies that provided a framework for data submission. Custom flags were recommended in analysis data sets to ascertain onset of hepatic injury and potential DILI-related adverse events. During evaluation of potential DILI, subjects with elevated transaminase levels at enrollment may show improvements in their transaminase levels and in essence, establish a new lower baseline during the trial for subsequent assessment of potential DILI. Use of the custom variable DILIBLFL (DILI Baseline Flag) to identify the baseline liver biochemistry values used for potential DILI assessment is recommended. Sponsors should seek review division agreement on derivations for alternate baseline calculations for assessment of potential DILI. The technical specifications also introduced custom derived parameters, such as calculated R values, and data sets, such as the DILI Analysis Data Set (ADDILI), to facilitate regulatory evaluation of potential DILI events. It should be noted that while structured and comprehensive data submission can support effective and efficient evaluation of potential DILI cases, it does not replace the role of DILI case narratives, which provide a clinical evaluation of the potential of the drug to cause DILI, potential DILI phenotype, and competing diagnoses for the patients of concern. It is also important to note that data submission recommendation for DILI evaluation related data elements is not unique for NASH development programs and can be generalizable to DILI evaluation for any clinical trial.

Conclusions

Indication-specific technical specifications can address unique data requirements to support regulatory determination of safety and efficacy. They guide data submission to facilitate effective and efficient regulatory review. In developing a technical specification, a multidisciplinary approach is recommended to ensure complete list of data elements required to facilitate

regulatory review. Technical specifications can provide data submission recommendations through various strategies including: 1) use of existing controlled terminology; 2) proposing a new model or controlled terminology for data submission where existing modeling is inadequate; 3) creating supplemental or custom domain(s) or data elements when more granular details may be needed. Technical specifications can also serve as groundwork for future collaborations on data modeling strategies between regulatory agencies and data standards development and maintenance organizations.

Competing Interests

The authors have no competing interests to declare.

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