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Design and rationale for a real-world observational cohort of patients with nonalcoholic fatty liver disease: The TARGET-NASH study

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is highly prevalent and can lead to cirrhosis, hepatocellular carcinoma, and end-stage liver disease. NAFLD comprises the spectrum from simple steatosis (nonalcoholic fatty liver, NAFL), to steatosis with inflammation (nonalcoholic steatohepatitis, NASH). Current primary therapy recommended for NAFLD is weight loss induced by lifestyle modification. The difficulty in achieving this has led to robust pharmacological therapy development. While new drugs may show efficacy in selected phase II/III clinical trial populations, their real-world effectiveness is unknown. TARGET-NASH is a 5-year, longitudinal, observational study of patients with NAFLD designed to evaluate the effectiveness of clinical practice interventions and provide practical information unobtainable in registration trials. A biological specimen repository is included in TARGET-NASH for translational studies of genomics and biomarkers of disease activity. Patients are enrolling at adult and pediatric sites representing multiple specialties. All patients being managed for NAFLD are eligible, whereas those in other NASH registries or clinical trials will be excluded. Enrolled patients range in age from 6 and up and will have 3 years of clinical data reviewed. Patient comorbidities, concomitant medications, disease progression and off-label interventions will be assessed, and adverse outcomes, monitored. Confirming the use, safety and effectiveness of NAFLD interventions in children and adults and establishing pragmatic methods of assessing disease progression under real-world conditions are key study outcomes. Ultimately, TARGET-NASH will establish a large, diverse registry of NAFLD patients at academic and community practices to be leveraged to improve health and reduce development of cirrhosis and hepatocellular carcinoma.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) refers to the presence of hepatic steatosis without evidence of other causes of hepatic fat accumulation (such as heavy alcohol consumption). It is a highly prevalent, progressive liver disease ranging from simple steatosis to NAFLD

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; U.S., United States; FDA, Food and Drug Administration; IRB, Institutional Review Board; NAS, NAFLD Activity Score; PRO, Patient-Reported Outcomes; BEVQ-15, Beverage Intake Questionnaire; PROMIS, Patient-Reported Outcomes Measurement Information System; BSB, Biorepository Specimen Bank; DNA, deoxyribonucleic acid; TPS, TARGET PharmaSolutions; AE, adverse events; HIV, human immunodeficiency virus; NHANES, National Health and Nutrition Examination Survey; AUDIT, Alcohol Use Disorders Identification Test

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Table 1
Current distribution of sites enrolling in TARGET-NASH.

Site	Investigator	Community	Academic	Gastroenterology/ hepatology	Endocrinology	Pediatric
Advanced Gastroenterology Associates	Jawahar L. Taunk, MD	X		X		
Asheville Gastroenterology Associates	William Harlan, MD	X		X		
Atlanta Gastroenterology Associates	Norman Gitlin, MD	X		X		
Banner - University Medical Center Phoenix	Anil Seetharam, MD		X	X		
Center for Liver Disease and Transplant at Carolinas Medical Center	Andrew deLemos, MD	X		X		
The Children's Hospital at Montefiore	Bryan Rudolph, MD		X	X		X
Connecticut Gastroenterology	Raffi Karagozian, MD	X		X		
Digestive Health Specialists, PA	Marcum Gillis, MD	X		X		
Emory University/Children's Healthcare of Atlanta	Miriam Vos, MD, MSPH		X	X		X
Gastro Florida	L. Michael Weiss, MD	X		X		
Gastrointestinal Specialists (Louisiana Research Center)	Humberto I. Aguilar, MD	X		X		
Houma Digestive Health Specialists	Nathaniel Winstead, MD	X		X		
Liver Institute of Virginia	Mitchell L. Shiffman, MD	X		X		
Liver Specialists of Texas	Joseph S. Galati, MD	X		X		
Mercy Medical Center	Paul Thuluvath, MD	X				
North Well Health	David Bernstein, MD		X	X		
San Jose Gastroenterology (Silicon Valley Research Institute)	Huy Trinh, MD	X		X		
Pinnacle Clinical Research	Stephen Harrison, MD	X		X		
University of Florida Health	Kenneth Cusi, MD		X		X	
University of Florida Health	Roberto Firpi-Morell, MD		X	X		X
University of Florida Health - Jacksonville	Miguel Malespin, MD		X	X		
University of Louisville	Craig J. McClain, MD		X	X		
University of Miami	Kalyan Ram Bhamidimarri, MD		X	X		
University of Miami/Schiff Center for Liver Diseases	Cynthia Levy, MD		X	X		
University of Michigan	Anna Lok, MD		X	X		
University of Nebraska	Fedja A. Rochling, MD		X	X		
University of North Carolina at Chapel Hill	A. Sidney Barritt, MD		X	X		
University of Oklahoma	Sirish Palle, MD		X	X		X
University of Pennsylvania	K. Rajender Reddy, MD		X	X		
University of Washington	Charles Landis, MD		X	X		

induced cirrhosis. NAFLD is divided into nonalcoholic fatty liver (NAFL), in which hepatic steatosis is present without signs of inflammation, and nonalcoholic steatohepatitis (NASH), in which hepatic steatosis is associated with inflammation that is often histologically indistinguishable from alcoholic steatohepatitis. NAFLD is closely linked to the metabolic syndrome and is associated with diabetes, dyslipidemia, and obesity [1]. NAFL is estimated to be present in one-third of the adult U.S. population [2,3], and in about two-thirds of people with obesity or type 2 diabetes [4]. NASH is the intermediate stage on the pathway to cirrhosis and occurs in 5–8% of the adult U.S. population [5]. The prevalence of NAFLD is also rising among children, likely due to the increased prevalence of obesity. NAFLD affects approximately 70% of children with obesity in the U.S. (~7 million children total), 70% of children with obesity in Asia and 35% of children with obesity in Europe [6,7]. Left untreated, NASH can progress to cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Multiple therapeutics have been studied to reverse its course, but none have yet been approved by the Food and Drug Administration (FDA). While lifestyle modification, including diet and exercise, remain the cornerstone of therapy for NASH, multiple treatment modalities could come to market soon. Future FDA approved pharmacologic interventions will need to show safety and efficacy in clinical trials. Confirming the safety and effectiveness of these interventions under real world conditions and establishing pragmatic methods of assessing disease diagnosis and progression are critical for developing appropriate clinical practice guidelines.

Phase III clinical trials are performed in highly selected, adherent study participants who often lack significant comorbidities outside the disease area in question. This has been the case in several areas within hepatology [8]. These trials are good measures of clinical efficacy; however, the more germane question for clinicians and their patients is one of real-world effectiveness. This assessment can only be made in post-marketing surveillance, when new medications are incorporated into general practice among patients with multiple comorbidities and variable levels of treatment compliance. Ongoing monitoring of side effect profiles of these emerging therapeutic agents for NASH and determining whether proposed management plans within clinical trial protocols are effective in mitigating adverse events in clinical practice are essential for guiding policies on NASH management.

TARGET-NASH is a cooperative consortium of principal investigators from academic institutions and community sites that treat patients with NAFL and NASH. It will provide unique opportunities to engage networked physician teams in evidence-based evaluation of NASH therapies, and to involve these teams in clinical research. TARGET-NASH is designed to leverage the multidisciplinary expertise within this network through biological specimen banking, high-throughput technologies, and biomedical informatics to generate the power to analyze effectiveness data at different levels of resolution, ranging from subsets of patients to very large populations.

2. Methods

2.1. Overview

TARGET-NASH is a 5-year, longitudinal, observational study that seeks to describe the real-world practice of diagnosis, management and natural history of NAFLD. TARGET-NASH is based on HCV-TARGET, a cooperative academic consortium that guides safe and effective use of direct-acting antivirals approved for the treatment for chronic HCV infection. Like that in HCV-TARGET, the overarching aim of TARGET-NASH is to demonstrate the clinical effectiveness of therapies in a real world setting. The model in HCV-TARGET “allows rapid data acquisition across multiple regimens being utilized in a disease population receiving care in routine clinical practice… and a robust platform for