American Association for the Study of Liver Diseases

AASLD

EASL

European Association for the Study of the Liver

Forum for Collaborative HIV Research

Working Group Report:

Baseline Data: Current Status, Opportunities for Standardization, Increasing Compatibility and Recommendations for Future Studies

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Working Group

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Joint Leadership

American Association for the Study of Liver Diseases AASLD
EASL European Association for the Study of the Liver
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Overall Goals

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- Facilitate process of validation and acceptance of non-invasive diagnostics
- Establish clarity regarding baseline parameters collected for NAFLD/NASH Clinical Trials
  - Where we start from determines whether we can measure progression
  - Standardized baseline data from placebo arms can be pooled for future natural history studies

Strategies to Achieve Goals

- Placebo arm based natural history cohort
- Create guidelines for baseline data collection in clinical trials to allow compatibility in comparison of clinical trial findings
  - Facilitate cross-study comparisons
  - Increase comparability of baseline data

Working Group Mandate

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- Assess baseline data from recently completed and ongoing studies
  - How compatible? How heterogeneous?
- Recommend a common (minimum) data set for baseline data for clinical trials and natural history studies

Clinical Trials Inventory

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- Search: ClinicalTrials.gov
  - Phase 2, 3 and 4 placebo controlled clinical trials of drugs and biologicals
  - Advanced searches conducted for trials including the following terms
    - NAFLD
    - NASH
    - Metabolic syndrome
    - Obesity
    - Type 2 diabetes mellitus

Search Results

- Approximately 60 trials identified
- 24 trials met Working Group criteria
  - Liver Forum member companies
  - NIDDK
- Majority registered as Phase 2

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Summary Results – Target Population

Target Population	Number of studies
Isolated steatosis only	2
Isolated steatosis and NASH (without fibrosis)	1
Isolated steatosis and NASH (with and without fibrosis)	5
Isolated steatosis and NASH (with and without fibrosis and cirrhosis)	1
NASH (with and without fibrosis, but not cirrhosis)	7
NASH with fibrosis (only)	1
NASH (with and without fibrosis, including cirrhosis)	4
NASH with cirrhosis (only)	2
HBV related fibrosis	1

Inclusion/Exclusion Criteria: Summary

- Age: most enrolled patients 18-75 y/o
- Liver biopsy
  - 20 trials required patients meet histologic criteria
  - Of those 20, 10 different sets of criteria were used
- Imaging
  - 18 trials did not require imaging at screening
- No consistent use of BMI, T2D, lipid panels
- Liver enzymes

  ALT used as inclusion criterion by 14 studies with little consistency as to cut-off levels

  No consistent use of AST, bilirubin, platelets, etc.

Trends & Strategy

- Earlier/completed vs. current trials
- Stage of drug development
- Focus on recommendations for planned studies

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Most frequently used outcome measures

- Multiple outcome measures were used by each trial

Outcome Measure	# of trials
Steatosis by biopsy or imaging	15
ALT	14
AST	12
% Liver Fat Content	11
Histologic fibrosis stage	11
Resolution or reduction in steatosis/ steatohepatitis with no worsening of fibrosis	8
Insulin sensitivity	8
NAS Score	7

Validation Process

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- To validate information from ClinTrials.gov and expand information on baseline parameters
  - Telephone interviews are being conducted with all study sponsors using a standardized interview protocol
  - Summary sheets have been prepared for each trial, which study sponsors review, correct and complete

Development of Recommended baseline parameters (ongoing)

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- Essential versus ideal
- By phase of trial
  - Proof of Concept
  - Dose Ranging, early phase or 2A (with surrogate markers)
  - Dose Ranging, later phase or 2B (with surrogate markers)
  - Trials to support marketing application or Phase 3 (with surrogate markers)
  - Clinical Benefit (with surrogate or clinical endpoints measurable within reasonable time)
- Separate sets of parameters for anti-fibrotic and anti-inflammatory trials

Categories of Baseline parameters

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Demographics	Chemistries and other labs
Metabolic factors	Liver Histology
Comorbidities, including other liver disease	Imaging and Other Diagnostics
Liver enzymes	Concomitant Medications
Lipids	Health Related Quality of Life
Hematology	Alcohol Consumption Measures

Ongoing Work

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- Mini-groups advising on
  - Alcohol consumption
  - Biomarkers
  - QoL measures
  - Nutrition
  - Pediatrics

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