Standardization of Clinical Trial Design for Youth-Onset MASLD

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FDA Guidance

- FDA recognizes four distinct pediatric patient populations:
  - **Neonates –** birth through 27 days, corrected for gestational age
  - **Infants –** 28 days to 23 months
  - **Children –** 2 to 11 years
  - **Adolescents –** 12 to 17 years

- The Food and Drug Modernization Act of 1997 (FDAMA) established incentives for conducting trials in pediatric patients. Congress subsequently passed the Best Pharmaceuticals for Children Act (BCPA, 2002) and Pediatric Research Equity Act (PREA, 2003)

Looking Back 1 Year Ago

Why This Group is Needed:

- Approved medications in adults will soon need trials in pediatric patients with MASH
- Regulatory guidance (EMA and FDA) differ
- 5-11-fold increased risk of increased mortality in children and high burden of comorbidities (e.g., diabetes)
- Prior pediatric Liver Forum consensus documents needs updating

Process:

- Sept 2024: first meeting to discuss literature vis-à-vis prevalence, NITs, outcomes
- Subsequent meetings (N=5) focused on reaching consensus on optimal trial design
- Goal: produce a standardized framework for pediatric clinical trial

Reviewing the Literature

- High prevalence of MASH and associated adverse health outcomes in children
- Diagnosis and outcome assessment challenging
  - Literature on non-invasive tests (NITs) limited
  - NIT data (when available) often does not show same predictive values as in adults
  - Biopsy recognized as current gold standard diagnostic test but is variably performed in the US, if at all (at some centers), and rarely performed in Europe

Consensus Recommendations

1. Youth included in a clinical trial with an investigational drug should have MASLD with evidence of inflammation and fibrosis. Liver histology is an accepted method of MASH diagnosis in children. Non-invasive tests (NITs) that assess fibrosis may be used when sufficiently supported by evidence.

2. Standard biopsy scoring systems (i.e., NAFLD Activity Score) should not be used in children. Instead, biopsy for inclusion should measure inflammation (zone 1 and 3), steatosis,* and fibrosis – but not ballooning

3. Children with all stages of fibrosis should be included in MASH trials (i.e., the study population should not be limited to F2-F3)

4. Biopsy may be historical (i.e., within 2 years, evidence of ongoing disease such as continued elevation of ALT and PDFF) and would provide an opportunity for sub-group analysis

Consensus Recommendations

5. MRI-PDFF, ALT, and GTT were agreed upon endpoints for Pediatric MASH clinical trials

6. Additional outcomes (secondary or exploratory) should measure safety (e.g., height, creatinine, pubertal stage), liver improvement (e.g., CT1, elastography, NIS2+, ELF), metabolic response (e.g., BMI, lipids, blood pressure), and explore use of novel biomarkers (e.g., single nucleotide polymorphisms)

7. Recent Pediatric MASH guidelines on lifestyle modification (i.e., sugar reduction, increased physical exercise, and encouragement to see a dietician) should be implemented

8. The next Pediatric Liver Forum group should be convened to discuss trial design and funding challenges vis-à-vis pediatric NITs

Topics of Ongoing Discussion

- Should genetic markers (SNPs) be used for stratification? If so, which ones?
- Which PROs should be implemented in pediatric trials?
- Should concomitant medications with indications beyond MASH (e.g., GLP-1 use in obesity) be allowed in pediatric MASH trials?
- Importance of proper site selection