Agenda

12:00 PM ET  Begin

12:00 PM  Welcome and Meeting Goals
Veronica Miller, Forum for Collaborative Research
Jessica Weber, Forum for Collaborative Research
Saul Karpen, Emory University School of Medicine/Children’s Healthcare of Atlanta
Henkjan Verkade, University of Groningen
Pam Vig, Mirum Pharma

12:20 PM  Stakeholder Perspectives on Demonstrating Efficacy and Safety in Clinical Trials
• Patient Representative: Roberta Smith, Alagille Syndrome Alliance
• FDA: Ruby Mehta, U.S. Food and Drug Administration
• EMA: Chrissi Pallidis, European Medicines Agency
• Industry: Pam Vig, Mirum Pharma

1:00 PM  Next Steps
• Logistics
• Subgroups
• Outputs
Jessica Weber, Forum for Collaborative Research

1:10 PM  Discussion
All

1:30 PM ET  Adjourn
Goals of this WG

Overall: to improve the lives of children with rare liver diseases (by development of novel efficacious treatments)

Sub-goals

- Develop, for 4 diseases, agreed-upon outcome measures for trials
- Identify gaps in our understanding of needs and natural history for each disease
- Define the minimal and reachable needs for regulatory approval
  Inclusive “round table” approach to incorporate input from stakeholders \(\rightarrow\) academia, families, regulators, industry
- Global, short-term and long-term mindsets
Rationale for this WG

- Now is the time, with available registry data and new drugs in this space, to help outline outcome measures for clinical trials addressing Pediatric Cholestasis.
Groups

Pediatric Cholestatic Disease Working Group

Sub-WG’s
- Alagille Syndrome sub-working group
- Biliary Atresia sub-working group
- PFIC sub-working group
- PSC sub-working group

Co-Chairs:
- Saul Karpen
- Henkjan Verkade
- Pam Vig

Members
- Mixed stakeholders
Plans to initiate trials or inform trial design
A current review of the literature
DILI classification
Output from each WG

- Outcome measures: (multiple suggestions expected)
  - Primary
  - Secondary
  - Experimental

- Crucial clinical issues

- Crucial gaps that can be filled by Registries

- Natural history highlights
<table>
<thead>
<tr>
<th>Disease</th>
<th>Working Group Members</th>
<th>Definition</th>
<th>Is there a registry?</th>
<th>Define the natural history that inform outcomes</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alagille Syndrome</td>
<td></td>
<td>Must have pathogenic JAG-1 or Notch-2 variant that experts agree on</td>
<td>- GALA</td>
<td></td>
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</tbody>
</table>
| Biliary Atresia    |                       | Developmental cholangiopathy with obstruction of the biliary tract                                                                      | - NIDDK-supported CHILDren consortium  
- Canadian Biliary Atresia Registry  
- European Biliary Atresia Registry  
- Japanese Biliary Atresia Registry  
- Netherlands Study group for Biliary Atresia Registry |                                               |                                                                      |
| PFIC           |                       | PFIC1 and PFIC2 caused by impaired bile salt secretion due to defects in ATP8B1 encoding the FIC1 protein and in ABCB11 encoding bile salt export pump (BSEP) protein. | - NAPPED             |                                               |                                                                      |
| PSC            |                       | Diagnosis of chronic cholestasis of more than six months duration with either a MRCP/ ERCP showing sclerosing cholangitis, or a liver biopsy taken at any time consistent with PSC in the absence of a documented alternative etiology for sclerosing cholangitis. If diagnosis of PSC was made by histology alone, it must require the presence of fibro-oblitervative lesions. | - PSC Partners Patient Registry  
- IPCKSS  
- PROGRESS  
- North American PSC Registry  
- UK-PSC  
- Pediatric PSC  
- Dutch PSC  
- European Reference Network  
- Canadian PSC Registry |                                               |                                                                      |