THE FORUM
For Collaborative Research℠

The Rare Diseases Forum 1

Veronica Miller, PhD

Forum for Collaborative Research

UC Berkeley School of Public Health

October 17, 2018

Washington, DC

Berkeley Public Health

Welcome

Welcome to all

- 106 (in person + remote)
- Stakeholder groups represented
  - Academia: 21
  - Advocacy: 16
  - Government: 36
  - Industry: 29
  - Other: 4

Thanks & Acknowledgments

THE FORUM For Collaborative Research℠

Steering Committee

- **Co-Chairs**
  - Academic: Marshall L. Summar MD NCMC/NORD
  - Industry: John F. Crowley Amicus Therapeutics
  - Forum: Veronica Miller PHD UC Berkeley
- **Members**
  - Regulatory –US FDA
    - Dragos Roman MD CDER/DGIEP
    - Dina J. Zand MD CDER/DGIEP
    - Rachel Witten MD CBER/OTAT
  - Regulatory – EMA
    - TBN
- Members
  - **NIH**
    - Anne Pariser NCATS
  - **Advocacy/Policy**
    - Sandra Lehrman Advocate/Forum EC Co-Chair
    - Caroline Loewy KCNQ2 Cure, Global Genes Project
    - Peter L. Saltonstall NORD
    - Tara Britt NC Rare Diseases Advisory Council
    - Susan Nichols Advocate, Falcon Therapeutics
  - **Industry**
    - Jeffrey Sherman MD Horizon Pharma Inc
    - Timothy J. Miller PHD Abeona Therapeutics
  - **Academic**
    - Steven Gray PHD UT SW Medical Center
    - Scott J. Steele PHD University of Rochester MC

Initial Sponsors

Amicus Therapeutics®

PTC THERAPEUTICS™
20 YEARS OF COMMITMENT

Special thanks

- Marshall Summar & NORD for facilitating this meeting space

Forum Staff

- Luis Javier Hernandez
  - Rare Disease Forum Project Manager
- Terry Daniels
  - Office Administrator
- Katherine Greene
- Jessica Weber
- Ryan Anderson

The Forum for Collaborative Research

Catalyzing Clinical Research to Improve Global Health

THE FORUM For Collaborative Research℠

Guiding Principle

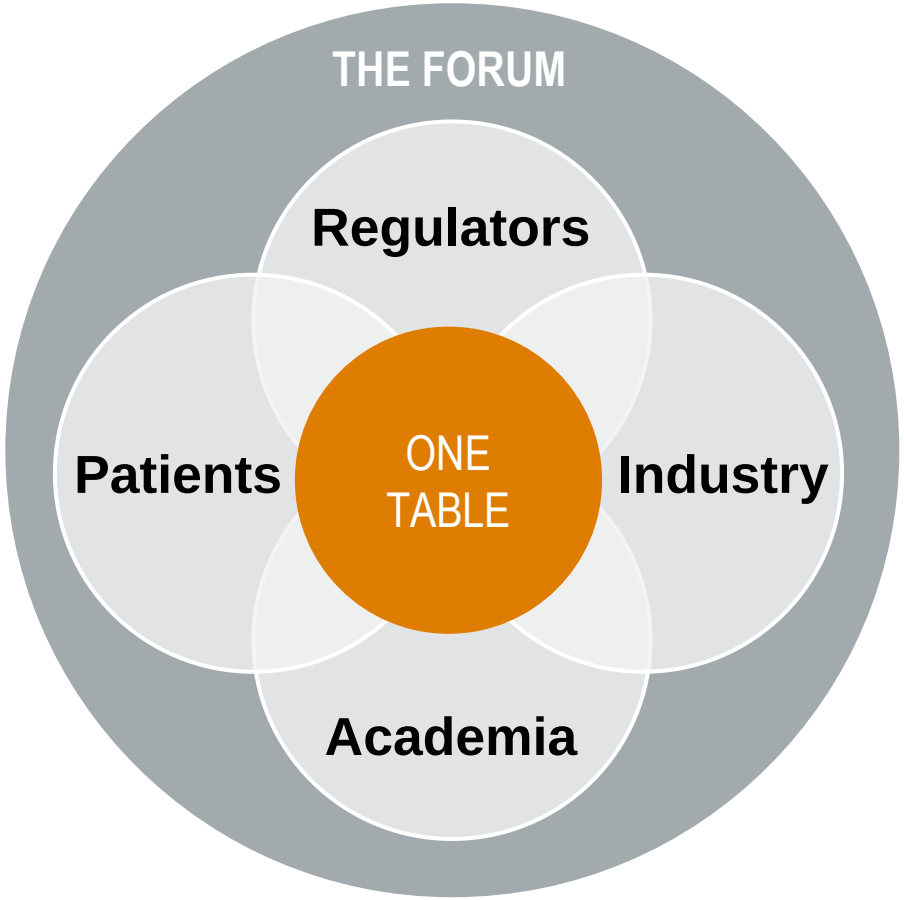
Once new drug candidates and therapeutic strategies are identified, their efficient and safe development is in the best interest of all stakeholders, most of all, the patients.

"The Forum accelerates drug development by increasing efficiency through collaboration, not by lowering standards."

Veronica Miller PhD, Executive Director, The Forum for Collaborative Research

THE FORUM
For Collaborative Research℠

The Concept



Increase Efficiency

- Enhanced clarity
- Innovation
- Collaboration

Decrease Uncertainty

- Redundancy
- Development time
- Risk

"Starting with HIV, the Forum consistently and effectively applies the multi-stakeholder model to advance the development path for new treatments in multiple disease areas. " Eric A. Hughes, MD, PhD, Development Unit Head, Novartis Pharma AG

THE FORUM For Collaborative Research℠

Characteristics

- Non-competitive
- Safe environment
- Independence
- Neutrality
- Transparency
- Information democracy
- Synergy vs duplication
- Equal voice

The traditional process:

Single sponsor communicating independently with single regulatory agency

- VS -

The Forum process:

All sponsors communicating at the same time with multiple regulatory agencies

"The Forum bring together stake holders from around the globe with cross-Atlantic and -Pacific perspectives to reduce interagency discordance."

Laurent Fischer MD, Senior VP, Allergan

THE FORUM
For Collaborative Research℠

Results

- Advance development of regulatory strategies
  - Evolving science and evolving consensus
- Generate evidence through collaboration
  - Efficient use of data
- Provide mechanism for patient-centered drug development
- Provide mechanism for innovation in data use and analytics

"The Forum addresses cutting edge regulatory science and policy issues with proven results."

George Hanna MD, VP Infectious Diseases Global Clinical Development, Merck & Co., Inc.

Disease Areas

- In order of appearance
  - The HIV Forum 1997- present
  - The HCV Forum 2006-2016 (completed)
  - The Liver Forum 2014 - present
  - The CMV/transplantation Forum 2014- present
  - The HBV Forum 2016 - present
  - The PSC Forum 2017 - present
  - **The Rare Diseases Forum 2018 →**

Some Highlights

- HIV
  - Clinical trial design with two novel agents
- HCV
  - Historic controls vs. current standard-of-care for all-oral DAAs

THE FORUM
For Collaborative Research℠

An Example: The Liver Forum

Work Streams, Working Groups & Activities

- Definitions
- Standardization
- Pediatrics
- Biomarker
- Approval to Reimbursement
- Novel Analytics
- Alcohol related liver disease

- Baselines Case Definitions
- NASH Improvement Definitions
- Compensated Cirrhosis
- Decompensated Cirrhosis
- Standardization of Baseline Parameters
- Standardization of Life Style Mgt & Data
- Standardization of Co-Morbidities Mgt & Data
- Placebo Arm Cohort
- Biomarker Workshops
- Novel Analytics Workshops
- Collaboration with CMTP

Liver Forum Meetings

- Liver Forum 1 Nov 2014 Boston, MA
- Liver Forum 2 Apr 2015 Vienna, Austria
- Liver Forum 3 Nov 2015 San Francisco, CA
- Liver Forum 4 Apr 2015 Barcelona, Spain
- Liver Forum 5 Nov 2015 Boston, MA
- Liver Forum 6 Apr 2017 Amsterdam, The Netherlands
- Liver Forum 7 Nov 2017 Washington, DC
- Liver Forum 8 Apr 2018 Paris, France

THE FORUM For Collaborative Research℠

The Liver Forum (2014-present)

Productivity in standardizing case definitions

- Increase precision of case definitions at baseline
- Increase precision of definition of NASH improvement
- Increase precision of definitions for compensated and decompensated cirrhosis

Efficiency in biomarker development

- Maximize efforts of consortia in FDA biomarker qualification process

Agility to maximize data use

- Standardize parameters to facilitate cross-trial comparison

"The Liver Forum quickly surpassed our expectations of what could be achieved."

David Shapiro, MD, CMO, Intercept

Agency US

US Food and Drug Administration

Agency EU

European Medicines Agency

Pharmaceutical Industry

Afimmune
Allergan
AMRA
AstraZeneca
BMS
Boehringer Ingelheim
Celgene
Cirius Therapeutics
Conatus Pharmaceuticals
ConSynance Therapeutics
CymaBay
Deuterx
DiaPharma
Eli Lilly
Enanta Pharmaceuticals
ENYO Pharma
Ferring Pharmaceuticals
Fractyl
Genentech
Genfit
Gilead
GSK
Immuron
Intercept Pharmaceuticals
Inventiva Pharma
Janssen Pharmaceuticals
Madrigal Pharmaceuticals
Mallinckrodt Pharmaceuticals
Morphic Therapeuitc
NGM Biopharmaceuticals
NorthSea Therapeutics
Novartis
Novo Nordisk
Nusirt
Pfizer
ProSciento
Shire
Takeda
VLVBio
Zafgen

Diagnostic and Other Industry

Echosens
HepQuant
HistoIndex
Humedics
ICON
Nordic BioScience
Perspectum Diagnostics
Quest Diagnostics
Resonance Health
Resoundant
TARGET PharmaSolutions

Patient and Community Representatives

Global Liver Institute
ELPA
At Large

Consortia

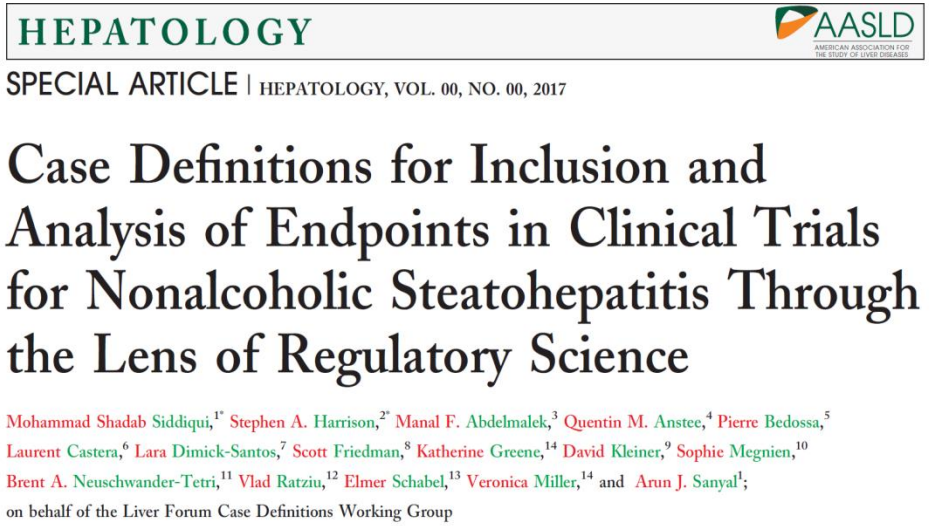
LITMUS
NIMBLE

Professional Societies

AASLD
EASL

Liver Forum Issues: Better Definitions increase Precision and Power

- Need to standardize disease stage definitions to facilitate trial data interpretation and transition from pathology defined (liver biopsy) to non-invasive biomarker defined
  - Fuzzy, imprecise definitions for disease stages
    - Baseline Case Definitions (Siddiqui et al)
    - Define NASH improvement (submitted)
    - Define cirrhosis as disease stage and endpoint
      - Compensated
      - Decompensated



HEPATOLOGY AASLD

SPECIAL ARTICLE | HEPATOLOGY, VOL. 00, NO. 00, 2017

Case Definitions for Inclusion and Analysis of Endpoints in Clinical Trials for Nonalcoholic Steatohepatitis Through the Lens of Regulatory Science

Mohammad Shadab Siddiqui,[1*] Stephen A. Harrison,[2*] Manal F. Abdelmalek,[3] Quentin M. Anstee,[4] Pierre Bedossa,[5] Laurent Castera,[6] Lara Dimick-Santos,[7] Scott Friedman,[8] Katherine Greene,[14] David Kleiner,[9] Sophie Megnien,[10] Brent A. Neuschwander-Tetri,[11] Vlad Ratziu,[12] Elmer Schabel,[13] Veronica Miller,[14] and Arun J. Sanyal[1]; on behalf of the Liver Forum Case Definitions Working Group

THE FORUM For Collaborative Research℠

Liver Forum Issues: Standardization Increases Efficiency of Data Use

- Need to increase cross-trial standardization to facilitate interpretation of results
  - Standardize data collection (CDE)
    - Baseline (Patel et al)
    - Lifestyle
    - Co-morbidities
  - Placebo-arm Cohort
    - Natural history cohort
    - Mechanism to reduce placebo burden

Baseline Parameters in Clinical Trials for Nonalcoholic Steatohepatitis: Recommendations From the Liver Forum

Gastroenterology 2017;153:621–625

YUVAL A. PATEL
Duke University School of Medicine
Durham, North Carolina

JOANNE C. IMPERIAL
Conatus Pharmaceuticals
San Diego, California

ANDREW J. MUIR
Duke University School of Medicine
Durham, North Carolina

QUENTIN M. ANSTEE
Newcastle University
Newcastle Upon Tyne, UK

DAVID DEBROTA
Eli Lilly & Company
Indianapolis, Indiana

LARA DIMICK-SANTOS
US Food and Drug Administration
Silver Springs, Maryland

CLAUDIA FILOZOF
Covance Clinical Development Services
Maidenhead, UK

RUBY MEHTA
US Food and Drug Administration
Silver Springs, Maryland

ARUN J. SANYAL
Virginia Commonwealth University
Richmond, Virginia

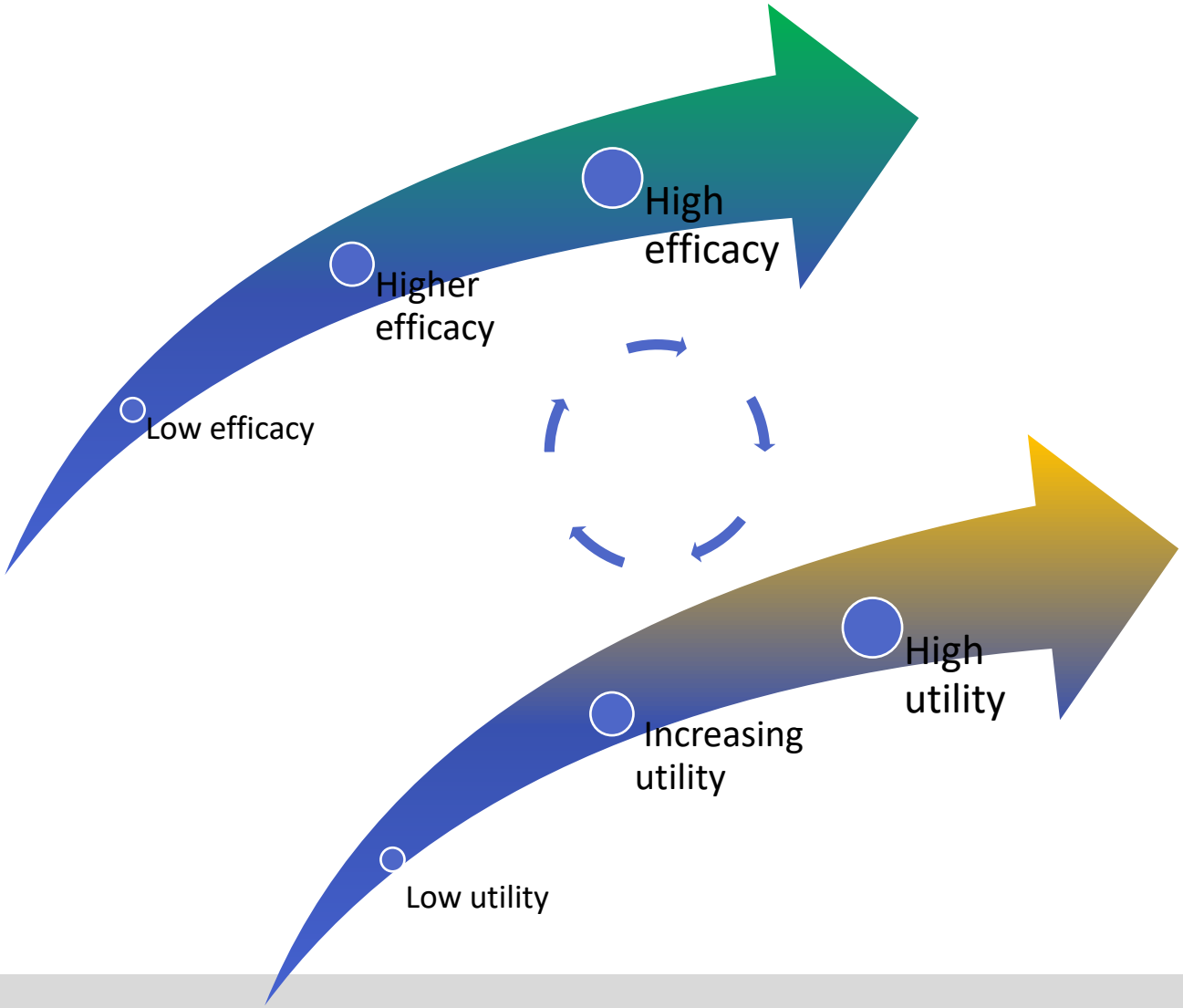
ELMER SCHABEL
Bundesinstitut für Arzneimittel und Medizinprodukte
Bonn, Germany

BRENT A. NEUSCHWANDER-TETRI
Saint Louis University School of Medicine
St. Louis, Missouri

VERONICA MILLER
On behalf of the
Liver Forum's Data Standardization Working Group
University of California Berkeley
Washington, DC

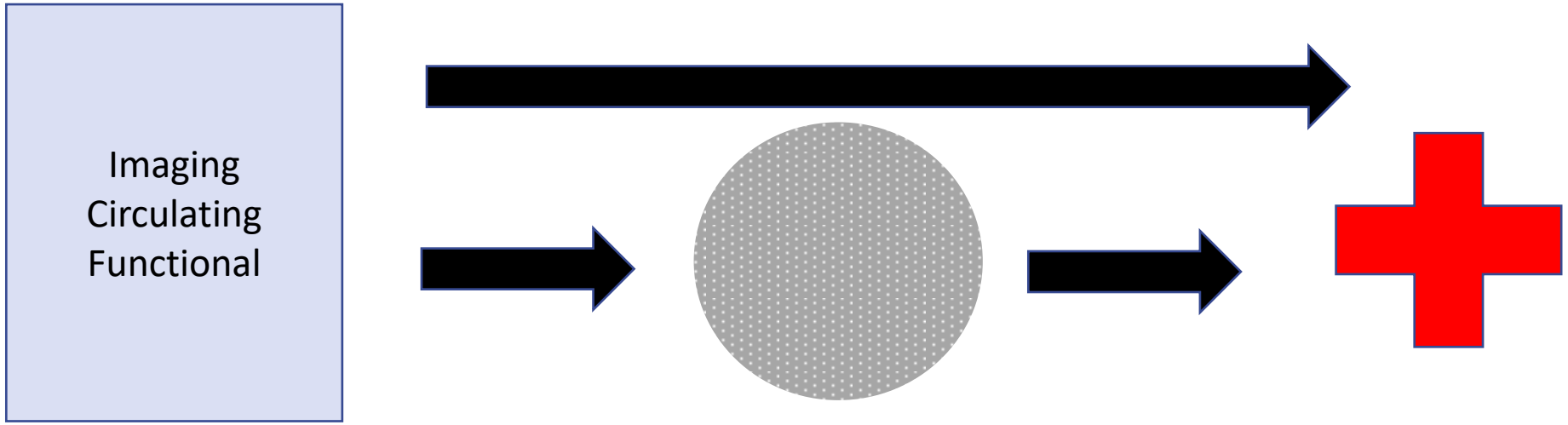
THE FORUM For Collaborative Research℠

Liver Forum Issues: Biomarker Development Requires Collaboration



- Liver Forum + Consortia
  - NIMBLE (FNIH)
  - LITMUS (IMI)
  - FDA (OND)

LF Biomarker: Challenges & Opportunities



Non-Invasive Biomarkers

Accepted Surrogate
Histology

Hard/Clinical Endpoint

The Rare Diseases Forum
Goals & Objectives

Facilitate Development of New Therapies for Rare Diseases

- Advancing regulatory science for rare diseases
- Maximize efficiency through collaboration and innovation
  - Innovation in clinical trial design and endpoints
  - Innovation in data analytics and data use
  - Innovation in gene-therapy approaches
  - Innovation/improvement of diagnostic platforms

Launch The Rare Diseases Forum

- First RD Forum meeting
  - Introduce Forum concept
  - Identify key gaps and needs
  - Start charting a path forward
- After today
  - Establish multi-stakeholder work streams and working groups
    - Do the hard work: evolve consensus, increase clarity, decrease uncertainty, etc.
  - Assemble all Rare Disease Forum members for updates & networking approximately twice a year

Note:
We will not resolve all issues today
We will work on them one by one over the next months and years

Output:
Peer-review publication outlining today's deliberations

Rules of the Game

- Open, constructive, dialogue and deliberation
- Bring your expertise
  - Leave your hat at the door
- What's said in the room, stays in the room
  - Reports and publications not for attribution

Welcoming Remarks

Marshall L Summar

John F Crowley