Liver Forum 7:
Summary of Proceedings

Thursday, October 19, 2017
Washington D.C.

Facilitating Collaborative Research in Drug Development and Health Policy
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For more information or questions about the Liver Forum, please contact Katherine Greene at kgreene@forumresearch.org, or visit our website at http://www.forumresearch.org/projects/liver-forum

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LIVER FORUM 7 AGENDA

12:30 PM	**Welcome Reception and Registration**	
2:15 PM	**Session I: Project Overview**	
2:15 PM	Welcome and Introduction	Katherine Greene, *Forum for Collaborative Research*
		Moderator: Veronica Miller, *Forum for Collaborative Research*
2:25 PM	Regulatory Perspective Updates and Remarks	Lara Dimick-Santos, *U.S. Food and Drug Administration* Elmer Schabel, *European Medicines Agency* Irene Tebbs, *U.S. Food and Drug Administration* Daniel Krainak, *U.S. Food and Drug Administration*
3:10 PM	**Session II: Defining Endpoints for Advanced Disease**	
		Moderator: David Shapiro, *Intercept Pharmaceuticals*
3:10 PM	Compensated Cirrhosis & Clinically Meaningful Benefit	Naga Chalasani, *Indiana University School of Medicine*
3:25 PM	Cirrhosis Endpoints: ACLF & MELD	Rajiv Jalan, *University College London*
3:40 PM	Decompensated Cirrhosis: Endpoints and Experience in U.S. Phase 2B/3 Trials	Arun Sanyal, *Virginia Commonwealth University*
3:55 PM	Group Discussion	
4:35 PM	**Break**	
5:00 PM	**Session III: U.S. Payer and Care Delivery Perspectives**	
		Moderator: Veronica Miller, *Forum for Collaborative Research*
5:00 PM	Lessons Learned in HIV & HCV	Carl Schmid, *The AIDS Institute*
5:15 PM	Medicare Coverage: A Review	Louis Jacques, *ADVI*
5:40 PM	Panel Discussion	Louis Jacques, *ADVI* Heather Patton, *Kaiser Permanente* Hal Yee, *LA County Department of Health Services*
6:20 PM	**Session IV: Working Groups**	
		Moderator: Katherine Greene, *Forum for Collaborative Research*
6:20 PM	Case Definitions	Sophie Megnien, *Genfit* Brent Tetri, *Saint Louis University*
6:30 PM	Pediatric Issues	Miriam Vos, *Emory University*
6:40 PM	Placebo Arm Data	Eric Lefebvre, *Allergan*
6:50 PM	Standard of Care	Manal Abdelmalek, *Duke University* Sven Francque, *Antwerp University Hospital*
7:00 PM	**Session V: Wrap-Up**	
7:00 PM	Meeting Close	Veronica Miller, *Forum for Collaborative Research* Arun Sanyal, *Virginia Commonwealth University* David Shapiro, *Intercept Pharmaceuticals*

SESSION #1: INTRODUCTION

Moderator: Veronica Miller, Forum for Collaborative Research

Introduction and Liver Forum Updates

Slides: http://www.forumresearch.org/storage/documents/LiverForum/LiverForum7/01_greene.pdf
Presenter: Katherine Greene, Forum for Collaborative Research

Review of Liver Forum 6 in Amsterdam

- Attendance and Demographics:
  - 124 in-person and 47 remote attendees
  - 73% industry, 14% academia
  - 64% United States, 26% Europe, 9% Asia
- Evaluation results:
  - 93% Strongly Agree or Agree that they would recommend joining the Liver Forum to a colleague; 95% Strongly Agree or Agree that the Liver Forum is valuable to their work
  - 87% Strongly Agree or Agree that the presentations from Liver Forum 6 will be helpful for their organization, and also that new collaborations or interactions had been facilitated.
  - Primary motivations to attend were to hear the latest developments in the field, and the regulatory updates, as well as the networking opportunities.

Membership and Participation Reminders

- Attendance Rules:
  - Meetings are not public and are for members of the Liver Forum only. As such, registration information, including the remote connection, is not to be distributed.
  - The Liver Forum provides an independent and neutral venue for ongoing multi-stakeholder dialogue, and the integrity and transparency of the dialogue is threatened when it is not clear who is on the phone.
  - A detailed meeting summary as well as all meeting materials are posted online, which are available to the public
  - Industry organizations are allowed up to two representatives from the company to attend in-person.
  - The meeting has grown dramatically in size, and in order to maintain the focus of the meeting and continue doing what has made us successful, the attendance limit is firm.
  - Any special circumstances (steering committee/working group chairs) are pre-arranged and signed-off on in advance.
  - Representative “slots” are not transferable between companies.
  - Representatives from industry organizations must be from research and development, and we do not allow marketing or commercial staff to attend in-person.
  - Investors, venture capital firms, and consultants are expressly prohibited from the meetings, including remote participation.
- Liver Forum Membership:
  - Membership is restricted to experts with necessary scientific knowledge that are from organizations or entities with a clear commitment to and active engagement in advancing the diagnostic and therapeutic field of NASH and liver fibrosis.
  - Members are recruited from all relevant stakeholder groups, and must have an introductory meeting or conversation prior to joining. Introductory meetings ensure members understand how to participate and that there is alignment between the organization or individual and the Liver Forum. This applies to all types of members, not just industry.

  - Refer colleagues to Katherine Greene (kgreene@forumresearch.org) for more information about joining.
  - Members are expected to be active participants in the meetings and working groups, and passive observation is strongly discouraged.
- A formal membership agreement will be developed between LF7 and LF8 and distributed to Liver Forum members.

Liver Forum Recent Activity

- The Placebo Arm Data Working Group had an in-person meeting just prior to the Liver Forum (**see Session #4: Working Group Updates**), and Forum staff have been working on developing data sharing agreements and an action plan for the group.
- The Standard of Care Working Group was developed as a spin-out from the Placebo group, and will look specifically at issues surrounding standard of care for clinical trials and NASH.
- The 2017 NASH Biomarkers Workshop was co-organized by the Liver Forum and Expert Medical Events. This second iteration of the workshop was very successful and had 155 attendees. The next workshop will be May 18-19 2018. Registration for the workshop is now open: http://expertmedicalevents.com/event/upcoming/nash-biomarkers-workshop-2018
- The Forum for Collaborative Research organized two statistics workshops over the spring. These workshops were not disease-specific, but rather focused on statistical methodologies that could be applied to enhance efficiency of clinical trials.
  - Adaptive Enrichment: http://www.forumresearch.org/projects/liver-forum/related-meetings/1468-adaptive-enrichment
  - Causal Inference: http://www.forumresearch.org/projects/liver-forum/related-meetings/1467-causal-inference.
- Outreach to regulatory agencies has included engaging with additional divisions within the FDA, including CDRH, as well as additional regulatory agencies including Health Canada, CFDA, and Cofepris.
- The PSC Forum was recently established as a separate entity, and had its first in-person meeting (http://www.forumresearch.org/projects/psc-forum/psc-forum-meetings). Contact Jessica Weber (jweber@forumresearch.org) for additional details about the PSC Forum.

Manuscript Updates

- The first paper from the Data Standardization Working Group, “Baseline parameters in clinical trials for nonalcoholic steatohepatitis: Recommendations from the Liver Forum” was published September 2017 in Gastroenterology (https://doi.org/10.1053/j.gastro.2017.07.024)
- The first paper from the Case Definitions Working Group, “Case definitions for inclusion and analysis of endpoints in clinical trials for NASH” will be published in Hepatology (https://doi.org/10.1002/hep.29607)
- The second paper from the Case Definitions Working Group “Defining improvement in NAFLD for treatment trial endpoints: Recommendations from the Liver Forum” is currently under development (**see Session #4: Working Group Updates**).
- The first paper from the Pediatric Issues Working Group, “Regulatory considerations for clinical trials in pediatric nonalcoholic fatty liver disease” is completed and under internal review.

FDA Introductory Remarks

Slides: http://www.forumresearch.org/storage/documents/LiverForum/LiverForum7/02_dimick.pdf
Presenter: Lara Dimick-Santos, CDER, U.S. Food and Drug Administration

FDA Update

- The team working on liver indications at the FDA has grown to include many new staff, including additional medical reviewers, team leaders, project managers, statisticians, and senior staff.
- The division continues to receive an influx of new applications, including NASH trials in all phases of clinical development, all phases of trials in patients with compensated cirrhosis, and phase 2 trials in patients with decompensated cirrhosis.

Cirrhosis

- Compensated cirrhosis
  - What is the best way to design clinical trials for advanced stage cirrhosis?
  - What is the correct way to stage cirrhosis?
  - Is Child-Pugh relevant for this population?
  - Should the presence or absence of ascites at trial entry be looked at?
  - Assess risk using HepQuant SHUNT test?
- Decompensated cirrhosis
  - Are patients with ongoing ascites the same as patients who had a variceal bleed or an episode of hepatic encephalopathy and are now stabilized? Is this the same stage of patient?
  - How can decompensation events be defined to use as endpoints?

Histology

- Inter-observer variability has been being looked at closely and have been using central readers
- Intra-observer variability hasn't been looked at as closely
- The same few histopathologists won't be able to read every trial
- Need to be looking at ways for quality control in histology in the future

Ethical Considerations

- Needs to be thoughtfulness in the way patients are being utilized and the risk they incur through involvement in clinical trials
- Currently recommend sponsors obtain histopathological data in phase 2B trials to inform the design and powering of phase 3 trials
- Is it ethical to go into a phase 3 trial without histologic data?

The Liver Forum: Regulatory update from Europe

Slides: http://www.forumresearch.org/storage/documents/LiverForum/LiverForum7/03_schabel.pdf
Presenter: Elmer Schabel, European Medicines Agency

EMA Reflection Paper

- EMA announced the development of a guidance document in an effort to help clarify the official position of the EMA, since the information presented at the Liver Forum is not necessarily an official position of the agency.
- The Concept Paper on the Need for the Development of a Reflection Paper on Regulatory Requirements for the Development of Medicinal Products for Chronic Non-Infectious Liver Diseases (PBC, PSC, NASH), released May 2017
  - Reflection papers are somewhat below full guidelines, and intended to be replaced later by a full guideline once CHMP has dealt with marketing authorization applications and have had experiences with evaluating trials.
- The main components of the concept paper deal with the characterization of the three disease entities (NASH, PSC, PBC), and the intended focus on adequate endpoints, validation of surrogates, suitable study populations, adequate trial designs, similarities and differences of diseases and impact on regulatory requirements, and unique needs of pediatrics.

- The Concept Paper received 16 stakeholder comments: six companies, five patient organizations, three academic groups or societies, and two multi-stakeholder organizations (PSC Forum and Liver Forum).
    - 14 comments general acknowledgement or welcome of the guidance, and others requested that the scope be either restricted of expanded (for example, rPSC, ALD, AIH), which could be considered but is unlikely.
    - Comments also received to include patient organizations, payer organizations, HTAs, and academic consortia.
    - Suggestions to amend the wording were received; however, the Concept paper will stay as it is and will be superseded by the Reflection paper.
- The public comment phase for the Concept paper was June-August 2017, and the customary stakeholder meeting was initially anticipated to occur in the 4th quarter of 2017 with the first version of the Reflection paper to be published in the 2nd quarter of 2018, and a public consultation phase before the final document is drawn up.
    - However, with the UK leaving the EU, there are many impacts on the work of the EMA and the stakeholder meeting has been postponed.
    - The first draft of the Reflection paper will be developed without direct input, but this process has been delayed to allow more time to collect information.
    - A stakeholder meeting being tentatively considered for early 2019 to discuss what has been drafted.
    - All of this is contingent on EMA relocation and associated considerations.

Perspectives on Validation of IVD Biomarkers

Slides: http://www.forumresearch.org/storage/documents/LiverForum/LiverForum7/04_tebbs.pdf
Presenter: Irene Tebbs, CDRH, U.S. Food and Drug Administration

Center for Devices

- CDRH may consider “biomarkers” slightly differently than CDER, and submissions include biomarkers being used in clinical practice for the diagnosis or management of a patient – and not necessarily in the context of a clinical trial.
- The foundation for the scientific review of an application is the intended use of the device. This is used to develop parameters for the review, including the expected validation testing, and includes a clinical indication.
- Recent example of novel kidney biomarker (The Astute Medical NEPHROCHECK® Test System) provides a clear description of how the biomarker would be used in clinical practice, and information on the population.
    - Example questions when reviewing evaluation include:
        - What kind of interference might be in that population?
        - What are going to be the relevant values in the people we’re interested in?
- Performance information for an IVD would include (most or all): accuracy, precision (or reproducibility), interference and cross reactivity (from similar protein or other analytes), limits of detection, measuring range of device/ linearity (if quantitative test), specimen stability.
- IVDs are subject to different labeling requirements than some other types of devices, which ties into how the devices are reviewed, because certain types of information are expected to be included in the label.
    - Information on the label includes: summary and explanation of the test, typical expected values, and performance characteristics (often including accuracy, precision, specificity, and sensitivity)

Perspectives on Imaging Biomarkers: Technical Performance and Analytical Validation

Slides: http://www.forumresearch.org/storage/documents/LiverForum/LiverForum7/05_krainak.pdf
Presenter: Dan Krainak, CDRH, U.S. Food and Drug Administration

Validation Expectations (from BEST glossary: https://www.ncbi.nlm.nih.gov/books/NBK326791/)

- Need to establish the performance characteristics are acceptable in terms of the relevant performance characteristics
  - Establish: demonstrated through data
  - Acceptable: need to know what the requirement or specification is
  - Relevant: the characteristics that you care about
- There are a lot of regulations around IVD labeling, but there is not similar regulation around radiological device labeling. Intended use is reviewed a lot and informs validation.
- Example of tool measuring volume: one version measures rectangular volume (w*h*d), another version measures ellipse volume ($\frac{\pi}{6}$w*h*d). Both measure volume, but measures will always be different. In this example, the requirement is based on the intended use, which is to measure volume, which both versions do.
- Example of tool measure tumor volume change: very specific intended use. Would be interested in the reproducibility of the device, mean bias, accuracy, and precision.
- Compared to IVD, most radiological devices have very general indications for use.
  - For example, an MR system is indicated for looking at images of inside the body based on MR characteristics. Clinical claim is not for a specific disease, but rather that it might be useful in clinical diagnosis.

Discussion

- Early data suggests imaging and some noninvasive biomarkers can provide information in patients with bridging fibrosis or patients with liver cirrhosis. Could the Agency accept proof of concept with noninvasive biomarkers to reduce the number of active arms in a phase 2B? Or do dose responses need to be histology based?
  - Using biomarkers instead of histology is allowed for proof of concept for dose ranging or for narrowing doses. It does not make sense to use histology for very early trials. But there should be an in-between step when moving from biomarker-only trials to phase 3 trials.
  - In principle it is very likely that biomarkers are needed to decide upon doses. For instance, even if histology is available, the endpoint in a trial that is reduced in duration and subjects could not provide the necessary information.
- The FDA has recommended that trials have histological data in phase 2B, is there a similar recommendation or requirement from EMA to have histological data to gauge for phase 3?
  - The EMA has also recommended to companies to include histological data in phase 2. With histology data, companies are able to estimate when and with how many patients the desired effect will be reached. This is very difficult to estimate if only biomarker data is available.
- Clinical endpoints used for trials need validated biomarkers that have to go through a validation process. Is that also true for imaging since there is a more general intended use statement?
  - Even though a device might be 510(k) cleared, it might not be cleared for the intended purpose in a trial, so it is important to validate it for the purpose. That applies to both clinical trials and clinical practice.
  - Most devices and in vitro diagnostics are 510(k) cleared, which doesn't mean validated, but rather evaluated based on performance characteristics.

        - To validate something that has been cleared, the device goes to DGIEP and all the departments get together to determine if there is enough data to support if the biomarker is reasonably likely to predict (still not validated).
        - Validation occurs after a clinical trial or trials with the biomarker, where patients are followed through phase 4 to a clinical outcome. Typically done with multiple drugs for the same indication.
- The biomarkers in imaging are often complementary- how much interaction is there at CDRH between IVD and imaging for the same disease area?
    - Departments are within the same office, though product areas are very different. When evaluating something novel for introduction to the general clinical market, the groups would be interested in understanding how the product interacts with standard of care, both in terms of imaging and other serum biomarkers, and would likely seek out the clinical experts.
    - If there were very specific questions, for example if there was a combination of an IVD with an imaging endpoint, the two groups would collaborate.
- There are shared concerns about the large, long-term phase 3 trials and the ability to recruit and maintain the patients. The most that can be expected from those trials is a reduction of progression to cirrhosis as one of the observable endpoints. If a trial is designed with a large enough number of patients, and can prove within two years that the active arm has less progression to cirrhosis than placebo arm, what is the conceptual obstacle to not provide registration for that drug?
    - The FDA and EMA would likely agree to such an endpoint if the trial is large enough, even in a reduced timeframe, this would most likely be sufficient for approval.
    - Questions could remain on what is necessary post-approval and what kind of data is missing, but likely some data will be available for decompensation events and liver transplantation, in an almost similar amount as the current studies, if enough patients are able to be recruited.
- There are many biomarkers being studied in advanced phase trials and it's not clear how or why biomarkers are being selected. It would be valuable to select biomarkers that are going to serve a specific function after the drug goes through approval; however, clinical trials are not being designed with this as a primary objective. How does that data fit into how the Agency will eventually write a label about how the biomarker can be used? Once a drug is approved, how can the average doctor use that information?
    - In terms of the regulatory acceptance of diagnostics and biomarker qualification, that data is useful. However, independent validation is highly desirable and there is a distinction between an exploratory study and a validation study where the intent was to look and see whether the same finding would hold up using an independent set of data.
    - A biomarker can be co-developed with a drug at the same time and used in phase 2 studies during which data is gathered to further understand how to use it in the phase 3, and then joint approval can be given. That biomarker may be needed to determine which patients need the drug or the test, and the biomarker then gets included with the drug on the label
    - The usefulness of biomarkers gathered as secondary endpoints is not reviewed, other than looking at the totality of the data for approval. Separately, the data from the trial could be presented to CDRH to review if the dataset is sufficient to show that the biomarker works for a particular context of use.
- The NASH CRN and FLIP hepatology consortium have looked at observer variability and have shown in general that it was very good, good, or acceptable for clinical trials. The suggestion to have several readings, with adjudication of discrepancies, seems complicated when there are several hundred biopsies and 20 items to evaluate. How could this be managed? What is the

position on the use of digitalized slides and whether using digital slides would help to resolve this issue?
    - The pathology experts at the FDA generally just want to know what the software is. And if that software is acceptable to them, it's okay. There's not a problem with the concept, but they might have questions about some of the details.
    - From a radiology perspective, if the digital pathology devices are already cleared or approved for clinical use, the same people who were involved in that approval would be involved in looking at the quality for specific tests.
- Are there regulations around mobile health-based apps for remote management of healthcare, for example prescribing apps for management of patients with liver disease?
    - The 21st Century Cures Act has altered the regulations around software specifically and mobile apps and regulation likely would depend on the function of the app. There is a lot of discussion at CDRH about digital health and mobile apps and all those types of activities.

SESSION #2: DEFINING ENDPOINTS FOR ADVANCED DISEASE

Moderators: David Shapiro, Intercept Pharmaceuticals

Compensated Cirrhosis & Clinically Meaningful Benefit

Slides: http://www.forumresearch.org/storage/documents/LiverForum/LiverForum7/06_chalasani.pdf
Presenter: Naga Chalasani, Indiana University School of Medicine

Review of Liver Cirrhosis

- Can compensated cirrhosis regardless of the underlying etiology be a standalone indication for marketing approval? If yes, what should the endpoints be?
- Are the hard endpoints such as death, time to liver transplant, or decompensated events simply not practical? And if they are indeed not practical, what surrogates are worthy of consideration as some of the top candidates?
- Categories:
    - Parenchymal cirrhosis is the largest category and includes alcoholic liver disease, non-alcoholic fatty liver disease, NASH, viral hepatitis, and some rarer etiologies such as Wilson's disease, autoimmune liver disease, and alpha-1 antitrypsin
    - Biliary cirrhosis includes primary biliary cholangitis, PSC, and secondary biliary cirrhosis
    - Vascular cirrhosis includes Budd-Chiari syndrome, and cardiac cirrhosis
- Common Causes
    - When designing trials, the researcher needs to consider the etiology of the disease, as the natural history is different, and the complicating events may also be different.
    - For example, in PSC patients with cirrhosis, in addition to the usual complications, there may be episodes of cholangitis.
    - Compensated cirrhosis can be broken down into two groups: those without clinically significant portal hypertension (gradient < 10 mm Hg), and those with clinically significant portal hypertension (gradient ≥ 10 mm Hg).
        - Treatment goals are to prevent development clinically significant portal hypertension, decompensation, and HCC, and to improve the quality of life.
        - The underlying etiology of the cirrhosis can still be addressed in compensated cirrhosis. Bariatric surgery can be effective and was included in the recent practice guidance.
        - Lifestyle modification can be effective.

  - Decompensated cirrhosis is where patients with cirrhosis have experienced a complication from cirrhosis such as ascites or variceal bleeding or hepatic encephalopathy.
    - Treatment goals are to prevent further complications, lower risk of HCC, and improve quality of life and survival.
    - Lifestyle modification can be effective up to a certain point.
- Any-cause cirrhosis
  - It is premature to use any-cause cirrhosis as a single indication, without attention to the underlying etiology.
  - Natural history is different for cirrhosis caused by different etiologies, for example, NASH cirrhosis progresses at a different rate than hepatitis C cirrhosis. Patients with alcoholic cirrhosis who are no longer drinking, have a very different natural history than an alcoholic patient who is drinking.
  - The treatment of underlying liver disease may change the natural history differently, for example, hepatitis B therapy in somebody with cirrhosis can be quite effective. The varying effects of treatment for underlying disease will be a problem if taking all cirrhosis as a single entity.
  - The effect of alcohol in different diseases is different, how to deal with alcohol consumption?
  - The development of hepatocellular carcinoma is rare but the risk of HCC for different causes of cirrhosis is different. Therefore, lumping them all of them together will create complications.
  - Trials of cirrhosis would likely enroll NASH patients, viral hepatitis, and maybe alcoholic liver disease. Would data coming from such trials be applicable to rare etiologies? For example, PSC?

Surrogate Endpoints

- Hepatic Venous Pressure Gradient
  - The gradient between wedged hepatic pressure and free hepatic pressure is what matters and defines the degree of portal hypertension. Under 5 is normal, 6-10 there is portal hypertension, but not thought to be clinically significant, and 10 or higher, it is clinically significant.
    - HPVG of 12 or higher, patients are at a higher risk for developing varices.
    - HPVG of 16 or higher, patients are at a higher risk for mortality.
    - HPVG of 20 or higher is linked to treatment failure and increased mortality when patients present with variceal bleeding.
  - Attributes as a surrogate
    - Biological Plausibility: Yes
    - Quantifiable: Yes
    - Reproducible: Unknown- studies have not yet been done where patients have serial HVPG to see what the variability is.
    - Repeatability: Yes- however is painful
    - Performance Characteristics: Well-known
    - Easily Deployed: Challenging- It can be, but it is challenging and it requires a fair bit of training
    - Supporting Evidence: Extensive
    - Risks/Costs: Not insignificant- Patients don't like it and it is expensive.
    - Risks due to Misclassification: Not insignificant- a 2-mm difference can result in misclassification.
  - Overall Comment: Invasive, uncomfortable, requires high level of expertise, and expensive.

- Model for End-Stage Liver Disease (MELD)
  - Based on three measurements: bilirubin, INR, and creatinine.
  - The score is the basis for putting patients on our transplant list, at least in the United States.
  - The MELD Score is dynamic, and changes as the liver disease gets worse; however, it is not as dynamic as one would like it to be to be applicable to clinical trials.
  - Attributes as a surrogate:
    - Biological Plausibility: Yes
    - Quantifiable: Yes
    - Reproducible: Yes
    - Repeatability: Yes
    - Performance Characteristics: Not well studied in the framework of a clinical trial. Would need more work to use in a phase 2B or 3 trial.
    - Easily Deployed: Yes
    - Supporting Evidence: Need more data to apply this in clinical trials, the change in MELD as a surrogate for outcomes is not well studied in compensated cirrhosis.
    - Risks/Costs: Negligible.
    - Risks due to Misclassification: Negligible, can be easily reconfirmed if unsure.
  - Overall Comment: Relatively static in compensated cirrhosis, cut-off not well studied (what amount of increase or decrease is clinically significant?), and influence of co-morbidities and warfarin.
- ^{13}C-Methacetin breath test
  - The patient swallows the ^{13}C-Methacetin solution, and the compounds in the exhaled air are measured and algorithms are used to estimate liver function.
  - Attributes as a surrogate:
    - Biological Plausibility: Yes- based on cytochrome P450 1A2, as the liver disease gets worse, its function goes down
    - Quantifiable: Yes
    - Reproducible: Not Known
    - Repeatability: Yes
    - Performance Characteristics: Not well studied- some trials being done now might address this.
    - Easily Deployed: Probably- compared to HVPG is easier.
    - Supporting Evidence: Modest- will be addressed as more publications come out
    - Risks/Costs: Negligible risks, costs unknown
    - Risks due to Misclassification: Unknown
  - Overall Comment: Limited published evidence to date and depends on a single CYP. Due to proprietary nature, external independent validation may not be possible.
- HepQuant Disease Severity Index
  - Is a dual cholate quantitative liver function test, where C13 is administered intravenously and D4 is administered orally. Using differential shunting, HepQuant is able to measure the Disease Severity Index. First tested in the Halt-C trial in patients with hepatitis C and has now accumulated a large body of data.
  - Published papers on DSI in peer-reviewed journals are sparse- hoping that abstracts presented become published so that the data can be scrutinized.
  - Attributes as a surrogate:
    - Biological Plausibility: Yes
    - Quantifiable: Yes
    - Reproducible: Probably
    - Repeatability: Yes
    - Performance Characteristics: Well studied but limited peer reviewed publications

        - Easily Deployed: Not as easy to deploy
        - Supporting Evidence: Many abstracts but limited peer reviewed publications
        - Risks/Costs: Negligible risks, costs unknown
        - Risks due to Misclassification: Unknown
    - Overall Comments: Limited scientific evidence to date and depends on cholate extraction/shunting (there may not be a lot of shunting in compensated cirrhotics). Due to proprietary nature, external independent validation may not be possible.

Patient Reported Outcomes

- Questionnaires are being used, but where do they come into the approval process?
- Generic as well as liver-specific quality of life instruments have been used, including the Chronic Liver Disease Questionnaire (CLDQ, 25 Likert items), Liver Disease Quality of Life (LD-QOL, 75 Likert items), Short-Form Liver Disease Quality of Life (36 Likert items), Liver Disease Sickness Index (LDSI, 18 Likert items)
    - Being used in clinical trials but not being utilized for approval purposes
- PBC has an instrument for itching, and at least one trial is testing a compound against itching as the primary endpoint.
- Cramps, disturbed sleep, and minimal hepatic encephalopathy are areas that are very relevant to patients

Decompensated Cirrhosis Endpoints: ACLF and MELD

Slides: http://www.forumresearch.org/storage/documents/LiverForum/LiverForum7/07_jalan.pdf
Presenter: Rajiv Jalan, University College London

Decompensated Cirrhosis

- Two categories for decompensation: acute decompensation (AD), and acute-on-chronic liver failure (ACLF)
- Natural history of cirrhosis changes when patient with acute decompensation (ascites, GI bleeding, encephalopathy, bacterial infection) develops another organ failure(s).
- Patients with cirrhosis and with acute-on-chronic liver failure (ACLF) are increasing, and in-hospital mortality rates for ACLF remain at nearly 50%.
    - Patients presenting with both ACLF and cirrhosis require large amount of resources
    - For example, ACLF costs $1.8 billion per year to treat 32,335 hospitalized patients and has 50% mortality. That is compared to the $17 billion cost of pneumonia which hospitalizes 1.1 million patients per year, and has a mortality of 4.1%.
    - The costs for pneumonia, chronic heart failure, sepsis, etc. are not that different from cirrhosis and ACLF, but the mortality rate for ACLF in particular is much greater.

Acute-on-Chronic Liver Failure

- ACLF Definition (AASLD/EASL Working Definition): acute deterioration of preexisting chronic liver disease, usually related to a precipitating event and associated with increased mortality at three months due to multi-system organ failure.
    - Mortality is not only related to liver failure- other organs play a role in the development of organ failure.
- European study of 1,400 patients admitted to the hospital with acute decompensation of cirrhosis showed that patients were easy to divide into different prognostic classes depending upon how many organs had failed.
    - For patients without ACLF (admitted with decompensated cirrhosis, but no associated organ failure), 28-day mortality rates were very low.

    - However, with increasing number of organ failures, the 28-day mortality rate increases: 20% with one organ failure, 25% with two organ failures, and 70% with three or more organ failures.
    - 90-day mortality for each category, but particularly for ACLF-1 and ACLF-2, is higher than 28-day mortality.
    - This classification of patients separates out patients that have compensated cirrhosis without organ failure, from those that do have organ failure.
        - Suggests what the endpoint of a clinical trial might be, and what the duration of therapy might be.
- Reversing ACLF is likely to improve survival
    - Whatever the initial grade of ACLF, if the patient is able to improve to a no-ACLF stage, mortality is reduced.
    - For example, a patient with ACLF-1 that progresses to ACLF-3 has a mortality rate of 87.5%. However, if the patient reverts to no-ACLF stage, the mortality rate is 6.7%.
    - This is a clear endpoint that changing ACLF stage in a patient with acute decompensation with organ failure is likely to result in reduced rates of death.
- Differences in ACLF
    - Regardless of leucocyte count, the mortality rate for patients with no-ACLF is very low; however, the mortality rates for patients with ACLF correspond with leucocyte count.
    - ACLF appears to be agnostic in terms of predisposition. When looking at patients with underlying alcoholic cirrhosis and patients with hepatitis B virus related cirrhosis, very severe onset of hepatocyte death in these patients happening with ACLF compared with those without acute decompensation.
    - ACLF is associated with severe inflammation, systemic inflammation, and with very marked hepatocyte cell death.
- Clinical and biological features of acute decompensating events
    - Bacterial Infection: The occurrence of bacterial infection is greater in patients with acute decompensation who present with ACLF than it is in patients with no-ACLF.
        - Risk of mortality is much higher in patients with ACLF and a new infection.
    - Variceal Bleeding: 28-day mortality is 2.8% of patients with a variceal bleed without ACLF, but 46.3% of patients with ACLF.
        - In a treatment for variceal bleeding, could survival be an endpoint for this group?
    - HVPG: There is very wide heterogeneity in the portal pressure measurements in the different patient populations (Compensated, Decompensated, ACLF), and so it is not likely to work as a surrogate
    - Hepatic Encephalopathy: patients with ACLF associated with hepatic encephalopathy (HE) have an increased mortality rate (60%) compared with patients without ACLF (30%).
        - HE in both groups increases the risk of mortality, and thus is not only a symptom. Therefore, treatment of HE may result in increased survival.
        - Ammonia is the most important pathophysiologic parameter that's associated with the development of hepatic encephalopathy. An ammonia level greater than 80 micromoles per liter is associated with an increased risk of mortality.
            - Patients whose ammonia levels remain the same or increase have an increased risk of mortality compared with patients whose ammonia levels decrease.
            - Additional studies will be needed to determine whether ammonia levels can be used as a surrogate for HE.

- Acute Kidney Injury (AKI): The severity of AKI is associated with increased risk of death. The risk of death is significantly greater in patients with AKI that have associated ACLF, compared with the patients who do not have associated ACLF.

ACLF Prognosis

- Three independent factors associated with mortality for ACLF: CLIF-C Organ Failure score, Age, and white cell count.
  - These can be combined into a formula and used to compare the performance of the different scoring systems (CLIF ACLF, MELD, MELD-Na, Child-Pugh).
  - The CLIF ACLF score performed significantly better than other systems in both CANONIC study patients and in the validation database.
    - CLIF-C ACLF score seems to improve the performance of the MELD score by about 15 to 20% in predicting mortality at 28 days, 90 days, 180 days, and 365 days.
    - Suggests the need to think about disease-specific scoring system
  - Changes in both MELD and CLIF scores seem to be reasonable methods to identify which patients are likely to survive at 28 days and at three months. This needs to be further validated in future studies.
- Prognosis impacts patient selection for clinical trials: including patients with low risk of mortality is unlikely to reveal any results without very large numbers of patients in trials; including patients with high risk of mortality will be unlikely to show any benefit, and has been the graveyard for drug development for similar situations.
  - The key for clinical trials will be to identify a 'sweet spot' in the middle which allows trials to have appropriate power calculations and see effect.
  - For example, recent trial (Mookerjee et al, 2016) using CLIF-ACLF score demonstrating effect in the middle of range, but very little effect at the tail ends.
    - Can help investigators identify what endpoint to use and what population to study
- Independent factors associated with mortality for acute decompensation (without ACLF): Age, serum sodium, white cell count, creatinine, and INR.
  - Comparing performance against MELD, MELD-Na, and Child-Pugh, the CLIF-C AD score performed significantly better and is validated.
    - The main difference in CLIF-C AD score is a marker of inflammation (white cell count).

Summary

- In patients with acute decompensation of cirrhosis, ACLF defines the natural history and the underlying pathophysiology.
- In patients with traditional AD and ACLF, the CLIF-C scores are currently the best available clinical prognostic markers.
- A change in MELDs and the CLIF-ACLFs at day 5-7 are surrogates for mortality in ACLF patients.
- Additional biomarkers are needed:
  - HVPG in this context is not fit for purpose
  - Ammonia has potential, but will need much more data
- Other outcomes:
  - Reducing hospitalization/ ICU duration- likely a clear endpoint
  - Hospitalization readmission rate following an episode of decompensation- a clear endpoint.
  - Quality of life- likely an endpoint, particularly if you can develop a disease-specific QOL scores. Particularly in those with refractory ascites.

Decompensated Cirrhosis: Endpoints and Experience in U.S. Phase 2B/3 Trials

Slides: http://www.forumresearch.org/storage/documents/LiverForum/LiverForum7/08_sanyal.pdf
Presenter: Arun Sanyal, Virginia Commonwealth University

Clinical Trials in Cirrhosis

- Cirrhosis is a continuum, with milestones along the way, including:
  - Clinically significant hypertension (HVPG to >10)
  - MELD >10
  - MELD ≥15
  - Liver-Associated Clinical Events (LACE): ascites, encephalopathy, HCC, variceal bleed
  - ACLF, Sepsis
- Need to consider where in the progression a clinical trial is targeting, because the outcomes will depend on where in the process the intervention is, what the intervention is attempting to achieve, and what the mechanism of action is.

Salix 2131 Trial

- Goal: prevent decompensating event (ascites, encephalopathy, HCC, variceal bleed)
- Exploratory trial with six arms looking at traditional rifaximin vs. a new formulation of rifaximin with either immediate release or sustained release. Patients were then followed for six months.
- Inclusion criteria: Adults with cirrhosis, with ascites, but without esophageal variceal bleeding, spontaneous bacterial peritonitis, renal failure with ascites, or development of medically refractory ascites; MELD score ≥12 or Child-Pugh Class B; resolution of any documented HE.
  - A downside is that the study wanted to prevent decompensating events, but two such events had occurred in these patients.
- One treatment arm was associated with a significantly less time to hospitalization or all-cause mortality.
- Demonstrated the feasibility that investigators can select populations to show differences in real clinical outcomes in a manageable timeframe.
- Lessons learned:
  - Outcomes should not be present in patient prior to study
  - Outcomes should be specific to the mechanism of action
    - The difference seen in the treatment arm was almost entirely accounted for by changes in hepatic encephalopathy rates, which aligned with the mechanism of action for the compound.

Rifaximin Pivotal Trial

- Goal: Secondary prevention of HE
- Randomized control trial with 299 patients, lasting for 6-months. Open-label extension was offered to patients after 6-months.
- New onset or worsening of encephalopathy was the endpoint.
- Rifaximin was superior to placebo for the prevention of breakthrough encephalopathy, and for the reduction of hospitalization for encephalopathy. These factors were critical for getting approval. However, there was no impact on all-cause mortality.
  - During 4-year follow-up, almost 60% of deaths were related to complications of cirrhosis, 10.5% were attributable to sepsis.
    - Big issue is how death certificates are filled out. Statisticians can only analyze what is put into the system.

Terlipressin

- Drug is a vasopressor and was given in hepatorenal syndrome, type 1, and the pivotal trials targeted advanced stage patients.
- Results from two trials have shown that it improves creatinine and renal function; however, mortality did not improve.
- When patients get far enough along in progression, some of the immediate problems can be addressed, but patients continue to progress to multi-organ failure and mortality.
    - For patients with very advanced stage disease, mortality is not a great endpoint.
- Patients with SIRS have a much better response to Terlipressin than those that do not have SIRS, and led to improvement in survival.

Mortality as an endpoint

- Mortality may function well as an endpoint when the population is homogeneous in terms of drivers of mortality and there is a single primary drive of death on which to intervene; however, this is not the case in decompensated cirrhosis.
    - Six different pathways (encephalopathy, variceal hemorrhage, progressive liver failure, refractory ascites, renal failure), each which could kill the patient independently. Setting up for failure unless a drug affects all six pathways.
- With smaller incremental changes in mortality, the sample sizes balloon and it becomes very impractical for trials.
- Not a unique issue and also has come up in cardiovascular disease and sepsis. Recent article in the Journal of Intensive Care (2016): “Regulatory agencies have recently agreed to a primary, hierarchical, clinical composite endpoint in acute heart failure that combines global assessment of symptoms, persistent or worsening heart failure requiring an invention, and all-cause mortality”.
    - Ways to be innovative- not going to move forward if trials in cirrhosis and decompensated cirrhosis are anchored to a mortality endpoint.
    - Innovative machine learning endpoints are being developed, for example one for Sepsis (TREW score).

Discussion

- Could a trial be conducted involving different causes of cirrhosis, for example, can a study involve NASH patients and ASH patients?
    - Cirrhosis consists of a population that includes a variety of etiologies and treating the individual symptoms such as encephalopathy and renal failure are very different than treating cirrhosis.
    - Regulatory agencies have been open to accepting an indication that picks only aspects of liver failure in cirrhosis. It is a more difficult to approach to select cirrhosis and all its features as the indication.
    - The usual regulatory thinking requires taking into account which symptoms will be addressed, and what is the mechanism of action of the compound.
    - Getting an indication for treatment of cirrhosis may not be feasible because the underlying disease causing the cirrhosis needs to be treated and each cause progresses differently.
        - A treatment that addresses acute-on-chronic liver failure and prevents the occurrence of other organ failure will not have an indication for “treatment of cirrhosis”, it will be more specific.
    - To address mortality or treatment of the disease condition, the trials need to stay within a specific disease. But trials could address an indication like hepatic encephalopathy, variceal bleeding, or a complication of cirrhosis and include different kinds of patients

that have hepatic encephalopathy in that trial, so as long as the focus is on a specific outcome.
    - There is a small window for “any cirrhosis” indication in the sense that it really does depend on the mechanism of action of the drug. For example a drug working to regenerate the liver or restoring synthetic function, then that would be able to address that issue.
    - In the Alzheimer’s field, some early studies included all-cause dementia and did not have as tight criteria for trials. However, on follow-up, many patients, maybe 30% didn’t truly have Alzheimer's. Although there might be a desire to try to have an all-cause cirrhosis indication, the limitations and the desire to have it ultimately lead to a regulatory success may not necessarily be the best way to eventually get an approval.
- When patients with NASH cross the pathological border from pre-cirrhosis to cirrhosis, they are now stage 4; however, they progress a great deal over the next five to ten years with increasing amounts of fibrosis and vascular changes. Yet, throughout that entire spectrum, these patients are stage 4 by the CRN classification. When liver biopsies are included in the evaluation of patients with cirrhosis, what other things are appropriate to include?
    - Within stage 4 compensated cirrhosis, HVPG can stratify patients. Looking at histology, studies could include the collagen proportional area and the thickness of the septa. How thick the septa is between the nodules has been linked to HVPG and to outcomes.
        - Both collagen proportional area and the thickness of the septa have been used. There is a staging system that Ian Wanless came up with which is based on the widest thickness of the septa that you see, but measuring them just using a microscope and a measuring system will work. Collagen proportional area is also a good choice. There is not a lot of eagerness to biopsy cirrhotic patients, but if it is used, then these other methods become available.
    - Once verging on cirrhosis, there is the opportunity to engage functional readouts of the liver. Zach Goodman showed in an old trial that fibrosis continues to accrue well into the cirrhotic phase. That’s where the 1, 2, 3, 4 categorization fails the field. Once patients are in the cirrhosis category, fibrosis should still be quantified, but that can’t be done using standard methods. Whether the three functional tests that were measured—C13-methacetin, HepQuant, HVPG—turn out to be predictive, alone or in aggregate, remains to be proven. But unlike earlier stages, cirrhosis gives us the opportunity to assess latent reserve.
        - There are also these dynamic markers that are now being developed. And something that’s very simple and can be done is this whole pro-C3, pro-C5 collagen fragment new epitopes which give us a handle on both the fibrogenic and the fibrolytic response. So you can actually model whether you are more fibrogenic and less fibrolytic or vice versa. This will need to be validated to show that it translates into something clinically meaningful, but those are the kinds of things we need to be thinking about now. And the clinical trials provide a good format to validate some of those things.

SESSION #3: U.S. PAYER AND CARE DELIVERY PERSPECTIVES

Moderator: Veronica Miller, Forum for Collaborative Research

Lessons Learned in HIV and HCV

Presenter: Carl Schmid, the AIDS Institute

- The first thing needed when a drug comes on market is to get the drug on a payer’s formulary. We all are concerned about high deductibles and prior authorizations, but if the plan doesn't cover the drug, patients have no access to it.

- Under Medicare law, every plan must cover two drugs per class. HIV is one of the six protected classes and each plan has to cover basically all HIV drugs.
    - Some problems getting access to Hepatitis C drugs, but generally not many issues.
- Plans that administer Medicare part D like high priced drugs because they also get high rebates.
    - This money funneled back into lower premiums.
- With Medicaid, the law is that every state has to cover every drug by a manufacturer that participates in the Medicaid rebate program.
    - States get at least 23% off of the list price for the drug in the form of a rebate, and therefore, they must cover every drug that manufacturer produces. Nearly all manufacturers participate in this program.
    - States can have preferred drugs and non-preferred drugs, and include prior authorizations. This is a way of negotiating with the companies to get additional rebates.
        - This may change – Massachusetts has a Medicaid waiver that proposes to a closed formulary with only one drug per class, instead of covering every drug.
- As a result of the Affordable Care Act, private plans have 10 essential health benefits, one of which is prescription drugs.
    - Every plan has to cover the greater of one drug per class, or the same number of drugs in a state-benchmarked plan. Usually, a state benchmarked plan is a large, employer-based plan in the state. Every state is going to differ as to the number of drugs they are required to cover. It doesn't specify which drugs, just that plans must cover the same number of drugs.
    - With HIV, a lot of the single-tablet regimens weren't covered, and a lot of the new drugs were not getting covered. Because of this, the government developed additional regulations which stipulate that plans have to evaluate new drugs as they come on the market, they must use a pharmacy and a therapeutic committee, and must follow treatment guidelines.
- When a drug is approved, it doesn't guarantee access to patients, as there are high deductibles, co-pays, and co-insurance. There is utilization management, prior authorization, and step therapy.
    - In Medicare, this is not seen in HIV because class doesn't have prior authorizations. Hepatitis drugs do have prior authorizations.
    - In Medicaid, drugs for hepatitis may be covered, but access is limited to only the sickest people, and some have provider requirements and sobriety requirements.
        - Medicaid is supposed to be covering hepatitis drugs that are medically necessary.
        - The federal government wrote a letter to all state Medicaid programs saying that these restrictions are illegal, but many states are still not lifting these restrictions, leading to litigation
- Private insurance: There is a section in the Affordable Care Act on non-discrimination, and states that you cannot discriminate based on someone's health needs; however, there are still problems being identified.
    - In Florida, four plans put every HIV drug on the highest tier with prior authorization including generics and 50% or so co-insurance. After a discrimination complaint was filed, the health commissioner acted and stated that plans cannot charge more than $150 for a co-pay.
    - Regulations for private insurance includes no excessive prior authorizations; every drug cannot be in the highest tier; and need to review the plans for discrimination at the state and local levels.
        - Important to bring complaints to state insurance commissioners and the federal government, and to talk to the plans themselves.

- Bring issues to press, include patient advocates and doctors.

Medicare Coverage: A Review

Slides: http://www.forumresearch.org/storage/documents/LiverForum/LiverForum7/10_jacques.pdf
Presenter: Louis Jacques, ADVI

Social Security Act 1862

- Reasonable and Necessary standard (R&N): there is more than one R&N standard within the act, including for hospice care, research, and others. See examples A and E.
    - Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—
        - (A) which, except for items and services described in a succeeding subparagraph or additional preventive services, are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member
        - (E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section
            - CMS uses this for coverage with evidence development which is essentially, in a European paradigm, would be coverage in research
    - Both CMS and its predecessor Health Care Finance Administration (HCFA) attempted to define R&N through rulemaking, but efforts were unsuccessful.
    - For about 15 years, CMS has used the operationalized definition: “Adequate evidence to conclude that the item or service improves clinically meaningful health outcomes for the Medicare population”
        - This has been upheld by a federal appeals court ruling (Kort v. Burwell, 2016), “consideration of health outcomes and disease management was permissible under the Medicare Act itself.”
    - R&N is not the same as the FDA standard of “reasonable assurance of safety and effectiveness”.
        - FDA standard is risk-based (PMA, 510k); CMS doesn’t have a risk-based standard. FDA’s language of “reasonable assurance” leaves room for interpretation.
        - While the FDA is largely centralized; CMS is decentralized, in part due to the political rhetoric of the 1960’s where public sentiment was against centralization.
            - Much of current debate on healthcare ties into what will be decentralized to the states and what will be done nationally.
            - Something covered by CMS in California may not be covered in Maine; this doesn’t happen with the FDA- if something is approved, it is approved everywhere.

National Coverage Determinations

- The process for National Coverage Determinations was described by Congress in 2003 in the Medicare Modernization Act. Essentially, it is a 9 to 12-month process, depending on whether or not CMS solicits outside opinions either through a technology assessment or through a MEDCAC meeting.
    - MEDCAC is CMS’s equivalent of an FDA panel meeting.
    - In contrast to FDA, CMS solicits public comment on draft decisions, so the paradigms really are very different here.
- Historically, there have been about 300 decisions made nationally by Medicare. Many of them predate the late 1990s and evidence-based medicine. Most of them tend to be about 80 pages

long, and this is because there is an expectation that if the federal government makes a decision, the evidence considered and the rationale for the decision will be publicly available.

- The analysis conducted for National Coverage Determinations is divided into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

Health Outcomes:

- Longer lifer and improved function is a health outcome of great importance
- Arresting the decline of a disease or slowing an inexorable decline is persuasive.
    - There is no requirement that you have to cure people.
    - Following any clinical trial long enough, both arms in a Kaplan-Meier curve end up at the bottom. We all die. So at some point mortality is non-informative as an outcome.
- Outcomes of progression-free survival, improved scans, or improved biomarkers are not as impressive. For example with cancer, improved PET scans are not very meaningful if the patient is still bed bound and unable to complete most executive functions.
- CMS is interested in Quality of Life.
    - By the time companies come to CMS with quality of life, it's because their pivotal trial failed primary and secondary outcomes.
    - If the trial pre-specifies quality of life and if uses an instrument that is validated for the condition being looked at, Medicare loves to see that sort of stuff.
- Even if one agency needs some particular metric, there's no real scientific reason why that study can't include some other outcomes because otherwise the sponsor is stuck doing two or three trials. The outcomes need to demonstrate that the patient's experience of disease is better.

General Evidentiary Requirements

- Preferred Route for Therapeutics:
    - Provide adequate evidence that a treatment strategy using the new therapeutic technology compared to alternatives leads to improved clinically meaningful health outcomes in Medicare beneficiaries
        - Published, peer-reviewed evidence.
        - Not a head-to-head comparison of effectiveness or cost effectiveness, rather, compare the typical patient experience through the medical system, and how the new technology is different and results in improved health outcomes.
        - Must be in Medicare beneficiaries, a typical beneficiary as a 74 year old woman.
            - Excluding older patients and patients with comorbidities from clinical trials will make generalizability argument difficult.
            - Doesn't necessarily mean older patients are needed in every trial- for example, when reviewing dermal fillers for facial lipodystrophy syndrome, CMS recognized that a typical HIV patient was not a 74-year old woman, and therefore looked at the cohort of patients who would be in Medicare due to a disability or renal failure.
- Preferred Route for Diagnostics:
    - Provide adequate evidence that the incremental information obtained by new diagnostic technology compared to alternatives changes physician recommendations resulting in changes in therapy that improve clinically meaningful health outcomes in Medicare beneficiaries
        - Without robust evidence of clinical utility, the diagnostic is unlikely to get covered. Clinical utility for a payer, as has been articulated by the Institute of Medicine and

CDC is improved patient outcomes for the patient if their care is managed based on the result of that diagnostic test.
    - Evidence of sensitivity and specificity is not enough.
- The evidence will need to show a comparison of patients managed based on the test result, and patients managed without the test result. Physicians hopefully did something different based on the test result, and the results will show what difference it made for the patient in the end.
    - For example, given this test result, a patient might avoid surgery.
- For Medicare coverage, the test actually has to be ordered by the patient's treating physician. So paradigms that round up patients for mass testing simply won't pass muster legally for CMS.

Innovation

- Innovation at this stage of medical care is challenging because there comes a point where proving something is better than the previous method is very difficult. Why keep trying to invent the next version of something that is already relatively mature, instead of trying something completely different"?
    - Something may be technically better, but if there's no value proposition, it is meaningless or irrelevant.
- AHRQ did a study on how often preliminary results actually agree with a mature evidence base, and they found that it's 50/50 and it's kind of random.
    - Need to come to CMS with more than one trial that looks kind of promising

Common Concerns

- Inadequate randomization, blinding, and controls
- Unrealistic comparators.
    - Medicare loves real world comparators of standard of care therapy.
- Composite outcomes with asymmetry between the arms.
- Non-inferiority trials
- Exclusion Medicare beneficiaries from trial
    - Ensure adequate numbers of women unless studying disease not applicable to women.
    - Ensure adequate numbers of subjects over 65 unless disease is only found in younger patients.
- Providing different information to FDA and CMS
    - FDA and CMS can share information without the sponsor's consent.
        - Cannot disclose the information.

Parallel Review

- Parallel review was meant to try to streamline and get some synergies between CMS and FDA approval, and is only for PMAs. There's no fundamental reason why it couldn't be applied to a therapeutic drug, but the FDA's side of the agreement is really through CDRH and it has really been focused on devices.
- Three technologies have entered parallel review: 1.) Exact Science's Cologuard stool DNA screening testing, which is nationally covered, 2.) Medtronic's renal denervation which is still in limbo, and 3.) Foundation One had announced that their tumor assay was in parallel review.
- The hope is that for certain important technologies where there is a clear benefit to both agencies working together in the pre-market space, there can be some things that happen much more quickly.
    - As an example, CMS proposed national coverage of Cologuard on the same day that FDA actually approved the Cologuard test

- The biggest value of parallel review is getting some harmony between the requirements of both agencies for the clinical trial.
- The secondary benefit is around labeling. Sometimes there are words that are agnostic to the sponsor and agnostic to FDA, but because of the way Medicare's law is written, there are loaded issues for Medicare. So having the payer look at your proposed labeling can also be helpful.

Review of Kaiser Permanente

Presenter: Heather Patton, Southern California Permanente Medical Group

- Kaiser is a fully integrated healthcare system with three arms: physician medical groups (eight in the U.S), the hospitals and facilities, and the healthcare plan.
    - All three arms are in mutual agreement with each other.
    - The physician group is self-governed and physicians are really charged with developing clinical care pathways, evaluating the data, and determining how to pursue care in a given disease.
- There are inter-regional groups that review specific areas. For example, there's an Inter-Regional Liver Therapeutics group that would be involved in evaluating new therapies for fatty liver and also in helping to sort out issues within the integrated healthcare system.
    - For example what to inform the primary care providers about how they should be looking at fatty liver in their patient population; how to create workflows to evaluate these patients and bring them to care; and also figuring out how to incorporate things like new therapies into their treatment.
- Because Kaiser is a fully integrated care system, there are things like Wellness Center available in all of the regions.
    - Include weight management programs and fitness programs as part of the healthcare plan.
- New therapeutics for fatty liver are definitely on the radar right now. Have started holding a number of interregional meetings to figure out how to take this on within the system.
    - Recognizing that there are going to be therapeutics coming, the first task is figuring out how to manage the disease right now.
        - How to evaluate patients currently? How to bring them to appropriate care? How to engage them in the wellness programs that are available?
        - Evaluating how the different regions are each doing this, and what seems to be working best in the healthcare system.
- In terms of new therapeutics, the physician and pharmacist evaluation of what is deemed to be evidence-based best practice is what drives the contracting process, not vice versa.
    - Use the best available evidence to determine the right thing to do for the patient population, and then use that to leverage contracting negotiations.

Review of LA County's Department of Health Services

Presenter: Hal Yee, Los Angeles County Department of Health Services

- There's a difference between the federal government and the county government: the federal government can run up a deficit, but the county government cannot.
    - As a result, everything discussed already regarding the FDA and CMS is true for the county health department, in addition to extra stuff.
        - This includes effectiveness as opposed to efficacy. Not as much focus on randomized control trials, instead, really care about figuring out how to deliver the care in a real-world situation with limited resources.

        - Focus on effectiveness and a holistic approach of thinking about cost. It's not just how much the medication costs, it's all the other costs—diagnostic tests, clinical cost, lab cost, IT cost, etc.
    - As a governmental organization, one of the fundamental principles of the system is equity- do not discriminate against people because of their race, insurance status, gender, or orientation. Also do not want to discriminate against people because of the condition they have or what specialty they're seeing.
        - As a result, the Department needs to be very careful about prioritizing and making sure that the fixed budget can be applied across the entire system in a very rational way to provide the highest quality, patient-centered care.
- Utilize a matrix to make some of these decisions, including a Pharmacy and Therapeutics Committee that broadly oversees all specialties.
    - A unique feature is something coined Specialty Primary Care Work Groups, which are groups that are empowered to decide in a given specialty what the practice of care will be.
        - That practice needs to be signed off by primary care and specialty care regardless of which hospital they're at.
        - The idea is to get rid of the hierarchy of specialism so that the primary care providers are in the best position to determine what the priority for that given patient is.
    - Another novel tool that the department has developed for standardizing is called Expected Practice.
        - The perspective is that we should be able to negotiate within one of these Specialty Primary Care Work Groups what the right care is, what the right medication is, what the right device might be.
        - And then expect all the providers to follow that expected practice unless they have a clinical or social reason they can't do it.
            - Expected to document the compelling reason for varying care with that patient.
    - The Department does everything discussed in the CMS presentation, plus ensuring it can be applied in a manner that helps all of our patients within our fixed budget.

Discussion

- In some cases Medicare may be willing to pay for the drug if used off label, whereas insurance companies often don't want to do that. This puts drug companies in a dilemma because they get in trouble for promoting drugs for off label use. Insurers and/or Medicare may be willing to reimburse for a drug that's used off label if they see a publication that looks pretty good; however, the patient population can be unlike the one for which the drug was approved. There are all kinds of safety issues that can come up by promoting a drug for off label use or reimbursing for it.
    - Congress and the Omnibus Budget Reconciliation Act of 1993 instituted a compendium process for Medicare which listed three compendia, two of which no longer exist. Currently, it's the National Comprehensive Cancer Network (NCCN), and a few others and they've essentially said if a drug itself is FDA approved and the indication is listed favorably by one or more compendia, CMS can use rulemaking to decide where the evidentiary cutoff is. For NCCN, it's a 1 or a 2A recommendation. That was considered a medically acceptable use of a drug.
    - This process was not put in the reasonable and necessary statue, but in the definitional part of the statute. This means that if it is a medically accepted use for Medicare, Medicare needs more than 'it's an unlabeled use' to not cover something. Private plans have their own relationships with compendia.

    - In general, what CMS wants to look at is clinical trial evidence.
- Is there any precedent in the U.S. for the coverage in another disease area with an accelerated approval, in which the clinical benefit is going to be demonstrated in a post-marketing setting? The pre-cirrhotic population doesn't have many symptoms, and changes in quality of life cannot be detected. Regarding the coverage with evidence development, is there a certain timeframe or is there flexibility with what the clinical trials needs are?
    - There is some flexibility with the coverage with evidence development and in some cases CMS has stipulated a window period. It really has not been applied much to drugs, and has mostly been used with devices.
        - There are some fundamental differences between drugs and devices, particularly that devices clearly have a learning curve. If a patient is receiving an aortic valve, they will want a very experienced operator to put it in, not a medical student.
        - There is also a device iteration process where the device is essentially a different device nine months later.
    - Regarding accelerated approvals, there was the Duchenne drug Sarepta that caused some controversy that was widely reported almost a year ago. They are a challenge for payers because on occasion there are some labeled indications that are subsequently revoked. The hardest thing for a federal agency to do is to take away something they've already given in the past.
- It sounds like in terms of approving drugs, the field needs to think about patient pathways to benefit and outcomes as opposed to effect of drugs. Would it be possible to consider using multiple interventions in a single clinical setting so that each element of the pathway is approved as opposed to individual drugs? For example, an investigator might have two or three phase 2b drugs or devices which are combined in a single patient pathway. And the evaluation at the end of it is whether the patient receives benefit in six months or 12 months. There are issues with testing two or three different agents in the patients' pathway, and it's particularly true of decompensated cirrhosis. In the scenario where the goal is to get a patient out of the ICU, and keep them alive for three months and then perhaps a year. This might require the use of three or four agents to be able to demonstrate that this patient has a clinical, beneficial outcome—effectiveness as opposed to efficacy. Is there a conflict between what FDA is proposing, what Medicare is proposing, and what Kaiser is doing?
    - The way that drugs come to FDA review and approval is somewhat artificial to what Kaiser does in practice. The question is, how is 'real world' practice brought into clinical trials? How can investigators create a trial that incorporates a pathway rather than a single, randomized invention? Because in reality, that's how it will be done in practice.
    - It's hard to believe that there's going to be one single agent that's going to work for fibrosis or fatty liver. It's hard to believe that that agent is going to exist without connecting it to diagnostic studies to monitor, or even better yet, determine which sub-population of patients is it going to work with or not.
        - The secret probably is going to be in randomization because that's the only way to tell something that works from what doesn't. This will need to use big data from big systems because otherwise there's not a large enough sample size to do it. The field is being cursed by the scientific method because it teaches to make things as fundamental as possible and find the signal. There is probably no signal, and the field will need to learn from the implementation science world which can manage the messiness of these kinds of studies.
        - One of our challenges will be the FDA because we have to get off that model and find a different way of doing these studies if we're going to make any difference, drive down costs, and provide better healthcare. And it gets to patent law and intellectual property- there can't be each company working on only their one

thing, somehow we have to develop groups and teams where we figure out how to finance that stuff.
    - Medicare is open to practical, clinical trials. In fact, a common question to ask companies would be, "Where does this fit in the pathway of the patient? What happens before? What happens after? What happens with?"
        - The hard part about doing that trial is how do you get three sponsor's legal departments to all sign off on the same protocol? And how do you avoid people gaming the outcomes so that the adverse events are attributable to your product and all the blessings accrue to mine? That's a hard trial to pull off unless a specialty group itself of practitioners is willing to do that and probably ask NIH for the money. And that's clearly a post-market trial at that point.
- Thinking about lifestyle changes and outcomes, how is the closed system of Kaiser Permanente the same or different from a closed system like the Veteran's Administration?
    - They're probably quite different. Kaiser is consciously addressing this right now in anticipation of what's to come, which is important in order to figure out how to identify and triage patients, bring them to appropriate care, and get them plugged in for services that are there but often not taken advantage of.
    - One of the complicating factors is that there is an additional fee for being in a weight management program, and that's something that healthcare delivery systems are going to have to figure out. If that's going to be a barrier to people pursuing lifestyle modification, then that might be something that is in the overall long term best interest to eliminate for patients.
- There is a huge problem with liver cancer, which is molecularly very complex and there will not be one-size-fits-all for liver cancer. How can oncology trials be translated to minor subsets in liver cancer? What kind of data would be necessary? It is very difficult to do a randomized control trial once investigators start to look at small subsets of patients- what kind of innovative thinking is being proposed? Should investigators be doing crowd sourcing where patients are treated prospectively when the drugs are approved for other indications, and then ask the physicians to provide feedback on how those patients are doing? Should the field think about other ways, using current technology, which would allow us to translate drugs from other disease areas to address high unmet medical needs?
    - Basket trials have been a bit of a challenge- the SHIVA trial was a French study reported in Lancet Oncology almost two years ago. And the results were basically that there were adverse events, and there wasn't much benefit when they went off label based simply on pathways or biomarkers. That's only one, relatively small trial, and there are other going on. It's a tremendously important question, for example looking at the recent labeling change in Keytruda, there is now a specific biomarker tumor-type agnostic aspect of that label which is certainly fascinating. Some payers are okay with that, while others are finding that some payers a little bit resistant to that.
        - Maybe the field should be willing to accept more risk in that setting, and lower evidentiary standards because the medical need is so high.
        - One could argue there's a medical need for stuff that works. And if there is no evidence that something works, is access actually the metric we should be looking for? Because if a patient is poisoned they are worse off than if they had been simply left alone.
            - Have to balance the desire to be optimistic about all sorts of potential interesting things because otherwise what ends up happening is essentially putting that patient in a non-randomized, non-supervised clinical trial of one. It is possible that there is a paradigm that allows those one-offs to happen but in a very structured way.

    - With new technology where data can be gathered from a clinical setting, this could allow investigators to put that N of 1 into an N of 5,000. But in a less structured way than a prospective randomized trial.
- Would it be worth thinking about biomarkers of risk and then balance those against biomarkers of efficacy? The field is spending a lot of time thinking about biomarkers of how things work, but it would be great to predict who's going to get in trouble.
    - There's no area better than in liver disease for that. Whatever the disease is, a third of patients progress, and two-thirds don't. That would be a great idea except for, who's going to be motivated, besides health plans and delivery systems, to find something that reduces revenues for the liver ecosystem?
    - There is a lot of interest in, for example, pharmacogenomics around anxiety and depression drugs. The nice thing about those trials is those outcomes become apparent usually in three months, versus a prostate cancer trial and waiting 12 years for outcomes to accrue. As long as there's reasonable clinical study evidence, Medicare has been paying for a lot of biomarker testing.
        - As long as somebody can make the argument and sustain it with some evidence that a patient will be meaningfully helped- patients can be meaningfully helped if they don't get something bad. CMS did that with FDG-PET and cervical cancer and said, "If a woman has a positive supraclavicular node, she can avoid surgery." Unfortunately, curative intent isn't realistic anymore; nonetheless, avoiding pelvic surgery is a significant benefit.
    - Regarding the question of, "can we find things to reduce risk?" a corollary of that in at least a fixed revenue system or budget system, is "can we identify treatments that have lower benefit for less people?"
        - For example at LA County Department of Health, everybody is treated for hepatitis C, which is an expensive treatment. To do this, dollars are extracted out other areas that do not have as much demonstrated effective value. If everybody is screaming for, "pay for this!" the system dries up. For fixed systems, gaining a better understanding of what doesn't work- the corollary of who's not going to progress- has great value.
- If a new drug comes out of the drug approval process with accelerated approval based on a surrogate marker, it then needs to be translated into a system that's looking for the clinical effectiveness in the real world and looking for a lot of information on how patients feel and function.
    - PCORI is an agency which is all about patient-centered outcomes research, and they are very interested in some of these topics and probably a group to engage. Another group to think about bringing in would be the VA.
    - This has been the beginning of a discussion that will need to continue because obviously there are decisions being made based on data that may or may not be the same data sets. Or it may be the same data sets and may be interpreted differently.

SESSION #4: WORKING GROUPS UPDATE

Moderator: Katherine Greene, Forum for Collaborative Research

Case Definitions Working Group

Slides: http://www.forumresearch.org/storage/documents/LiverForum/LiverForum7/11_case%20def.pdf
Presenter: Brent Tetri, Saint Louis University
Sophie Megnien, Genfit

- The Case Definitions Working Group has this paper just recently accepted in Hepatology: “Case definitions for inclusion and analysis of endpoints in clinical trials for NASH through the lens of regulatory science”.
    - The goal was to establish uniform definitions of disease states that meet regulatory standards which would allow comparisons of trial results amongst different trials, allow pooled analyses of studies in the future, and ideally facilitate development of biomarkers of disease response for therapy.
        - Recommendations were not developed for clinical management, and the audience is those who are working on clinical trials.
        - The goals of phenotype definition are to be objective, to be quantifiable and analyzable using quantitative approaches. They need to be sensitive to change and logistically feasible, operationalized in the context of multi-center clinical trials.
    - The Case Definitions Working Group decided to break the condition NAFLD, down into 1.) NAFL which is fat without enough inflammation or liver injury to call it NASH, 2.) an indeterminate group, and 3.) NASH.
        - If plotted on a grid, NAFLD severity would be the horizontal axis, and the fibrosis severity would be the vertical axis. This is a way of conceptualizing it with varying degrees of severity from none at the bottom all the way up to decompensated cirrhosis and death or liver transplant.
        - The group first considered seven phenotypes—NAFL with any degree of fibrosis, and indeterminate with any degree of fibrosis. These aren’t good patients for clinical trials right now, so we lumped them all together. And then looking specifically at NASH, we got a lot more granular and divided it into those with no fibrosis, early fibrosis, all the way up to decompensated cirrhosis.
            - Keep in mind that these are not meant to be clinically used.
        - The 7 phenotypes was a little bit complex, so the group was more pragmatic and divided it up into not-NASH, independent of how much fibrosis there was, NASH without cirrhosis, and NASH with cirrhosis.
            - The paper goes into recommendations and defined how those groups are identified, and what the characteristics of those are histologically and clinically.
- The Data Standardization Working Group published a paper in Gastroenterology: “Baseline parameters in clinical trials for nonalcoholic steatohepatitis: Recommendations from the Liver Forum”, which further defines patients in more detail.
    - The paper includes recommendations presented in tables on metabolic measures and lab, demographics and genetics, history of diet and lifestyle exercise, concomitant medications, histology, comorbidity, surgery, anthropometrics, imaging/non-invasive markers, and then lastly the health-related quality of life measures.
- The second paper being developed out of the Case Definitions working group is focused on measuring changes in clinical trials. Amanda Cheung is a transplant fellow at Northwestern and has been doing the heavy lifting on this paper.
    - Considering the grid from before, with NAFLD severity on one axis and Fibrosis severity on the other- a baseline biopsy shows a patient’s NAFLD severity as NASH, with steatosis, inflammation, ballooning, and Mallory bodies; and their fibrosis severity as bridging fibrosis.
    - Comparing the baseline biopsy with the post-treatment biopsy, current method of measuring change is to look at the change in fibrosis and the change in disease activity or severity.

        - Need to be more granular with histology and to better understand what changes in the other parameters that are being measured are going to be meaningful and predict hard outcomes.
    - Reviewing the patient pathway and ways of assessing and treating each part of the process:
        - The first step we think is there's a metabolic stress. There's increased lipogenesis in the liver and increased delivery of fatty acids to the liver, impaired oxidative disposal of fatty acids. There's oxidative stress, mitochondrial dysfunction, ER stress. All these things have been well described in the literature. There are probably others that are involved as well.
            - Assessments include blood tests: lipidomics, proteomics, metabolomics, transcriptomic signature, genetic signature
                - Hopefully, some of these factors will help us characterize patients in terms of stratifying when we have treatments and we have efficacy to understand how we can enrich our trials to identify the appropriate patients and match them up with a treatment.
            - Treatments take the approach of weight loss, healthy eating, exercise, and drugs that will change body metabolism and satiety.
        - The metabolic stress leads to a phenotype of injury characterized by ballooning, inflammation, and apoptosis (steatohepatitis).
            - Assessments include blood tests: ALT, AST, cytokeratin 18 fragments, in addition to many other panels and algorithms; liver biopsy; and in imaging, the multiparametric MRI is thought to have some utility in identifying the injury.
            - Treatments include antioxidants, wound repair, anti-inflammatories, anti-apoptotics.
        - Steatohepatitis is a driver for the accumulation of excess extracellular matrix that we describe as fibrosis.
            - Assessments include blood tests: APRI, FIB4, and other panels; liver biopsy: staging, collagen proportional area; and imaging: MRE, VCTE, ARFI, SSI.
            - Treatments include anti-fibrotics
        - As fibrosis accumulates over time, it leads to cirrhosis and the hard outcomes.
            - Assessments include clinical outcomes and patient reported outcomes (PROs).
            - Treatments include liver transplant
    - With interventions for the different stages of disease progression, will start looking at the changes in the assessments mentioned. There is very little data on most of the changes- there is data on liver biopsy, and some data on imaging including MRI and MR fat fraction, but not much else.
        - Important to gather as much information as possible, in a strategic way, since trials can't gather data on everything.
- The paper will attempt to include concrete recommendations to the extent that the current data allows.

Pediatric Issues Working Group

Presenter: Miriam Vos, Emory University

- The Pediatric Working Group has been a little quiet over the last few months and is overdue to have a call. The first manuscript is almost complete and working on a nearly final draft, and the

group will also be writing up the proceedings of the in-person pediatric meeting that was held in March 2017.

- One suggestion is that instead of trying to write a whole separate set of pediatric papers that parallel topics and have very similar issues to the papers that we're doing right now, it might be more advantageous to include the particular challenges that the pediatric aspect brings into each of these current working groups and papers.
    - Whenever the Liver Forum announces a new working group, the information is sent out to everyone with the request that people get involved and sign up. The groups should definitely have a pediatric perspective involved, and so pediatricians should actively sign up for those groups.
    - Once the working group forms it is usually fairly large, but it becomes pretty clear who will be on the writing committee just by the level of engagement. The Liver Forum would highly encourage people who haven't yet been involved to get involved at that level.
    - Some of the other groups, for example the Standard of Care group, will be an extremely important group for pediatricians to be involved in.
    - There doesn't need to be a separate working group for pediatrics on every issue, but some will make more sense than others to have a separate pediatric perspective.
        - Logistically it has been challenging because there weren't as many pediatricians when the other manuscripts were starting, but the group is bigger now and has the bandwidth to participate in other groups.
        - This topic will be discussed on the next call of the Pediatric Working Group, and determine volunteers to participate in the current working groups.

Placebo Arm Data Working Group

Slides: http://www.forumresearch.org/storage/documents/LiverForum/LiverForum7/13_placebo.pdf
Presenters: Eric Lefebvre, Allergan

- The Placebo Arm Working Group had a very interesting meeting earlier in the day and it was clear from the turnout that there was a lot of interest in learning from the placebo data that we're generating from completed phase 2 and phase 3 studies. The meeting was full actually. And we started a really good conversation, talking about the pros and also some of the limitations maybe of what the collection of this data would entail.
- Summary of key points from the meeting:
    - There is general interest in the possibility of pooling placebo data from completed phase 2 and 3 randomized clinical trials.
    - Pros:
        - Further characterizing the natural history of NASH by collecting available RCT data.
            - Investigators are collecting this data anyway for placebo patients, so this is an opportunity to leverage that and to learn from it.
        - An effort such as this would harmonize the data collection to potentially aid in identification of predictors of disease progression, which is certainly something that we need to better understand.
        - Collecting this data would foster drug develop, inform future study design, and clinical endpoints, and potentially also reduce the need for placebo patients in studies
        - Provide some clinical safety context for interpreting data, occurrence of rare events.
    - Recognized limitations:
        - The observation period in these phase 2 and 3 studies is relatively short, so that's really not so reflective of real natural history.

    - We expect that most of the outcomes that we would see in these studies would be histological, namely progression to cirrhosis, with really few hard outcomes such as liver transplantation or death.
    - The population that we enroll in these studies will be targeted and also have a therapeutic intent, not just a population that is willing to comply with standard of care.
        - Need to understand how these data would compare to registries and the real-life setting.
    - Duplication of efforts needs to be avoided; rather, look for ways to complement other efforts going on. Each approach will have its own inherent set of limitations.
- Key Takeaways and Next Steps
    - Agreement that this was a unique opportunity at hand now with all these clinical studies that are ongoing, to learn from the available placebo data in these completed studies
    - Need to clarify the study aims, the advantages, the limitations of this data, analysis plans that would be put in place, and also the resources that would be required to do this.
    - Assessing the data gaps we have currently and how complementary this placebo data would be with ongoing registries and the real-life setting.

Standard of Care Working Group

Slides: Coming soon
Presenters: Manal Abdelmalek, Duke University
Sven Francque, Antwerp University Hospital

- The Standard of Care Working Group is the newest working group, and has had one meeting so far. The writing team will be led by Dr. Oliver Glass who is an exercise physiologist at Duke with an interest in inflammation and immunity and lifestyle interventions for patients with chronic disease.
- The mission of the group is to create a framework and open dialogue between all stakeholders on how to 'standardize' a standard approach to care in the context of clinical studies.
- The goals include:
    - Review the current standard of care being used in clinical trials
    - Develop recommendations (not guidelines) for standard approaches in NASH clinical trials
        - Physical activity
        - Diet
        - Approaches to capture data
        - How to account for global variations and standards
    - Propose standard with which to manage co-morbidities within scope of existing practice guidelines.
    - Ensure standards can be implemented in a way that is feasible, cost effective, and sustainable over length of the trial.
- Focus on NAFLD/NASH stage 0-3, and leave a different standard for patients with cirrhosis or decompensated cirrhosis.
- Originally thought to focus on adults, due to perception that standard of care would be different in children because many of the pharmacologic therapies recommended for treatment of metabolic syndrome in adults may not apply to children. But the lifestyle interventions would, so would be open to including pediatrics within this component.
    - If combining pediatrics, would consider one manuscript on lifestyle and diet, and one for management of comorbidities.
    - Pediatric and adult populations have many of the same comorbidities- dyslipidemia, type 2 diabetes, pre-diabetes, hypertension, sleep apnea.

        - Would be good for pediatricians to join this working group.
- Proposed manuscript outline:
    - Background discussion on the importance of lifestyle in relation to NAFL, the lack of current standardization of lifestyle modification, and the lack of a standardization in capturing those and qualifying those elements in the context of clinical trials.
    - An introduction including an interpretation of results and efficacy and potential confounders as they currently stand in the literature.
    - Review of current practice and appropriate tools by which to capture and standardize for analytical purposes the intervention and dietary approaches in the context of clinical trials or the systematic approaches to managing these comorbidities.
    - Recommendations will encompass
        - The diet and exercise that is provided, who should be providing it, and how it should be captured;
        - Standardizing the approach to management of comorbidities
        - Consideration of lead-in phases for clinical trials to normalize the confounders in patient care or biases and introduction of variables we can't account for in the context of clinical trials when patients are recruited.
    - Discuss the limitations of the proposed standard and differences in the guidelines in regional practices, accounting for how we would standardize a standard when there are differences in reimbursement even for certain pharmacologic therapies that manage lipids or glycemic control, and the applicability of the standard to a real world, even global variances.
- Next Steps
    - Review how to capture data
    - Review current validated tools, likely have been used in obesity trials and diabetes trials, and may be a good resource to use.
    - Tentative timeline: first draft in early 2018, and final draft in spring 2018

Discussion

- It's going to be very important to capture data, but it has to be practical. When asking patients in a clinical trial about the percent of fat calories that come from saturated fat, patients don't know how to answer that question. How can the data be captured if the patient doesn't know how to respond or the provider doesn't know how to interpret the response?
    - Have talked about apps that can help calculate dietary composition
    - Trying to get detailed dietary questionnaires has not been useful and is very resource intensive. It adds to burden of study. We have to be practical about this, and we need to not make an invention out of the standard of care because that creates a very artificial construct. A randomized control trial is an artificial construct. And then you're making it doubly artificial. We have to be sensitive to those aspects.
    - How much guidance in the context of clinical trials do we propose moving forward, if any? We're all struggling with the variables in this 10-35% placebo response rate and the elements of that. And is it that because we have no standard? Or would we then diffuse the real-world experience in the context of clinical trials?
    - There is evidence that all these tools tend to underestimate energy intake. And in most obese patients, they underestimate more than in lean patients. And in general, they are inaccurate and they are not used in obesity trials.
        - An additional hurdle is that there is enough data showing that dietary inventions are useful during the first six months. And then patients tend to drop off. So it can bring a bias in short term trials, mainly in those patients that will be more compliant to the diet. And in a six-month period, the potential placebo effect can be difficult to be interpreted.

- There's a lot to work through with this particular manuscript, but another fairly important need in the area of lifestyle is alcohol use. We all do questionnaires and look backs, but in terms of lifestyle, alcohol use and whether there are any validated moderate to long term indicators of alcohol use might be an interesting thing for the working group to take up. All trials are generally using the same recommendations that have been around since the NASH CRN started, but not clear how it is being monitored.

SESSION #5: WRAP-UP

Moderator: Veronica Miller, Forum for Collaborative Research

Open Discussion/Meeting Close

Presenter: Arun Sanyal, Virginia Commonwealth University
David Shapiro, Intercept Pharmaceuticals

- The perspectives of the regulatory agencies as always was very insightful and it was very helpful and informative to have the perspective of CDRF join in the conversation this time.
- The payer discussion is a whole new area to explore and definitely needs to be explored more. Including the payer perspectives and what kind of evidence is needed is going to be very valuable as more and more groups move into advanced phase trials.
  - This will allow the needed evidence to be worked into the design plan for those types of studies.
- The cirrhosis session framed what is known, but obviously there is still more that isn't known.
  - With the more focused, NASH-specific context, there is a great opportunity to redefine the continuum of cirrhosis and how interventions at different points in time might work, and what can be realistically expected.
- The publication of the first two manuscripts is a big milestone for the Liver Forum and a very tangible successful outcome of those working groups. The proposal for the Placebo Arm cohort is very exciting and such an initiative would absolutely add value to the field and should be pursued.
- For academics – the Forum works with "Fellows" (for example, the two published manuscripts had a "Fellow" as the first author), and this is a fantastic opportunity for any post-docs or graduate students who are interested in regulatory science to gain hands-on experience.