Webinar Moderator

Norah Terrault, MD, MPH, FAASLD

- Professor of Medicine and Chief of Gastroenterology and Liver Diseases
- Keck School of Medicine at University of Southern California, Los Angeles, CA, USA
Webinar Agenda

- Housekeeping Items – Dr. Norah Terrault
- Webinar and Presenter Introductions – Dr. Terrault
- Clinical Research in Hepatology during the COVID-19 Pandemic & Beyond – Dr. Terrault
- Adaptation of Clinical Research during COVID-19 Pandemic – Dr. Anna Lok
- Clinical Research in Hepatology during the COVID-19 Pandemic: Early-Mid Career Investigator Viewpoint – Dr. Alina Allen
- Panel Discussion / Q&A
Webinar Q&A

• Submit your questions anytime during the webinar in the Q&A box at the top or bottom of your screen.

• Questions will be answered at the end of the presentations.
Webinar Presenter

Anna S. Lok, MD, FAASLD

• Dame Sheila Sherlock Distinguished University Professor
• Alice Lohrman Andrews Research Professor of Hepatology
• Director of Clinical Hepatology
• Assistant Dean for Clinical Research
• University of Michigan, Ann Arbor, MI, USA
Webinar Presenter

Alina Allen, MD

- Assistant Professor of Medicine
- Director Fatty Liver Clinic
- Mayo Clinic, Rochester, MN, USA
Webinar Panelists

Michael W. Fried, MD, FAASLD
- Director UNC Liver Center
- University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Averell H. Sherker, MD, FAASLD
- Director, Center for Liver Diseases
- NIH/NIDDK, Bethesda, MD, USA

Andrea E. Reid, MD, MPH
- Associate Dean for Student and Multicultural Affairs and Director of the Office of Recruitment and Multicultural Affairs
- Harvard School of Medicine, Boston, MA, USA
AASLD’s COVID-19 Clinical Oversight Subcommittee

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- Norah Terrault, MD, MPH, FAASLD, Keck Medicine of USC (California)
- Andrew Reynolds, (Patient Advocate)
- Raymond Chung, Massachusetts General Hospital (Massachusetts) (ex-officio)
- K. Rajender Reddy, University of Pennsylvania Medical Center (Pennsylvania) (ex-officio)
Clinical Research in Hepatology during the COVID-19 Pandemic & Beyond

Norah Terrault, MD, MPH
Keck Medicine of University of Southern California
COVID-19 Arrived…….

Seemingly overnight:

• Non-essential clinical research put on hold
  • Halt to new enrollment in existing trials
  • Focus on safety -- change to remote visits, IP delivery at home

• No new clinical research except COVID-19 related
  • IRBs and CTSI’s or other clinical research infrastructure shifted to support COVID

• Clinical researchers impacted
  • Shifted clinical responsibilities to cover COVID and non-COVID activities
  • Challenges at home related to the ”sheltering in place” environment
First wave, second wave ......

United States of America Situation

4,582,276
confirmed cases

Canada Situation

116,599
confirmed cases

France Situation

175,920
confirmed cases
Reopening…varies by state, city, institution

Source: New York Times July 31, 2020
• Innovation and creativity in study design and execution
• Hybrid models of on-site and remote strategies for achieving study goals
• Greater role for EHR-based data, data linkages
• Flexibility on the part of sponsors, regulatory authorities, and NIH of need to adapt to this changing environment

COVID-19
Today’s focus

- A look at COVID-19’s impact on clinical research in Hepatology through different “lenses”
  - Earlier versus later career
  - Phases of shut-down and reopening
  - Clinical trials, real-life observational studies, big data

- Discuss potential strategies to sustain and expand clinical research in the post pandemic era
  - Trial design, monitoring, data collection
  - Disparities
Hot off the press…. Clinical Research in Hepatology in the COVID-19 Pandemic and Post-Pandemic Era: Challenges and the Need for Innovation

Adaptation of Clinical Research during COVID-19 Pandemic

Anna S. Lok, MD
Dame Sheila Sherlock Distinguished University Professor
Alice Lohrman Andrews Research Professor of Hepatology
Director of Clinical Hepatology
Assistant Dean for Clinical Research
University of Michigan, Ann Arbor, MI, USA
Outline

• Perspectives of investigator and research administration
• Response to ramp down
• Preparation for ramp up
• Adaptation during COVID-19
• Clinical research in the new world
Ramp down: early phase

• Abrupt lock down → confusion, clinics and clinical services limited to emergent care, inadequate PPE
• Focus on clinical trials, enrolled participants in intervention phase
• Administration of investigational products
  • Pause or delay
• Safety monitoring
  • Phone follow-up
Ramp down: adaptation phase

- Maintain safety and well-being of clinical trial participants
  - Resume administration of investigational products: courier or home nursing
  - Resume safety monitoring: video assessment, local labs, home nursing

- Consider entire research portfolio including observational studies
  - Impact on study outcomes, power, and completion: remote consent, electronic platforms for remote data collection

- Funding
  - Federal: funding received but unable to carry out all the work
  - Industry: no activities = no revenue

- Staff
  - Equip staff to work from home
  - Salary support: residual funds, philanthropic funds; reduction in effort, furlough
• Abrupt lock down
• We got it under control
• Business will be back to normal in 2-3 weeks

Chaos but not too concerned
• Abrupt lock down
• We got it under control
• Business will be back to normal in 2-3 weeks

• Cases continue to increase
• Hospitals fill up with COVID patients
• Redeployment of medical providers

Chaos but not too concerned

Anxiety, fear, distracted, survival mode
- Abrupt lock down
- We got it under control
- Business will be back to normal in 2-3 weeks

Chaos but not too concerned

- Cases continue to increase
- Hospitals fill up with COVID patients
- Redeployment of medical providers

Anxiety, fear, distracted, survival mode

- Curve begins to flatten but no end in sight
- Life and work have to go on
- Adaptation needed

New reality
Succumb or Thrive
Ramp down: institutional guidance and support

- Studies that may continue
  - If conducted remotely
  - Clinical trials that offer potential for immediate benefit and/or crucial safety monitoring
- IT provided support to work from home
- IRB provided guidance on protocol modifications, expanded options for remote consent
- Investigational pharmacy arranged courier delivery of investigational drugs
Ramp up: more complicated, slower, no play book

• In phases: timing for expansion and contraction, guiding principles for prioritization, training in safe practices
• Campus wide policies
  • 4 tiers based on benefit to participants vs. risk of COVID transmission
  • Start and stop of each tier linked to State COVID stage and safety plan
  • Investigators and staff complete training on safe practice
  • Study teams submit activation check list
  • Committee reviews and approves study and assigns tiers
  • Decisions including assigned tiers provided to IRB and departments
  • Random audits to ensure risk mitigation plans followed
## Linking activation of human research to State COVID stage and safety plan

<table>
<thead>
<tr>
<th>Tier 0</th>
<th>Tier 1</th>
<th>Tier 2</th>
<th>Tier 3 except immunosuppressed</th>
<th>All studies pre-COVID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled growth</td>
<td>Persistent spread</td>
<td>Flattening</td>
<td>Improving</td>
<td>Containing</td>
</tr>
<tr>
<td>Increasing # new cases every day, likely to overwhelm health system</td>
<td>Continued high case levels, concern about health system capacity</td>
<td>Case growth gradually decreasing</td>
<td>Cases/hospitalizations/deaths clearly decreasing</td>
<td>Continued case/death rate decreasing, outbreaks quickly contained</td>
</tr>
<tr>
<td>Stay Home, Stay Safe: Strict social distancing, travel restrictions, face coverings, hygiene, remote work</td>
<td>Stay Home, Stay Safe: Strict social distancing, travel reduction, face coverings, hygiene, remote work</td>
<td>Safer at Home: Social distancing, increasing face coverings, no gatherings</td>
<td>Safer at Home: Social distancing, face coverings, safe workplace practices, small gatherings</td>
<td>Stay Safe: Adherence to new guidelines. Social distancing, coverings, mitigated workplaces, increased size gatherings</td>
</tr>
</tbody>
</table>
**Benefit to Participant (not science) vs. Risk of COVID transmission (not study interventions or procedures)**

<table>
<thead>
<tr>
<th>Benefit Level</th>
<th>COVID Transmission Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td>1. Potential immediate benefit to the individual participant that is life-saving, including stabilization of a high risk psychological condition</td>
<td>Tier 0</td>
</tr>
<tr>
<td>2. Potential benefit to the individual participant for a condition with no current other intervention options</td>
<td>Tier 1</td>
</tr>
<tr>
<td>3. Potential benefit to the individual participant for a condition with existing intervention options</td>
<td>Tier 2</td>
</tr>
<tr>
<td>4. No benefit to the individual participant</td>
<td>Tier 3</td>
</tr>
</tbody>
</table>

- Incremental risk of COVID transmission:
  - None if all study procedures done remotely OR by clinical team (listed on IRB) concurrent with clinical encounter and not prolong visit by >15 min
  - High if participant immunosuppressed, >65 years, or cannot use PPE
Adaptation to allow activation in earlier Tier

• Benefit level determined by study design
  • 1-3 for clinical trials, 4 for observational studies
• Risk level can be reduced by modifying conduct of study
  • Convert all study activities to remote
  • Hybrid: remote consent and conduct as many study procedures remotely as possible + schedule study visit to concur with clinical encounter and add clinical team to research team (IRB, FDA 1572, sponsor, research and protocol training)
• High risk population: temporarily halt enrollment of >65 or modify conduct of study
Ramp up: institutional support

- IT continues to support work from home
- IRB fast track approval for minor protocol modifications, additions to study team, adding options for remote consent
- Investigational pharmacy continues to support courier delivery of investigational drugs
Ramp up: challenges

- Modification of study procedures might impact data collection and results.
- Disparity in access to and comfort with technologies among participants might impact enrollment, retention and data collection.
- Increased demand on investigators to catch up on back log of clinic patients and procedures.
- Space in clinics for research activities limited due to need for social distancing.
- Revenue loss during ramp down might have led to staff attrition.
Clinical research in the new world – now and post-COVID-19

• Study design:
  • Lean and efficient, focus on essential data necessary for outcome analyses
  • Incorporate options for remote consent and data collection, maximize use of technology and direct transfer of data from participants to study database, e.g. wearable devices, home monitoring devices with blue tooth, participants self-entering data
  • Fewer procedures, less in-person visits might increase enrollment and lower costs
  • Potential unintended consequence: increase disparity in subject participation due to limited access to technology and internet
Clinical research in the new world – now and post-COVID-19

• Study teams
  • TEAM of investigators, study coordinators and other staff
  • Balanced research portfolio: variety of studies and funding sources
  • Financial reserve to ride out gaps in funding
  • Investigators and staff trained and equipped to use mobile technology
  • Study documents: accessible remotely from secure storage platforms
We can let COVID-19 destroy and demoralize us OR we can use COVID-19 as an impetus for disruptive innovation in clinical research

What we were used to

What we have embraced and cannot live without
Clinical Research in Hepatology during the COVID-19 Pandemic

Early-Mid Career Investigator Viewpoint

Alina M. Allen, MD
Assistant Professor of Medicine
Director Fatty Liver Clinic
Mayo Clinic, Rochester, MN

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Outline

Discuss **challenges** and **opportunities** in:

- Funding/career development grants
- Career advancement
Grants/funding: challenges

• Closure of clinical research units
• Less research time as MDs were pulled to cover COVID-related clinical roles
• Major disruption in research teams: staff working from home or deployed → no in-person meetings, lost momentum
Grants/funding: challenges

- Pause in clinical research hinders progress reports on *active grants*
- Planned interventional studies for upcoming grants are uncertain, as patients may be hesitant to travel
- Delay in obtaining preliminary data for *planned grants*
- Institutional cost reductions resulting in loss of research funds
Grants/funding: opportunities

• Changes to proposal submission and award management

• Revised procedures for peer review

• Some agencies have extended the due dates for research proposals

• NIH updated policies on clinical trials and human research

• Additional accommodations for researchers

NIH Guidance on Human Research Affected by COVID-19

• Ensure the safety of all human participants and research staff involved in clinical trials and human subject studies

• Consult with IRBs and institutions about protective measures, such as:
  • Limiting study visits to those needed for participant safety or coincident with clinical care
  • Conducting virtual study visits
  • Implementing flexibilities for required laboratory tests or imaging needed for safety monitoring

• NIH will be flexible regarding project extensions and accommodating unanticipated costs

Learn more: NOT-OD-20-087
FAQs: grants.nih.gov/faqs#/covid-19.htm
Accommodations for Loss of Research Time

• NIH will be flexible with extending time constraints for career development and training awards

• **K awardees** and mentors should contact the awarding Institute or Center to request
  - an extension
  - reduced research effort
  - leave of absence (break in service)
  Requests will be considered on a case by case basis.

• Extensions for **Early Stage Investigator** eligibility due to COVID-19-related disruptions will be considered on a case-by-case basis

Revised NIH Grant Review Process for the June 2020 cycle

- Due date extensions to May 1
- Post-submission deadline – 14 days before study section
- All virtual review meetings after 3/14/2020
- Due date extensions to May 1
- Guidance for reviewers: assume that issues resulting from the coronavirus pandemic will be considered prior to award

Revised NIH Grant Review Process for the October 2020 cycle

- Standard due dates in effect
- Extended deadlines for IC FOAs and Institutional Ts only
- Post-submission deadline – 30 days before study section
- Preliminary data allowed as post-submission material
- All virtual review meetings
- Guidance for reviewers: assume that issues resulting from the coronavirus pandemic will be considered prior to award

The data for October 2020 will be more reflective of slowdowns, teleworking and school closures.

Table 1: Number of R01-equivalent applications received between May 1 and June 5 in 4 consecutive years.

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>All Women (%)</th>
<th>All Men (%)</th>
<th>Other (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>6398</td>
<td>24.6%</td>
<td>61.7%</td>
<td>11.5%</td>
</tr>
<tr>
<td>2018</td>
<td>6481</td>
<td>26.4%</td>
<td>59.8%</td>
<td>11.2%</td>
</tr>
<tr>
<td>2019</td>
<td>6171</td>
<td>25.8%</td>
<td>60.9%</td>
<td>10.7%</td>
</tr>
<tr>
<td>2020</td>
<td>6799</td>
<td>25.7%</td>
<td>56.8%</td>
<td>14.8%</td>
</tr>
</tbody>
</table>

Career advancement: challenges

• Decreased face-to-face interactions due to cancelled meetings→ scientific discussions and mentorship

• Working from home

• The responsibilities of working parents are exacerbated by this crisis

• Women will be affected more by this new challenge because they are more involved in household and childcare demands
Career advancement: opportunities

- New territory: implementation of institutional policies for employee support to allow childcare flexibilities (massive challenge for institutional leaders)

- Institutional efforts to consider these potential delays in publications and funding and extend tenure/promotion periods

- More proactive in requesting virtual mentorship meetings (institutional and other digital conferences)
Panel Discussion

- Please submit your questions to the Q&A Chat now.
For resources and updates on COVID-19 and the liver, visit aasld.org/COVID19
Registration Opens in August

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