AN ORGANIZATIONAL STRUCTURE TO MANAGE ANALYSES AND MANUSCRIPT DEVELOPMENT IN THE HEPATITIS C ANTIVIRAL LONG-TERM TREATMENT AGAINST CIRRHOSIS (HALT-C) TRIAL

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SUPPORTED BY: National Institute of Diabetes & Digestive & Kidney Diseases, National Institutes of Health
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HALT-C Study Overview

- Main Trial sponsored by NIDDK
  - 10 Clinical Sites and 2 sub-sites in US
  - 1050 patients followed up to 108 months post-randomization
  - Study funded in 1999; site funding end in 2010

- 41 Ancillary Studies
- NERI served as the Data Coordinating Center for the Trial
HALT-C Study Design

Chronic hepatitis C, liver fibrosis or cirrhosis, failed to clear virus with peg-IFN & ribavirin

Randomized study of maintenance peg-IFN therapy

Peg-IFN until Month 48  No treatment

Post-Trial Followup to Month 108

- Study outcomes:
  - Death, decompensated liver disease, liver cancer
Publication Goals and Key Concerns

- **Goal:** Disseminate key study results to scientific audience in a timely fashion
  - Number and quality of manuscripts must justify the money and effort spent on the study over 11 years

- **Concerns:**
  - How will authorship be equitably assigned across multiple investigators?
  - How can we best select publication topics?
  - How can we agree on priorities for NERI analyses?
  - How can we collaborate successfully?
NERI’s Concerns

- How can we:
  - best coordinate publication processes?
  - best facilitate writing group interactions?
  - get buy-in on prioritizing analyses?
  - complete all analyses/papers in a timely fashion?
  - maintain high quality through the end of the trial?
  - help everyone collaborate successfully?
Early Publication Committee Actions

- Publication Guidelines developed
  - Covered authorship, topic selection, writing group responsibilities, editorial functions, and approvals
- Trial Design paper published in 2004
  - Enabled later papers to cite the basic information about the study design
Concept Proposals

- Manuscript Concept Sheet template developed
- Pub Comm solicited Concept Sheets
  - Potential authors submitted 60 Concept Sheets
  - Reviewed at in-person Steering Committee meeting
  - ~40 Concept Proposals selected by consensus
Writing Groups

- 3-4 member writing groups work on each concept
  - A statistician worked with each writing group

- Volunteers for writing groups solicited
  - Investigators asked to list top four concepts of interest
  - NERI tabulated the list of volunteers
  - Pub Comm Chair distributed assignments equitably
Prioritization of concepts / analyses

- Pub Comm categorized papers into 9 priority levels (highest to lowest)
  - Steering Committee approved
  - Priorities could be revised at a later date
- NERI conducted analyses in order of priority
  - Statisticians developed focused Analysis Plan
  - Writing Group approved plan and had to follow it
Lead Author

- Directs analyses and writing of manuscript
  - Works one-on-one with statistician
  - Analysis requests go through lead author
  - Writes up action items for monthly calls
  - Makes writing assignments
  - Determines writing group authorship order
  - Submits manuscript to journal
  - Addresses reviewer comments, handles resubmissions
Timelines for papers

- Pub Comm Concerns:
  - How many analyses could NERI handle at once?
  - Could NERI complete all planned analyses?
  - Were some papers taking too much analytic time?
  - Did some writing groups need prodding to finish?

- We developed a Timelines spreadsheet
  - We forecasted NERI’s capacity for conducting analyses, each statistician assigned to 2-4 analyses/datasets
### HALT-C MANUSCRIPT TIMELINES

<table>
<thead>
<tr>
<th>Manuscript Abbreviated Title</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
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<tbody>
<tr>
<td>MS#24: Cog Moods/Biomarkers</td>
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<td>MS#28: TMA Long-term Follow-up</td>
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<td>MS#29: Randomized Results</td>
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<td>MS#30: Polymorphs &amp; Response</td>
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<td>MS#31: Automated SAE Reporting</td>
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<td>MS#33: QLFITs &amp; SVR</td>
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<td>MS#34: HCC Risk Factors</td>
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<td>MS#36: SF Markers in Lead-in &amp; Resp.</td>
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<td>MS#37: Changes in Hepatic Steatosis</td>
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<td>MS#40: Model to Predict Progression</td>
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<td>MS#41: Outcomes &amp; Viral Suppression</td>
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<td>MS#42: Fib Progression: Morphometry</td>
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<td>MS#43: Cognition Longitudinal</td>
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<td>MS#46: Liver Biopsy Complications</td>
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<td>MS#47: Value of Ishak Fibrosis Score</td>
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<td>MS#49: SF Markers in Rand Phase</td>
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<td>Letter: Heme Oxygenase-1 &amp; CHC</td>
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<td>MS#51: Effect of SVR on Outcomes</td>
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<td>MS#53: Long1 CTL &amp; LP Responses</td>
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<td>MS#55: Mortality Followup</td>
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<td>MS#56: Progression of Advanced CHC</td>
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<td>MS#57: Depression Longitudinal</td>
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<td>MS#58: Angiotensin Blockade &amp; Fibrosis</td>
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<td>MS#60: Gastropathy in HALT-C</td>
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<td>MS#62: Pre Study Serial Histology</td>
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<td>MS#64: HCC Incidence</td>
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**HALT-C**

**NERI**
Careful Oversight and Coordination

- Reviewed progress and priorities regularly
  - At weekly NERI Team meetings
  - At every Executive, Pub Comm & Steering Committee call
  - Used by NERI and NIDDK for forecasting
Authorship Criteria

- Authorship order had to adhere to Pub Comm guidelines
  - Writing group members listed first
  - Others listed in order of number of patients enrolled
  - Authorship required involvement in planning, analysis or writing of MS
    - contribution to concept, design, and analysis
    - role in drafting of the article and/or revising it critically for important intellectual content
Most Effective Strategies

- Concept Sheets
- Small writing groups
- Pub Comm approved analytic priorities
- Step by step publications process
- Tight control of Pub Comm reviews and approvals
- Careful planning for end of funding
Conclusions

- Goals met via collaboration and compromise:
  - Assigned authorship equitably
  - Selected publication topics
  - Determined priorities for analyses
  - Facilitated writing group activities
  - Disseminated key study results
  - Published in a broad range of high quality journals
  - 74 papers written, 60 published to date

- We collaborated successfully!
HALT-C Trial

Clinical Sites
- Liver Diseases Branch, NIDDK
- Massachusetts General Hospital and Harvard Medical School
- Saint Louis University School of Medicine
- University of Michigan Medical Center
- University of Massachusetts
- University of California - Irvine, and VA Long Beach
- University of Colorado School of Medicine
- University of Connecticut Health Center
- University of Southern California
- University of Texas Southwestern Medical Center
- Virginia Commonwealth University Medical Center

Virology Laboratory
- University of Washington, Seattle, WA

Data Coordinating Center
- New England Research Institutes, Watertown, MA

Principal Support
- National Institute of Diabetes and Digestive and Kidney Diseases – NIH, Roche

Data & Safety Monitoring Board
- Gary Davis, Guadalupe Garcia-Tsao, Michael Kutner, Stanley Lemon, Robert Perrillo