HFC Digital Health Working Group Quarterly Call
July 23, 2020

Participants:
Mitch Psotka (Chair, Inova)
David Kao (U. of Co.)
Mona Fiuzat (Duke)
Jonathan Fox (Eidos)
Elizabeth Kunkoski (FDA)
Rachel Lindstrom (Amgen)
Wei Ni (Eli Lilly)
Richard Nkulikiyinka (Bayer)
Christopher O'Connor (Inova)
Leonard Sacks (FDA)
Abhinav Sharma (McGill)
Heather Applegate (HFC)

Unable to join:
Bob Harrington (Chair, Stanford)
Tariq Ahmad (Chair, Yale)
Harlan Krumholz (Yale)
Whit Tingley (Tenaya Therapeutics)
Benoit Tyl (Servier)
Paul Varghese (Google/EMR)
Maulik Majmudar (Amazon)
Magnus Petersson (AstraZeneca)
Kuldeep Rajput (Biofourmis)
Joel Selcher (Myokardia)

Dr. O'Connor welcomed everyone to call and did introductions for new members. Due to COVID there is a great digital need for trials to augment communications and activities associated with development process.

Dr. Psotka reiterated to goal of the working group: harness digital opportunities to reform and revamp clinical trials.

Industry Reports from the COVID-19 Pandemic:
- Broad agreement on continued efforts to determine how to make trials more virtual while maintaining data integrity. Virtual and home data collections need standardization as well as validation, and novel data collection methods such as biosensors present opportunities.
- While on the surface many of the solutions such as 6-minute walk tests and actigraphy may appear straightforward, the validation and replication of data (such as intra-person and inter-person measurement errors) as well as the interpretation as a meaningful clinical outcome, remain barriers fur successful implementation.
- Patient reported outcomes (PROs) may also be useful and incorporated as remote data elements, and may be captured in a meaningful fashion. However, these also need standardization and validation with novel settings and collection mechanisms.

- Remains great interest in building up actigraphy as an acceptable and validated and reproducible clinical trial endpoint.
- Should consider the SPPB (short physical performance battery) which has been validated in the geriatric population and has been used in several NIH trials. Should investigate whether this has some validation in the home/remote setting, and how that might be remotely observed.

Digital Working Group Project Reports:

Abhinav Sharma:

1. Availability of Lean CRF data in the EHR at a single institution, manuscript currently under review at PLOS One.
2. Working on invited review on accelerometery in HF for the Canadian Journal of Cardiology. Research residents conducting the research review right now. **This should serve as a good background for proposition of standardization metrics for actigraphy.** Manuscript and data to be shared once collection complete.
3. Amazon Alexa study on screening for symptoms of Covid-19 in the hospital. In collaboration with AWS Canada Alexa: voice based technology for data collection: KCCQ can be collected, and using it to screen for COVID symptoms. Currently 60 patients screened, but finding difficult with masks, and has trouble with women>men. Particularly for elderly patients this might be useful, but usability crucially needs to be validated in this manner. Linked to a central CRF by giving each patient a number. Goal to recruit 200 patients. Will share more when data collected.

David Kao:

1. With the goal of identifying patients for clinical trial enrollment using EHR data, and then be able to extract their clinical data to the CRF: Have 6 million patients data over 10 years in OMOP in the google cloud from Colorado. Has mapped the lean CRF to the OMOP data standard, and building and testing the queries to extract data from the Colorado system for automated placement in the CRF. Using both direct Google queries as well as ATLAS queries, so that ideally anyone could use this to extract the lean CRF data elements. Then the goal is to eventually use those queries at separate institutions to show that can use this in separate institutions, and then use the AZ network in Europe with Magnus Petersson. Tentative timeline to have queries ready for sharing in 3 months, to be able to apply to a different institutions.
2. Has under review for publication exciting real-time use of COVID prediction models for a learning healthcare system.
3. Actigraphy: Has added apple watch functionality and data upload through the institutional EHR patient portal. Has not explored the granularity of the data, but this can be downloaded into the CRF; **this may serve as a method to evaluate the variability in patient actigraphy to help determine meaningful change values**.
4. Each data set from BioLINCC is now harmonized and mapped to the Lean CRF.

Richard Nkulikiyinka: Some experience with actigraphy data to report, but still in the learning process. The overall second attempt for actigraphy as part of a clinical trial was for VITALITY-HFpEF; Subset of 120 patients collected actigraphy data over about 8 months. Overall one of the major learnings is that it is difficult to find a constant device and data standard to use for each generation of clinical trials, and these are constantly changing; reiterating that standardization is needed. Data will likely be presented late 2020.

-Since actigraphy was planned but not discussed in HF-ARC 2.0, this group can take on the assignment of proposing a definition, standards for collection, and recommendation for meaningful change. Can be a short "mini" HF-ARC manuscript for actigraphy.
-D. Kao to send the BioLINCC data set to Mitch; will work together to review actigraphy data from Network trials.
-Richard N. to update group on next call with more info on actigraphy from VITALITY-HFpEF
-For automated EHR identification of patients would want to compare to coordinator screening and see if it is comparable or better than that system of patient identification.

Action Items:

1. Real World Identification of Patients for Care and Trials – Using Electronic Health Records to populate CRF

-Re-engage on previously identified action items (David Kao, lead)
(1) Determine contacts at ideal OMOP-based institutions.
(2) Reach out and encourage sites to perform this extraction once the extraction tool is ready (LEAD: David, Tariq & Mitch)
(3) Follow-up with David Kao regarding Query Construction & (4) Distribute Data Extraction Tool to pre-established contacts at OMOP-based institutions (Lead: Mitch, Tariq) DATE: Weekly? Monthly?
(4)Notify HFC members of availability of the extraction tool: HFC members should encourage the people at their own institutions who maintain that warehouse to use it, it will be purely voluntary. (LEAD: ?) DATE: TBD

2. Actigraphy:

This has been a subject of the group as an interest to validate actigraphy as a meaningful endpoint in clinical trials. Create a "mini HF-ARC" to establish and publish standards. Discussion will focus on standardized assessment and meaningful change.

1) Standardized collection; 2) Meaningful Change

- Review document for actigraphy for heart failure (Abhinav)
- Standardization proposal document for actigraphy for heart failure (Mitch, to build on scoping document)
- BioLINCC harmonized dataset (Dave to share with Mitch) for potential analysis of underlying actigraphy variability for standardization document

-Richard will share information he is able to provide to support discussions
-Wei Ni created a summary table (attached, below)
-Review all the data at next meeting and begin drafting standards.
-Invite Bill Abraham and others from HF-ARC to finalize proposals.

3. Virtual Clinical Trials

Topic for the next (Sept. 10) think tank meeting.
- HF collaboratory meeting in September: plan for session on virtual trials: **actively seeking presenters/examples for presentation** to generate discussion and learnings (all working group members, please provide recommendations).

Below is a summary of HF trials with actigraphy measurements from Wei Ni.

Accelerometer-based assessments in HF trials ---Updated on May 10th 2020- Wei Ni							
Product	Trial	Primary endpoints	Secondary endpoints	Comparator	Sample size	Device	Status/Outcome
Isosorbide Mononitrate	NEAT-HFpEF	Change at week 12 in Arbitrary Accelerometry Units (AAU) over 14-day intervals	• Daily activity -slope of daily averaged AAU • AUC of AAU during drug administration • Hours active per day	Placebo	110	KXUD9-2050, Kionix Figure S1 elastic, hip worn belt	Completed Neutral
Inorganic Nitrite	INDIE-HFpEF	Peak VO2 compared to placebo as assessed by CPET	• AAU during at least 14 days and up to 21 days	Placebo	105	Hip worn belt triaxis accelerometers (KXUD9-2050, Kionix)	Completed Neutral
Entresto (Novartis)	AWAKE-HFrEF Phase 4 Aslo see next two slides for details	AAU/min ratio during most active 30 min/day between week 8 and baseline	• Change in AAU/min during most active 30 min/day • Change in AAU/min during sleep	Enalapril	140	FDA-approved Philips Actiwatch Spectrum wrist-worn actigraphy device	Completed Neutral

Entresto (Novartis)	OUTSTEP-H FrEF Phase 3 daily physical activity continuously measured by a wrist-worn accelerometry device from -2 weeks to 12 weeks after therapy	• Change from baseline in 6MWT at week 12 • Change from baseline in mean daily non-sedentary daytime activity time over 14-day intervals	• Proportion of patients with ≥10% non sedentary daytime activity at week 12 • Change in physical activity intensity over 14-day intervals Change from baseline in peak 6 min AU calculated over 14-day intervals.	Enalapril	621	MotionWatch 8	Completed Neutral Protocol Stats plan
Empagliflozin (Investigator)	EMPIRE-HF rEF Phase 3	Change of plasma NT-proBNP over 90 days	amount of daily average accelerometer units	Placebo	190	no details disclosed	Completed Trial design
Dapagliflozin	DETERMINE-preserved	Change in 6MWT, KCCQ-TSS, KCCQ-PLS at week16	Change from baseline at the end of the study in the total time spent in light to vigorous physical activity [Week14] time spent non-sedentary	Placebo	504 (at least 100 for activity)	a wearable accelerometer	Active, not recruiting

(AZ)	Phase 3						
Dapagliflozin (AZ)	DETERMINE-reduced Phase 3	Change in 6MWT, KCCQ-TSS, KCCQ-PLS at week16	Change from baseline at the end of the study in the total time spent in light to vigorous physical activity	Placebo	313 (at least 100 for activity)	a wearable activity monitor (accelerometer) (no details disclosed)	Completed
Canagliflozin (Janssen)	CHIEF-HF Phase 3 Virtual trial 3-mon placebo controlled phase then 6-mo patients' option to switch treatment	Change from Baseline in KCCQ-TSS to Week 12	Change in Total Daily Step Count from Baseline to Week 12 Change from Baseline in KCCQ Individual Domain Scores to Week 12	Placebo	~1,900 (rEF and pEF)	fitbit	Recruiting
Vericiguat (Bayre/Merck)	VITALITY-HFpEF Phase 2	Change in KCCQ physical limitation score to week 24	Change in 6MWT ≈100 patients may consent to undergo activity tracking baseline,12-week, 24-week	Placebo	788 (~100 for activity tracking)	no details disclosed	Completed Trial Design

Omecamtiv (Amgen)	METEORIC-HF Phase 3	Peak VO2	Change in the average daily activity units measured over a 2-week period from baseline to Week 18-20	Placebo	270	no details disclosed	Recruiting
Device guided GDMT(Amgen)	HF-eVOLUTION	Time to Change or Decision That HF Therapy is Optimal			120 rEF patients	Biobeat Wrist Watch	Recruiting