Learnings from a Phase II, Open Label, Pragmatic Platform Trial I-SPY COVID

Design, Data, System & Regulatory Engagement

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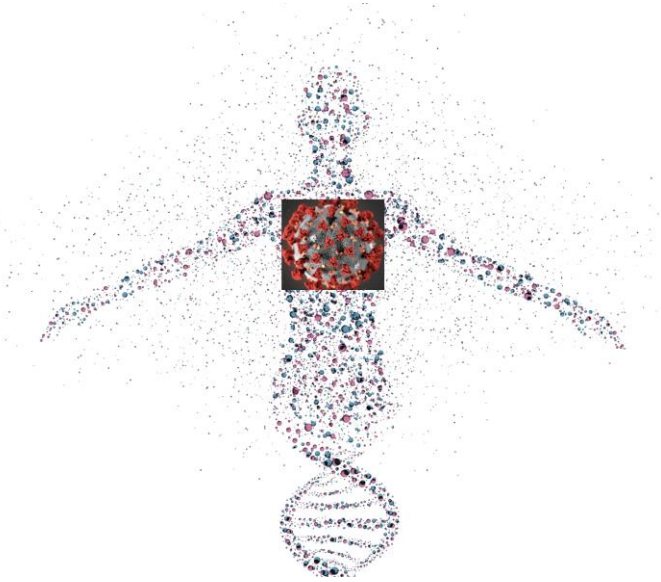
(on behalf of the I-SPY COVID Consortium)

BBSW, Nov. 3-5, 2021
Foster City, CA



Acknowledgement

- Our Patients
- I-SPY COVID Consortium
- BARDA & DTRA funding to I-SPY COVID trial through Operation Warp Speed partnership
- BBSW conference committee & volunteers

Agenda

Design

Data Strategy & Systems

Regulatory Interactions

Overall Learnings

I-SPY Trial

- I-SPY Trial is “Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And moLecular Analysis”
  - Neoadjuvant, adaptive, phase II, platform trial for locally advanced Breast Cancer since 2010
  - Started as a national public-private collaboration among NCI, FDA, more than 20 cancer research centers, and major pharma, biotech companies
  - Shaved several years and tens of millions of dollars off the drug development process.
  - Have evaluated 20+ agents over 10+ years
  - Rich in biomarker and imaging data
  - Evolved into an international model for translational research
  - https://clinicaltrials.gov/ct2/show/NCT01042379

- I-SPY COVID
  - Designed to rapidly screen high impact treatments to reduce mortality and time on ventilators.
  - Phase II, multi-center, multi-arm, open-label, randomized controlled, platform trial
  - https://clinicaltrials.gov/ct2/show/NCT04488081
- Quantum Leap Healthcare is the sponsor of I-SPY trials.

PIs:

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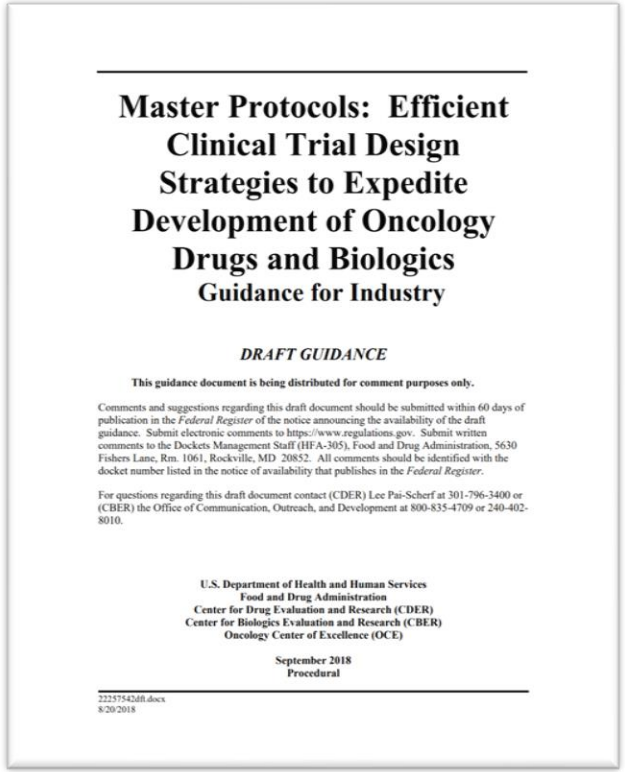
Carolyn Calfee, MD

Kathleen Liu, MD

COVID Drug Development : Challenges

- Urgent needs to rapidly screen promising agents
- New variants & hotspots
- Shift in patient populations, behavior
- Tight timeline of trial data collection, data cleaning & reporting
- Critically ill patients in ICU setting
  - Site implementation/activation
  - Motivate enrollment
  - Burden of data collections/cleaning

Platform Trial using Master Protocols



Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Lee Pai-Scherf at 301-796-3400 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2018
Procedural

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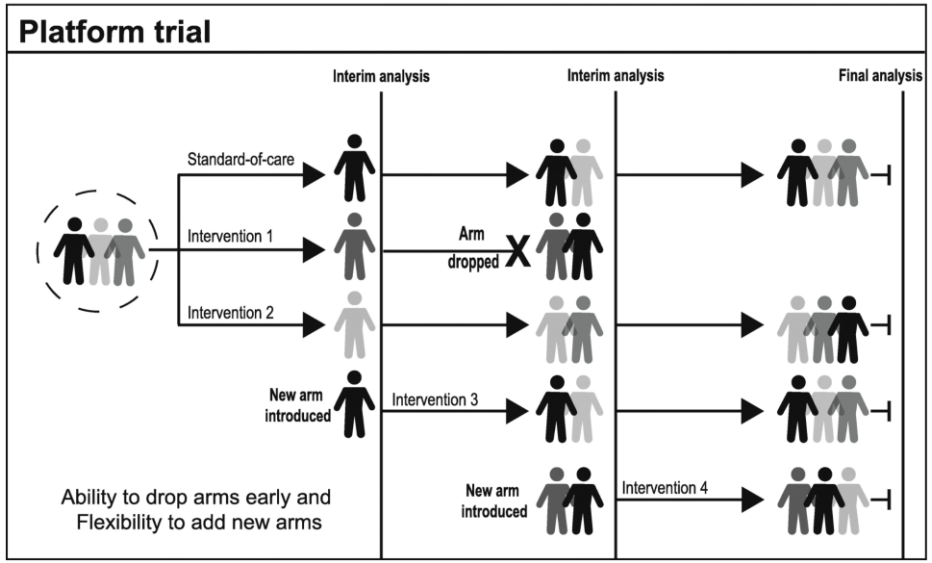


"In contrast to traditional trial designs, where a single drug is tested in a single disease population in one clinical trial, master protocols use a single infrastructure, trial design, and protocol to simultaneously evaluate multiple drugs and/or disease populations in multiple substudies, allowing for efficient and accelerated drug development."

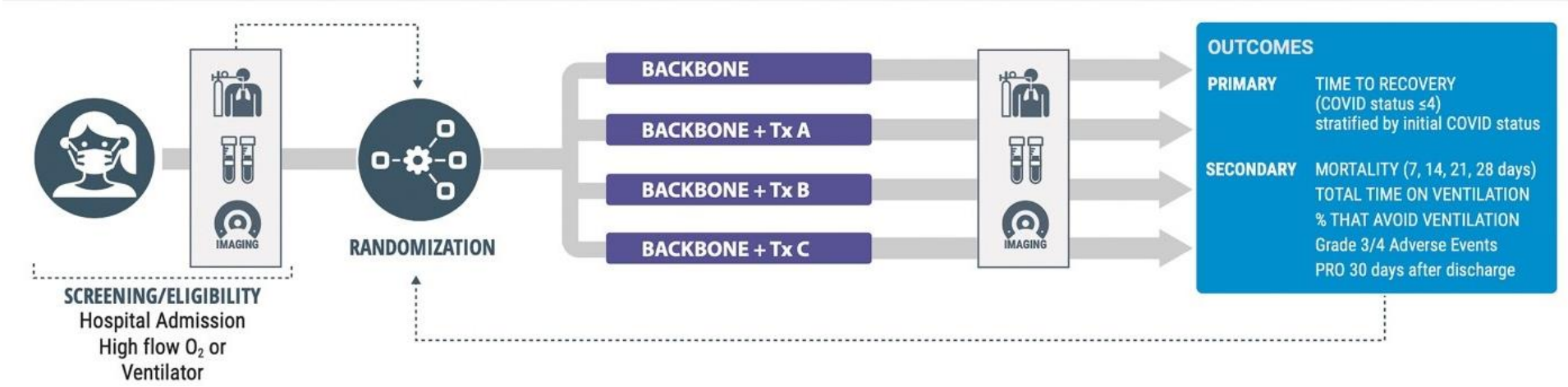
Figure from: Park, J.J.H., Siden, E., Zoratti, M.J. et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials 20, 572 (2019). https://doi.org/10.1186/s13063-019-3664-1

Design: Trade-offs

- More complex
- More challenging to accrue
- Complexity limits trial settings
- Higher numbers per arm

- Pragmatic
- Nimble
- Phase 2 signal finding
- Rapid searching for big signals to improve mortality and ventilator-free

Design – Set Up



- Primary and secondary outcomes follow-up up to 4-months
- Pre-specified interim analysis every 2 weeks – allow quick decision making
- Pre-specified Observational cohort with similar clinical stages of COVID-19 followed via medical records for those who decline to participate in the interventional arms.
- Pre-specified biospecimen collection for biomarker sub-studies
- ePRO (patient reported outcome) as exploratory analysis

Design - Open Label

- Platform design; up to 4 investigational agents + backbone control
  - If blinded, the complexity of multiple placebos should not be underestimated
  - Implementation issues across a wide diversity of sites
- Having more than one agent improves the benefit of shared controls
  - Analysis is to compare the investigational agent vs concurrent controls
- Monitor patient population and AEs to understand the biases
- Design is to be liberal in identifying a signal
  - Be ready to transition if seeing big signals
- Access to information
  - Tabular results of study outcomes by treatment allocation are not available to the research team, clinical investigators, clinical teams, or members of the steering committee.
  - The DMC and trial statisticians are unblinded.

Design- Statistical Considerations

Design considerations

- Family of endpoints to define graduation/futility criteria (time to recovery, overall mortality)
- How large of effect size is good enough?
- Use of concurrent controls
- Randomization ratios with different # of arms in the trial
- Interim analysis to allow quick decisions to drop agents, but need to understand the impact on type 1 errors with frequent interim looks

Simulations

- Assumptions of true efficacy
- Assumption of accrual rates over time
- Assumption of COVID baseline distribution, recovery rate, mortality rate
- Number of agents in the trial

Design- Statistical Considerations

- Graduation: at least 50 evaluable patients enrolled to the treatment arm
- Futility: at least 40 evaluable enrolled in the arm
- Calculate the posterior probability of hazard ratio (adjusted for baseline clinical factor), with priors for:
  - Intercept
  - Coefficients

Stopping criteria

- Graduation: $Pr(csHR_{\text{recovery}} > 1.0 | \text{ data}) \geq 0.975$ or $Pr(HR_{\text{death}} < 1.0 | \text{ data}) \geq 0.900$
- Futility: $Pr(csHR_{\text{recovery}} < 1.5 | \text{ data}) \geq 0.900$ and $Pr(HR_{\text{death}} < 1.0 | \text{ data}) \leq 0.500$
- Safety: $Pr(csHR_{\text{death-without-recovery}} > 1.3 | \text{ data}) \geq 0.700$

Data Strategy & System

Data Strategy

- Risk based monitoring
  - ✓ Focus quality control on the key data elements.
  - ✓ Prioritize monitoring, cleaning, reporting based on purpose. Phased approach.
- RWD/RWE from Observational cohort to monitor
  - ✓ Change in underlying patient characteristics (age, comorbidities, mortality rate)
  - ✓ Patient behavior in declining consents and/or switching to observational cohort

Data System

- OneSource is to integrate clinical care and research by streamlining the collection and distribution of patient health data
  - ✓ Improve data quality and speed through source capture via EHR integration.
  - ✓ Critical clinical data is entered once at the point of care and accessible to clinical providers and researchers.
  - ✓ Utilizes global data standards to integrate clinical care and research.
- Automated laboratory CTCAE v5.0 toxicity grading, and reporting integrated in EDC

Data System
Reducing Burden of Data Entry & Verification in ICU

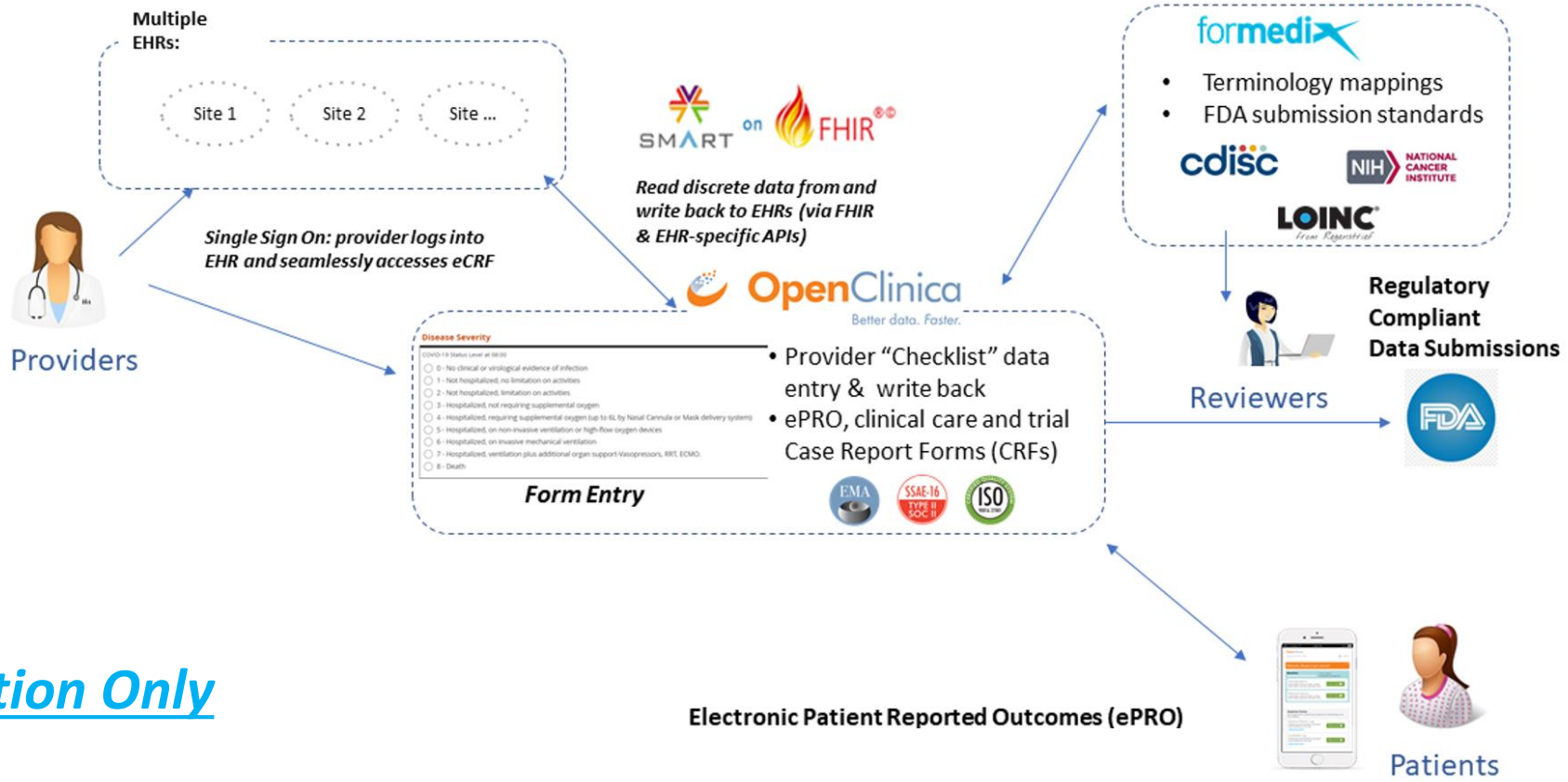


Illustration Only

https://www.fda.gov/science-research/advancing-regulatory-science/source-data-capture-electronic-health-records-ehrs-using-standardized-clinical-research-data

Biomarker Subtyping

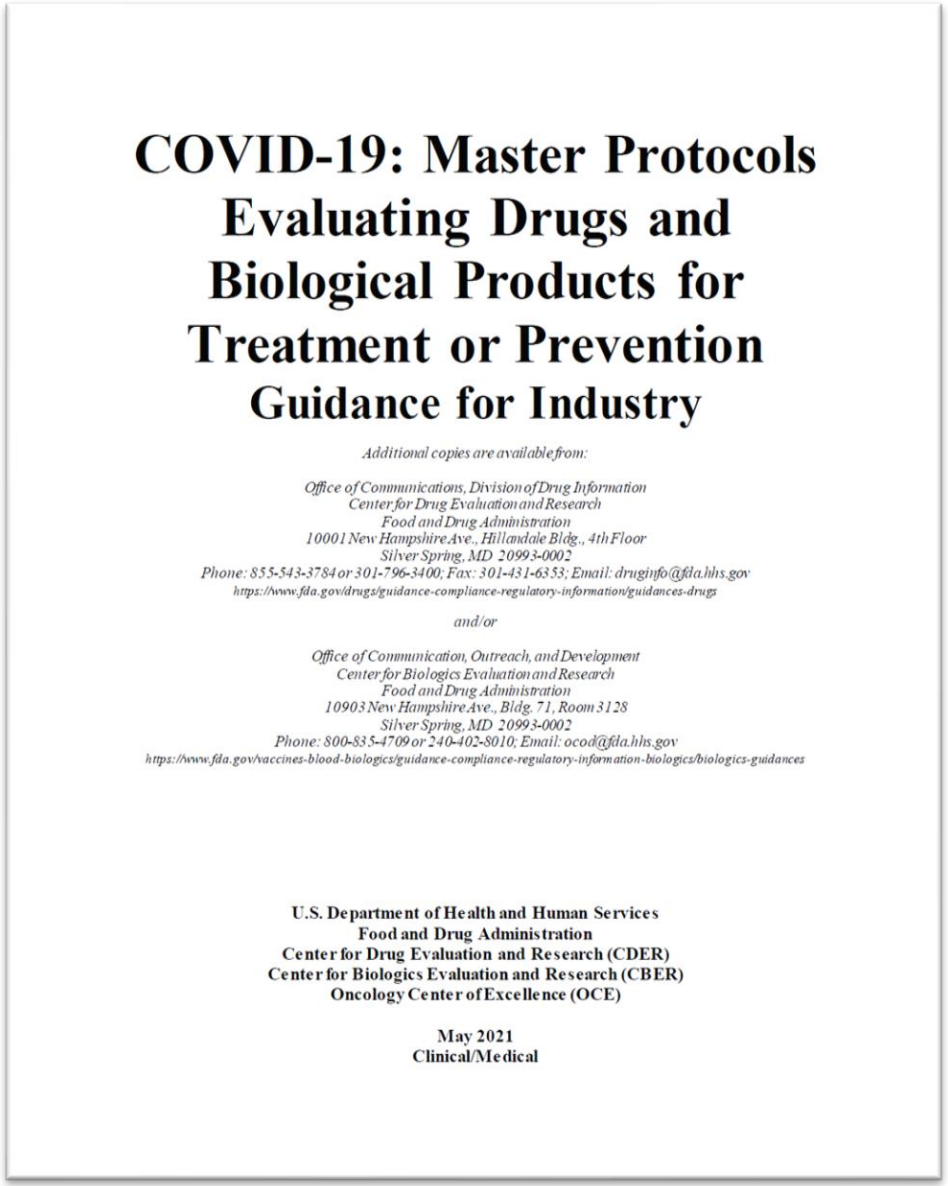
- Biomarker or disease subtyping is a promising pathway for COVID/ARDS for bigger signals in subgroup(s).

- Progress in treating difficult diseases with high mortality has come from better understanding the biology
  - Smaller targeted trials using biomarkers have demonstrated success.
  - Currently using central lab to process biospecimens
  - Implementation at sites could be a challenge if real-time biomarker assessment at sites

Regulatory Interactions

- Early and often engagement with FDA
  - FDA encourages master protocols and welcome dialogue with sponsors
  - Discuss/communicate with the FDA:
    - Study designs
    - Statistical consideration & decision rules
    - Data operation strategies & monitoring
    - Requirements of regulatory reporting
  - Leadership presents a clear and consistent core goal/philosophy to guide decision-making.

- What's next after signal finding?
  - How to confirm?
  - How/when to transition?



COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

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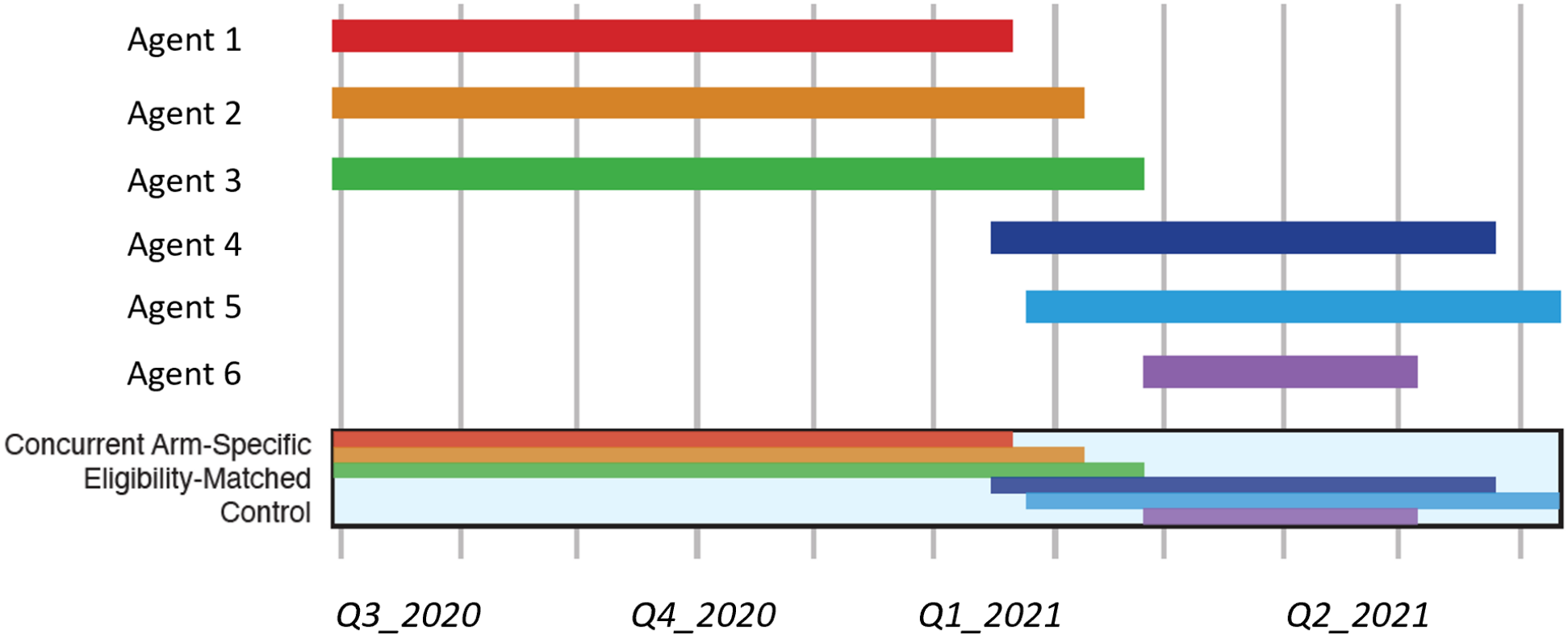
Clinical/Medical

Trial to Date

- Trial planning started in March 2020. Enrollment began in July 2020.
- Enrolled over 2,000 subjects at >25+ sites
- Tested 10+ regimens
- Improved efficiency and process
  - Accelerated the process of getting drugs approved for activation with FDA
  - Data completion
  - Data system innovation: OneSource substantially decreases work-load and increases accuracy of data captured
- Learned patient behavior in willingness to enroll

Enrollment Timeline
(Illustration using the first 6 investigational agents)



Overall Learnings

Design: balance pragmatism, safety, and discovery in the context of a phase 2 signal finding trial, even during a pandemic.

- Powerful and efficient to rapidly screen for big signals
- Enable biomarker sub-studies to investigate biological heterogeneity; may see bigger signals in subgroups

Data strategy & system: innovative and pragmatic data strategy could ease the burden of time-sensitive trial when resources are over stretched at sites.

- A moderately pragmatic approach to streamlined data collection
- Automate data collection from EHR using OneSource
- Automated lab toxicity grading and reporting in EDC

Regulatory engagement early and often

References

- Beyersmann, Jan, et al. Simulating competing risks data in survival analysis. *Statistics in medicine* 28.6 (2009): 956-971
- OneSource white paper: https://www.fda.gov/science-research/advancing-regulatory-science/source-data-capture-electronic-health-records-ehrs-using-standardized-clinical-research-data
- https://www.appliedclinicaltrialsonline.com/view/how-to-address-and-overcome-operational-challenges-in-master-protocol-studies
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-master-protocols-evaluating-drugs-and-biological-products-treatment-or-prevention
- https://www.nih.gov/research-training/medical-research-initiatives/activ
- https://www.fda.gov/science-research/advancing-regulatory-science/source-data-capture-electronic-health-records-ehrs-using-standardized-clinical-research-data
- Park, J.J.H., Siden, E., Zoratti, M.J. et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials 20, 572 (2019). https://doi.org/10.1186/s13063-019-3664-1