LEADERSHIP IN INNOVATION AND COLLABORATION

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GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH
Biostatistics

Outline

- Introduction – my career
- Leadership
  - Skills needed for successful collaboration
  - Teaching leadership
  - ASA Leadership Institute
- Case study: ASA statement on p-values
- Collaboration and innovation in industry and regulatory agencies
- Case study: ACTIV trials in Covid-19
- Conclusion

INTRODUCTION

My Career

- 16 years in non-profit research
  - Sample surveys and clinical trials
  - Introduction to management
- 10 years in pharmaceutical sector
  - Large global CRO and small start-up biopharm company
  - Increasing management responsibilities to VP level
- 11 years in academia (divided with govt service)
  - Coordinating center (CC) director (longest running NIH CC); CC PI on trials and epid studies
  - Taught clinical trials, statistical consulting, statistical leadership, and regulatory science
  - Developed MPH degree in public health data science (2019)
  - Dept Chair 2020 to date
- 6 years leading the Office of Biostatistics, CDER, FDA (2011-2017)

LEADERSHIP

Some basic concepts

Leadership

- Leadership skills needed for successful collaboration
  - Influence
  - Knowledge
  - Communication
  - Consensus building

Leadership Basics

- "Leadership is a process whereby an individual *influences* a group of individuals to achieve a common goal"
- "*Influence* is the sine qua non of leadership. Without *influence*, leadership does not exist."
- Note that we are defining leadership as a process rather than a set of innate qualities → leadership can be learned and is available to everyone, not just a pre-determined few
- Assigned vs emergent leadership
  - Assigned is based on the position occupied through authority conferred
  - Emergent is acquired through others supporting/accepting the individual as leader
- Leading a multi-disciplinary team requires emergent leadership
  - Characteristics for success include intelligence and confidence

Ref. Northouse (*Leadership: Theory and Practice*, 8th Edition, Los Angeles: Sage Publications, 2019)

Leadership Skills

- Influence
  - How to achieve a level of power sufficient to have influence over others?
  - Influence is particularly important for team leadership, because there is often no direct line of administrative authority between team leader and team members
- Expert power and referent power (Katz & Kahn, 1978)
  - Expert power derives from the critical and unique role that we as statisticians have, based on our education and statistical science skills; with time and experiences this same expertise then extends to team leadership skills
  - Referent power flows directly from the camaraderie of team members working together to achieve common goals and helping each other in a unifying effort

Ref. Northouse (2019) *Leadership: theory and practice.* 8th Edition, Los Angeles: Sage Publications.
Ref. Katz, D., & Kahn, R. L. (1978). *The social psychology of organizations*. New York: Wiley.

Importance of Influence

- Importance of statistician's influence in research teams

  "It is a common mistake to assume that the statistician need only be concerned with the analysis of results. …I think an experienced statistician should be a collaborating scientist in ensuring that both protocol design and interpretation of trial findings conform to sound principles of scientific investigation. In addition, the statistician is in a good position to act as policeman in ensuring that satisfactory organizational standards are maintained throughout a trial." (Pocock,1983,p.35)

Leadership Skills

- Knowledge
- Statistical knowledge and skills are essential
- In-depth understanding of content area is, as well
- Both needed for statisticians to be collaborators and not just consultants, to have a seat at the decision-making table
- Formal education and training is just the beginning
  - Field is constantly evolving, and statisticians must stay current

Leadership Skills

- Communication
- Effective communication
  - Requires being able to express yourself in a way that does not detract from the logic and science of your work
  - When successful, both parties sufficiently understand the science of the other's discipline
- As a statistician, you communicate to a variety of audiences in a variety of circumstances
  - Must be able to account for differing points of view
  - Must have ability to speak to others with different and varied skill sets, interests, and knowledge

Leadership Skills

Communication behaviors of emergent leaders:

- Being verbally involved
- Being informed
- Seeking others' opinions
- Initiating new ideas
- Being firm but not rigid

"We know that communication is a problem, but the company is not going to discuss it with the employees."

Ref: Fisher, Aubrey (1980). *Small group decision making: communication and the group process.* McGraw-Hill.

Leadership Skills

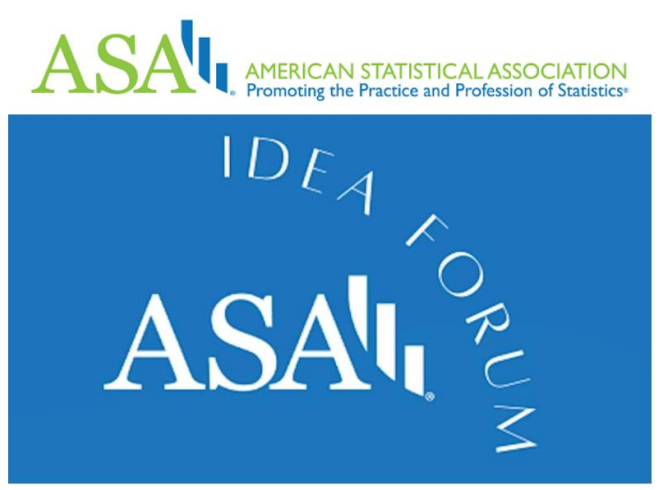
- Consensus building
- Effective leaders move a group towards a decision or action efficiently
- A commonly used and often successful definition of consensus:
  - Everyone may not agree, but no one disagrees to the extent that they are willing to hold the group back because of their disagreement
- We can draw on our training and experience as a statistician in leading a group to a decision

Teaching Leadership

- Biostatistics education
  - Methods versus applications
  - Limitations imposed by time in program and current rewards system
  - Collaboration versus consulting
- Formal coursework
  - Statistical consulting
  - Statistical leadership
- Continuing education opportunities in leadership

ASA Leadership Institute

- 2018 ASA Presidential Initiative
- 3 career points with opportunities for leadership awareness and training:
  - Graduate school → leadership challenge for ASA Student Sections
  - Early- to mid-career→ leadership cohort training modules in cultural competency, decision analytics, and strategic presence
  - Late career →C-suite event
- Expert witness training
- 2022 ASA Presidential Initiatives – Influencing Discovery, Exploration, and Action (IDEA) Forum Nov. 18
  - Goal is to build strategic partnerships with leaders from academe, government, and industry to grow the influence of statisticians and drive innovation
  - Climate science is 1st IDEA topic



ASA STATEMENT ON P-VALUES

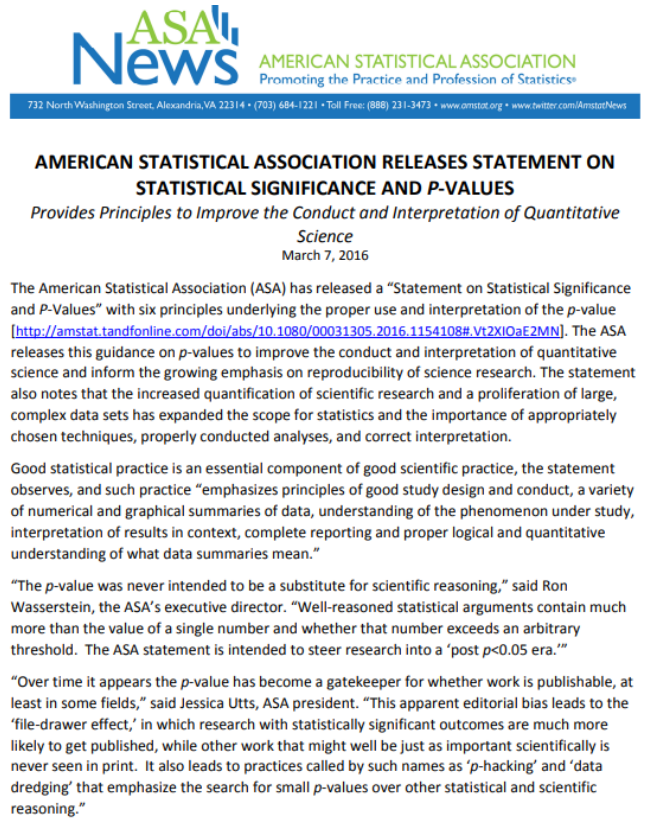
Case Study

ASA Statement on P-Values

- Series of articles appearing between 2010-2014 led to renewed discussion of p-values and their role in statistical inference among ASA Board members (see, e.g., Nuzzo, 2014)
- When a psychology journal decided to take things a step further and ban p-values from all published articles, the Board felt a call to action!
- ASA task force was formed with a charge to develop an official statement about statistical significance and p-values that would be issued by ASA
- Task force agreed upon a formal statement "clarifying several widely agreed upon principles underlying the proper use and interpretation of the *p*-value."

ASA Statement on P-Values

- Published in The American Statistician (TAS) with >20 commentaries from committee members
- Unusual step for ASA Board – does not typically wade into methods discussions



ASA News
AMERICAN STATISTICAL ASSOCIATION
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AMERICAN STATISTICAL ASSOCIATION RELEASES STATEMENT ON STATISTICAL SIGNIFICANCE AND *P*-VALUES

Provides Principles to Improve the Conduct and Interpretation of Quantitative Science

March 7, 2016

The American Statistical Association (ASA) has released a "Statement on Statistical Significance and *P*-Values" with six principles underlying the proper use and interpretation of the *p*-value [http://amstat.tandfonline.com/doi/abs/10.1080/00031305.2016.1154108#.Vt2XIOaE2MN]. The ASA releases this guidance on *p*-values to improve the conduct and interpretation of quantitative science and inform the growing emphasis on reproducibility of science research. The statement also notes that the increased quantification of scientific research and a proliferation of large, complex data sets has expanded the scope for statistics and the importance of appropriately chosen techniques, properly conducted analyses, and correct interpretation.

Good statistical practice is an essential component of good scientific practice, the statement observes, and such practice "emphasizes principles of good study design and conduct, a variety of numerical and graphical summaries of data, understanding of the phenomenon under study, interpretation of results in context, complete reporting and proper logical and quantitative understanding of what data summaries mean."

"The *p*-value was never intended to be a substitute for scientific reasoning," said Ron Wasserstein, the ASA's executive director. "Well-reasoned statistical arguments contain much more than the value of a single number and whether that number exceeds an arbitrary threshold. The ASA statement is intended to steer research into a 'post $p<0.05$ era.'"

"Over time it appears the *p*-value has become a gatekeeper for whether work is publishable, at least in some fields," said Jessica Utts, ASA president. "This apparent editorial bias leads to the 'file-drawer effect,' in which research with statistically significant outcomes are much more likely to get published, while other work that might well be just as important scientifically is never seen in print. It also leads to practices called by such names as '*p*-hacking' and 'data dredging' that emphasize the search for small *p*-values over other statistical and scientific reasoning."

ASA Statement on P-Values

- Ability to agree on the official statement, while still retaining many different opinions about what was next, led ASA to organize a symposium to continue the conversation
  - Symposium on Statistical Inference (SSI) held in October 2017
  - Attendance limited to engage discussion among all attendees
  - Invited speakers and panelists selected to cover a range of opinions about next steps
- All SSI speakers invited to contribute to the special issue of the *American Statistician*
  - 3 guest editors selected
  - 43 articles appeared in the special issue
  - Audience = all users of p-values, regardless of profession
- Accompanying editorial included a provocative call to action:

  "We conclude, based on our review of the articles in this special issue and the broader literature, that it is time to stop using the term 'statistically significant' entirely."
  - The editorial goes on to give four principles for action in a post-statistical-significance world: Accept uncertainty, be thoughtful, be open, and be modest (ATOM)

ASA Calls Time on 'Statistically Significant' in Science Research

Scientists should stop using the term "statistically significant" in their research, urges the authors of an editorial in a newly published special issue of *The American Statistician*.

The issue, *Statistical Inference in the 21st Century: A World Beyond p<0.05*, calls for an end to the practice of using a *p*-value of less than 0.05 as strong evidence against a null hypothesis or a value greater than 0.05 as strong evidence favoring a null hypothesis. Instead, *p*-values should be reported as continuous quantities and described in language stating what the value means in the scientific context.

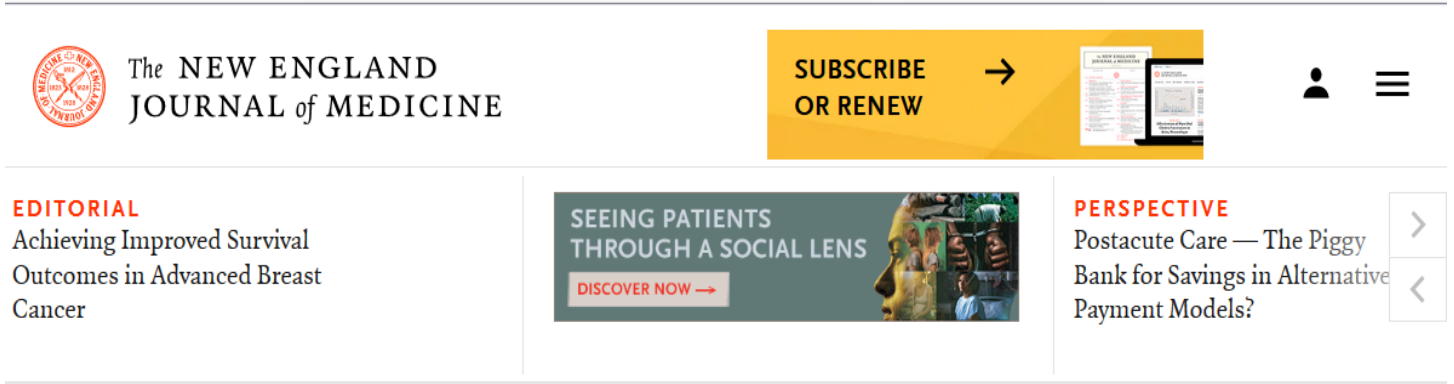
Containing 43 papers by statisticians from around the world, the special issue is expected to lead to a major rethinking of statistical inference by initiating a process that ultimately moves statistical science—and science itself—into a new age.

In the issue's editorial, Ronald Wasserstein, executive director of the ASA; Allen Schirm, retired from Mathematica Policy Research; and Nicole Lazar of the University of Georgia said:

> Based on our review of the articles in this special issue and the broader literature, we conclude that it is time to stop using the term 'statistically significant' entirely.
>
> No *p*-value can reveal the plausibility, presence, truth, or importance of an association or effect. Therefore, a label of statistical significance does not mean or imply that an association or effect is highly probable, real, true, or important. Nor does a label of statistical nonsignificance lead to the association or effect being improbable, absent, false, or unimportant.
>
> For the integrity of scientific publishing and research dissemination, therefore, whether a *p*-value passes any arbitrary threshold should not be considered at all when deciding which results to present or highlight.

Example of Impact of ASA P-Value Initiatives

"The new guidelines discuss many aspects of the reporting of studies in the *Journal*, including a requirement to replace P values with estimates of effects or association and 95% confidence intervals when neither the protocol nor the statistical analysis plan has specified methods used to adjust for multiplicity."



EDITORIAL

New Guidelines for Statistical Reporting in the *Journal*

David Harrington, Ph.D., Ralph B. D'Agostino, Sr., Ph.D., Constantine Gatsonis, Ph.D., Joseph W. Hogan, Sc.D., David J. Hunter, M.B., B.S., M.P.H., Sc.D., Sharon-Lise T. Normand, Ph.D., Jeffrey M. Drazen, M.D., and Mary Beth Hamel, M.D., M.P.H

July 18, 2019
N Engl J Med 2019; 381:285-286
DOI: 10.1056/NEJMe1906559
Chinese Translation 中文翻译

SIGNIFICANCE
ROYAL STATISTICAL SOCIETY
ASA AMERICAN STATISTICAL ASSOCIATION

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April 2021
Pages 16-19

Features

The *p*-value statement, five years on

Robert Matthews

First published: 26 March 2021 | https://doi.org/10.1111/1740-9713.01505

Read the full text >

PDF TOOLS SHARE

Abstract

The American Statistical Association's 2016 *p*-value statement generated debates and disagreements, editorials and symposia, and a plethora of ideas for how science could be changed for the better. Now, five years on, **Robert Matthews** asks what, if anything, has the statement achieved?

"Yet, ending the pandemic of unreliable research driven by NHST requires pragmatic acceptance that all inferential methods can mislead, but some are far more misleading than others. Unless researchers get the help they need from the statistical community soon, the threat posed by NHST could prove fatal to the scientific enterprise."

ASA Statement on P-Values

- Unintended sequelae of the official statement and TAS special issue:
  - Some were worried the statistician's role would be diminished with less demand for hypothesis tests and p-values
  - More serious problem (in my opinion) is that others (journal editors, e.g.) are deciding when p-values are appropriate, rather than statisticians!
- Error in anticipation, faulty leadership, or other?

COLLABORATION AND INNOVATION IN DRUG DEVELOPMENT

Industry and Regulatory Agencies

Role of the Statistician

- Industry experience
  - Leading groups of statisticians
  - Leading a development program
  - Leading innovation
- FDA experience
  - Collaboration versus consulting
  - One-way communication channel between clinicians and statisticians
  - We can learn from our pharmacometrics colleagues
  - Whose statistical analysis is this, anyway?
- Example: precision medicine and master protocols

Precision Medicine and Master Protocols

- Personalized medicine is getting the right product to the right patient (and in case of a drug or biologic) at the right dose
- Key challenge is to identify targeted subgroups at the right stage
- As medicines (or their targets) become more precise, traditional clinical trials become more difficult to conduct and/or less efficient
- Patients may need to be screened (sequentially) for several trials before finding an eligibility match
- Collaborations such as master protocols are of increasing interest, as a result
- At FDA--observed sponsors competing for patients, esp. in rare diseases or disease subsets
- Leveraged regulatory authority to encourage collaboration among sponsors for benefit of patients
- Advocacy of master protocols grew out of this desire → Woodcock and LaVange (NEJM, 2017)

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

HIGH-QUALITY EVIDENCE IS WHAT WE USE TO GUIDE MEDICAL PRACTICE. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease definitions. The common denominator is a need to answer more questions more efficiently and in less time.

A methodologic innovation responsive to this need involves coordinated efforts to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structure.[1-4] Such efforts are referred to as master protocols, defined as one overarching protocol designed to answer multiple questions. Master protocols may involve one or more interventions in multiple diseases or a single disease, as defined by current disease classification, with multiple interventions,

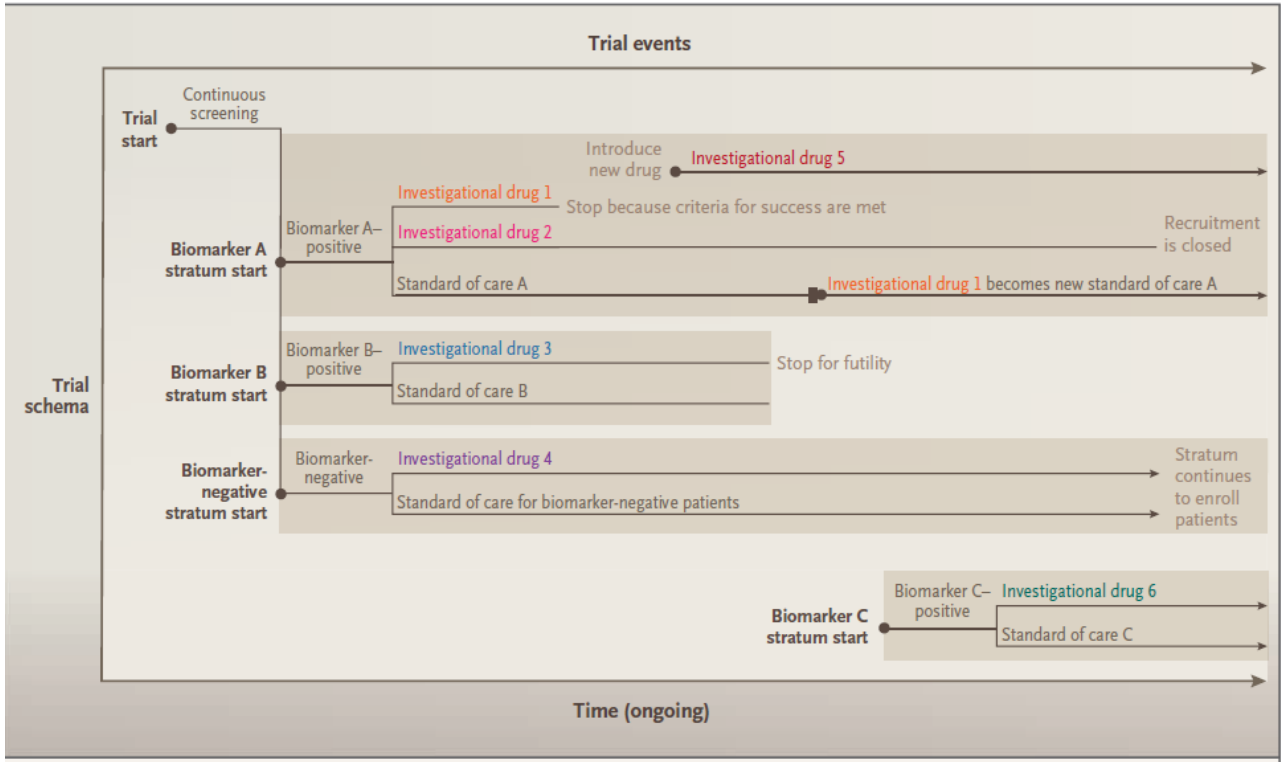


Figure 2. Potential Design of a Platform Trial Involving a Single Disease.

Master Protocols

- Multiple diseases, multiple patient subgroups (biomarker-defined), and/or multiple therapies studied under one, over-arching protocol
- Also known as:
  - Umbrella trials: one disease, multiple drugs (example: NCI Match)
  - Basket trials: one drug, multiple disease cohorts (example: B225 trial of imatinib)
- Exploratory: Identify best treatment for biomarker-defined patient subgroup (example: I-SPY II)
- Confirmatory: Evaluate different therapies relative to control for a single disease in parallel (example: Lung MAP)
- Capitalize on similarities among trials and shared infrastructure to realize efficiencies
- Need regulatory buy-in
- Need sponsors willing to test drugs in collaboration with others

Master Protocols -- Terminology

Several dimensions sometimes confused in talking about complex innovative designs – *consider the case of studying multiple therapies for a single disease*

- Master protocol simply refers to the study of more than one drug with a single protocol
  - Protocol document stands alone, without reference to specific drugs
  - Amendments used to provide details of each drug
- Platform trial refers to establishing the trial infrastructure and master protocol as a perpetuating effort, with drugs entering and leaving the platform
- Adaptive trial refers to a trial in which one or more design parameters may be modified during the trial
  - Platform trials are adaptive, because the analyses used to determine when a drug is discontinued (for futility or early evidence of efficacy) constitute adaptations to the design
- Bayesian vs frequentist refers to the statistical methods used for adaptations, data analysis, and decision making based on trial results.
  - Some features of adaptive platform trials align well with Bayesian methods

Master Protocols – Innovation

Two avenues for innovation:

1. Establish a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data sharing and new data collection
2. Develop a common protocol for the network that incorporates innovative statistical approaches to study design and data analysis

Innovative Design Possibilities

- Adaptive randomization (response adaptive or covariate adaptive)
- Sharing of control groups – when it makes sense, e.g., within a specific pathway or biomarker-defined subgroup
- Use of external or historical control data
  - In single-arm studies, or
  - In conjunction with concurrent controls (with 2:1 or higher) to increase power; potential adaptation
- Model-based analysis methods (e.g., hierarchical Bayes) for pooled analysis of multiple diseases or tumor types, markers, body sites, etc.
- Precision medicine analysis to refine target subgroups
  - Adaptive enrichment

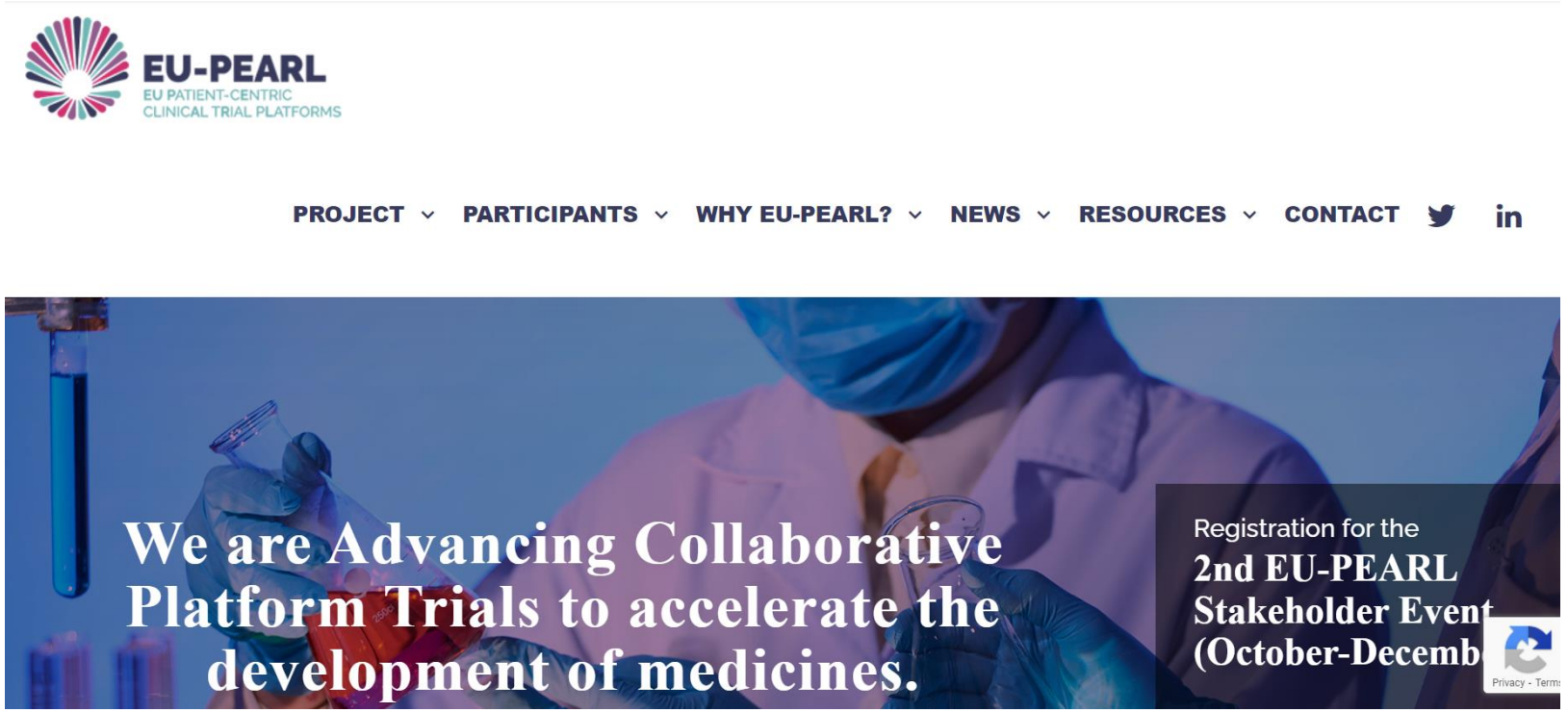
Leading the Innovation Discussion

Example: Multiplicity
EU-PEARL workshop
Oct 2020

Concept of trial success:

- Multiple drugs
- Multiple diseases

Impact of 'traditional' statistical thinking on innovation



Multiplicity in Master Protocols

- Multiple questions addressed in a single protocol →multiplicity issues should be carefully considered
- Phase 2 screening trials of multiple agents to evaluate which agents warrant further study
  - Decisions about agents independent of other agents
  - Trial is successful if an answer is obtained about each agent and not dependent on if any, or how many, agents graduate
- Phase 3 confirmatory trials evaluating therapies in parallel, each relative to a control
  - Concept of Type I error probability applies to each agent, independent of the other agents in the study
- For both cases, multiplicity adjustment not needed from a regulatory standpoint

Ref. Woodcock and LaVange, *NEJM*, 2016

Multiplicity in Master Protocols

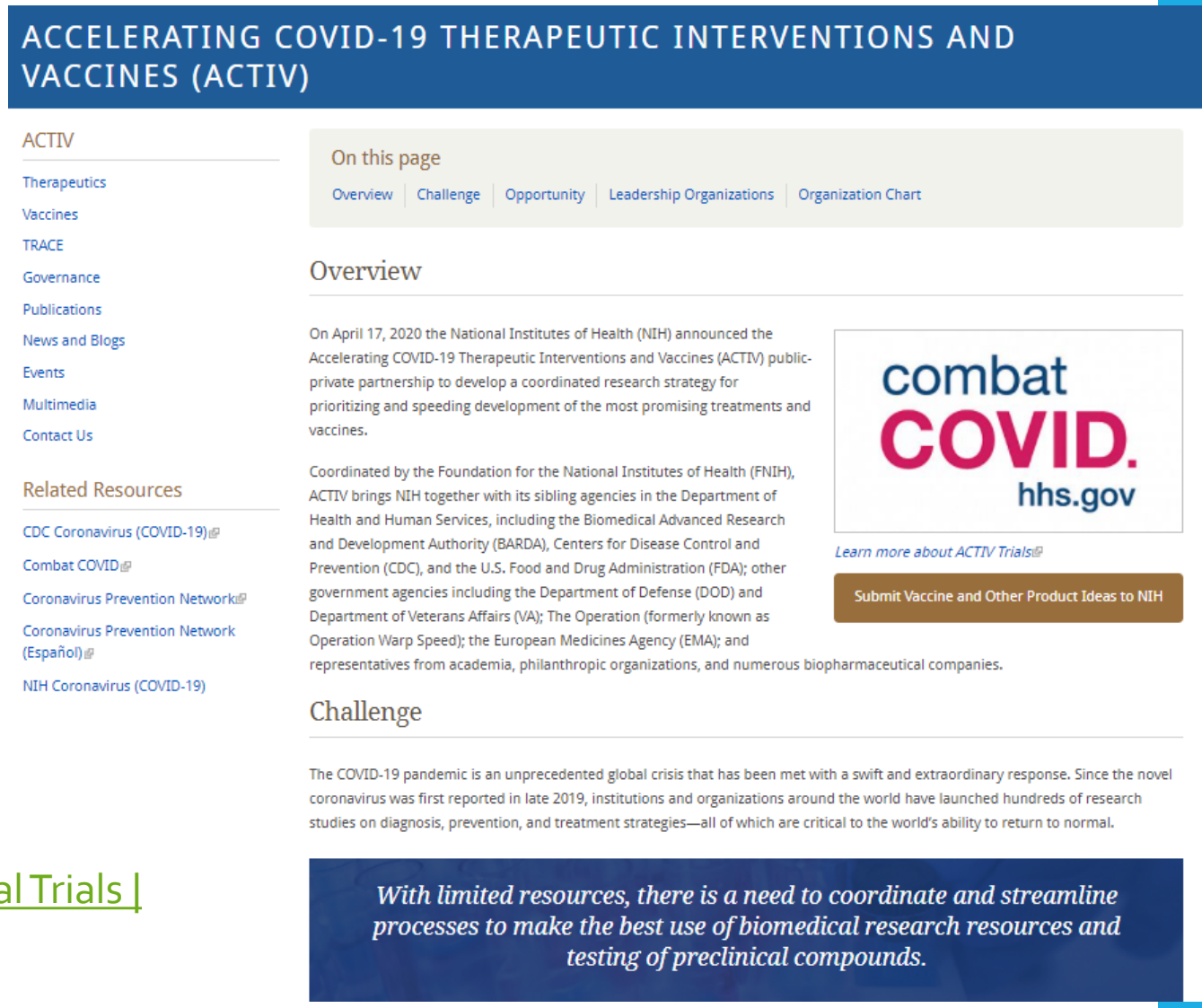
- Additional considerations
  - If goal of master protocol is to encourage collaboration among sponsors, requiring multiplicity adjustments across agents in the protocol would be counter-productive
  - Success as an agent-specific concept is straightforward to interpret
  - Success for the entire master protocol is measured by the ability of the protocol to address questions about each agent and not by the number of agents showing benefit
  - If agents enter and leave at different times, and decisions are made for each agent as it completes, issues of multiplicity become complicated

ACTIV

Case Study in Innovation and Collaboratio

Master Protocols in a Pandemic

- Development and implementation of the ACTIV Master Protocols incorporated innovative trial designs to respond to the emerging pandemic (beginning April 2021 to date)
- Lessons learned from the ACTIV experience provide a guide for addressing the next pandemic



ACCELERATING COVID-19 THERAPEUTIC INTERVENTIONS AND VACCINES (ACTIV)

ACTIV

Therapeutics
Vaccines
TRACE
Governance
Publications
News and Blogs
Events
Multimedia
Contact Us

Related Resources

CDC Coronavirus (COVID-19)
Combat COVID
Coronavirus Prevention Network
Coronavirus Prevention Network (Español)
NIH Coronavirus (COVID-19)

On this page

Overview | Challenge | Opportunity | Leadership Organizations | Organization Chart

Overview

On April 17, 2020 the National Institutes of Health (NIH) announced the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership to develop a coordinated research strategy for prioritizing and speeding development of the most promising treatments and vaccines.

Coordinated by the Foundation for the National Institutes of Health (FNIH), ACTIV brings NIH together with its sibling agencies in the Department of Health and Human Services, including the Biomedical Advanced Research and Development Authority (BARDA), Centers for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA); other government agencies including the Department of Defense (DOD) and Department of Veterans Affairs (VA); The Operation (formerly known as Operation Warp Speed); the European Medicines Agency (EMA); and representatives from academia, philanthropic organizations, and numerous biopharmaceutical companies.

combat COVID. hhs.gov

Learn more about ACTIV Trials

Submit Vaccine and Other Product Ideas to NIH

Challenge

The COVID-19 pandemic is an unprecedented global crisis that has been met with a swift and extraordinary response. Since the novel coronavirus was first reported in late 2019, institutions and organizations around the world have launched hundreds of research studies on diagnosis, prevention, and treatment strategies—all of which are critical to the world's ability to return to normal.

With limited resources, there is a need to coordinate and streamline processes to make the best use of biomedical research resources and testing of preclinical compounds.

[COVID-19 Therapeutics Prioritized for Testing in Clinical Trials | National Institutes of Health (NIH)]

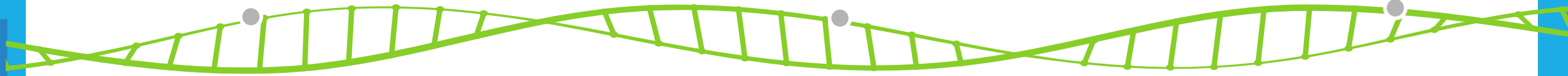
ACTIV Stakeholders

ACTIV is being coordinated by the Foundation for the National Institutes of Health (FNIH), and has brought together multiple partners from government, industry and non-profits.

8
Government Partners

20
Industry Partners

4
Non-Profits



BARDA
CDC
Department of Defense
European Medicines Agency
U.S. Food & Drug Administration
Operation Warp Speed
NIH
Department of Veterans Affairs
FNIH

abbvie
AMGEN
AstraZeneca
Bristol-Myers Squibb
dewpoint$_{tx}$
Eisai
Lilly
gsk
Johnson & Johnson
MERCK
moderna
NOVARTIS
RHYTHM THERAPEUTICS
Roche Genentech
Pfizer
SANOFI
Takeda
NOVAVAX
VIR

Bill & Melinda Gates foundation
Fred Hutch Cures Start Here
RTI International
FNIH

Master Protocol | Overview

ACTIV-1

Trial launched on Oct 15, 2020

- Inpatient, Phase III Master Protocol
- 3 Host-targeted Immune Modulators
  - Abatacept, Cenicriviroc, Infliximab
- Sample Size (Pts per Arm): 540
- NCATS TIN + DCRI + TRI

- 1971 pts enrolled (*final enrollment*) – (1291 from U.S. sites, 680 from Latin America sites)
- **Cenicriviroc** closed in Sep 2021 due to DSMB recommendation on futility; **Infliximab** reached target enrollment and closed Dec 20; **Abatacept** reached target enrollment and closed Dec 30
- **Topline results were unblinded May 2**; primary endpoint of time-to-recovery was not met for Infliximab or Abatacept**;** however, overall mortality benefit was shown for both; **manuscripts submitted to NEJM**
- Press release for both Infliximab and Abatacept results was issued Jun 2

ACTIV-2

Trial launched on Aug 3, 2020

- Outpatient, Phase II/III Master Protocol
- Neutralizing Monoclonal Antibodies and Oral Antivirals
  - nMABs (Lilly, Brii, AZ, RU-BMS), nPABs (SAB), IFN-beta (Synairgen), Camostat (Sagent), *DARPIn (MP-Novartis)*,* and S-217622 (Shionogi)
- Sample Size (Pts per Arm): 110 [Phase II] & 600 [Phase III]
- NIAID ACTG + CRO

- 4044 pts enrolled (as of Jul 25)
- The **SAB arm** has been closed due to operational futility of the study and final enrollment for Phase III was **734 participants** (367 in SAB and 367 in REGEN-COV); **SAB Phase II manuscript submission expected Fall 2022**
- **Synairgen Phase II manuscript submission expected Fall 2022**
- **Brii Bio Phase III manuscript submission expected Oct 2022**
- **ACTIV-2D: FPI was achieved on Aug 4;** 8 sites open; 30 patients enrolled (as of Sep 19); Shionogi protocol submitted for regulatory review and approval in South Africa

ACTIV-3

Trial launched on Aug 4, 2020

- Inpatient, Phase III (2 Stage) Master Protocol
- Neutralizing Monoclonal Antibodies
  - nMABs (Lilly, Brii, GSK-Vir, AZ), DARPin (Molecular Partners), protease inh. (Pfizer), and VIP (NeuroRx)
- Sample Size (Pts per Arm): [ACTIV-3] 500; [ACTIV-3b] 310
- NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VA + CRO

- 3067 pts enrolled (as of Jul 15)
- **AZ agent** was unblinded in Feb; primary endpoint not met; did show effect on overall mortality; AZ manuscript pre-print published in *Lancet*
- **MP data** was unblinded on Mar 11; MP did not meet predefined futility criteria; publication has been accepted and published in the *Annals of Internal Medicine*
- **ACTIV-3B/TESICO:** 40 sites open; 471 pts enrolled *(final enrollment);* the decision was made not continue the Aviptadil/Remdesivir (RDV) factorial arm due to futility; **manuscript on Aviptadil to be published in *NEJM***
- EPOC team is working on final specimen collection; manuscript in development

Master Protocol | Overview

ACTIV-4

Trial launched Sep 17, 2020

- Phase III Master Protocols: pre-hospitalized (4b), hospitalized (4a & 4HT), & post-hospitalized (4c) cohorts
  - LMWH, UFH, Crizanlizumab, SGLT2 inhibitors, and P2Y12 (4a); low- and high-dose aspirin and apixaban (4b); TXA127, TRV027, and Fostamatinib (4HT)
- Sample Size (Pts per Arm): [4a] 1000; [4b] 1750; [4c] 2660; [4HT] 300
- NHLBI-NINDS CONNECTS Network

- **Hospitalized:** 102 sites open; 3099 pts enrolled; P2Y12 (critically-ill group only) - 1637 pts *(final enrollment)*
- The DSMB recommended ACTIV-4 terminate enrollment in the P2Y12 inhibitor arm of the severe cohort; **Crizanlizumab arm stopped for futility, DSMB recommended SLGT2 to continue enrolling**
- **Post-hospitalized**: 120 sites open; 1219 pts enrolled *(final enrollment);* **DSMB recommended to stop enrollment for ACTIV-4C** due to slow enrollment and low primary outcome rates across the study; planned closing activities by the end of Nov 2022
- **ACTIV-4HT: Fostamatinib (138 pts enrolled as of Aug 30);** NHLBI has agreed to extend the trial through Dec 2023, with enrollment to be completed by May 2023; enrollment in Europe begins Oct 2022

ACTIV-5

Trial launched on Oct 9, 2020

- Inpatient, Phase II Master Protocol
- Proof of Concept study to identify promising treatments
  - Risankizumab, Lenzilumab, and Danicopan
- Sample Size (Pts Per Arm): [BET-A and –C] 100; [BET-B] 400
- NIAID + CRO

- 821 pts enrolled – (*final enrollment*)
- **BET-A (Risankizumab)** enrollment closed on Jul 13; **topline results showed no efficacy,** manuscript in development
- **BET-B (Lenzilumab)** closed enrollment Jan 9; **topline results showed no efficacy against the primary endpoint, but a positive trend to improved mortality,** Humanigen issued a press release on the results; manuscript in development
- **BET-C (Danicopan)** closed enrollment Feb 21; subgroup fully enrolled and study follow-up completed; topline results expected Oct 2022

ACTIV-6

Trial launched on Jun 23, 2021

- Outpatient, Phase III Master Protocol
- Approved prescription and over-the counter meds
  - Launched: Ivermectin, fluvoxamine, fluticasone
  - Pipeline & Confidential: Montelukast
- Sample Size (Pts per Arm): 1200
- NCATS + DCRI + PCORnet + SignalPath + CRO

- 50 sites open; 5170 pts enrolled (as of Sep 23)
- **Ivermectin (400)** press release issued June 13 indicating no differences in relief of mild to moderate COVID-19 symptoms between IVM (400) patients and placebo patients; **final revisions of manuscript have been submitted to *JAMA***
- Fluticasone arm press release was issued on Jul 13 **indicating no benefit;** manuscript **under review at *NEJM***
- **Ivermectin (600) arm closed on Jul 22** due to attainment of enrollment targets; TLR and **manuscript for *JAMA*** in preparation for Oct 2022
- **Fluvoxamine (50) TLR and preprint targets expected to be released Oct 2022**
- **Fluvoxamine (100)** arm opened on Aug 25**; 89 pts enrolled as of Sep 23**

Master Protocol | Overview

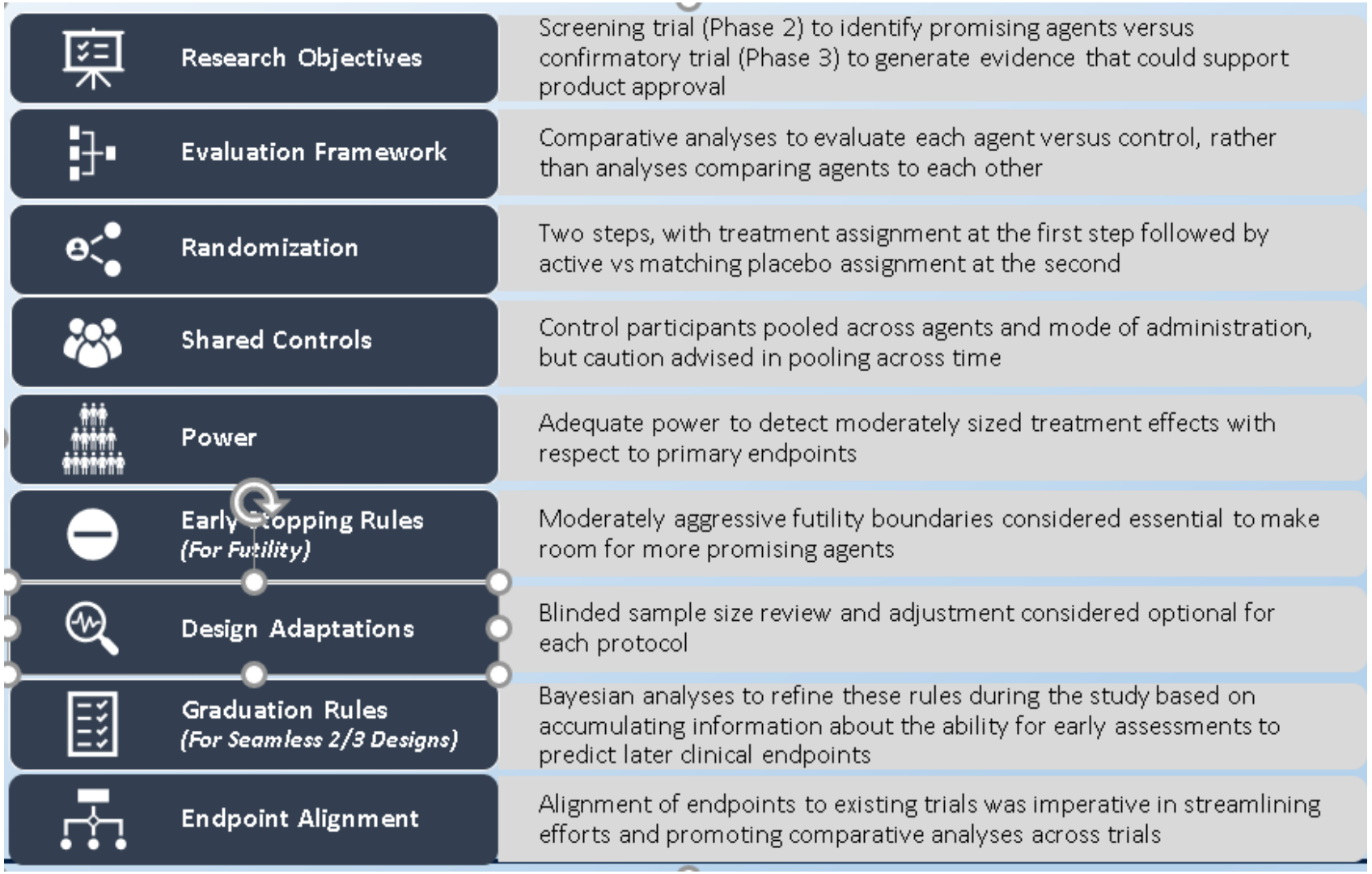
STRIVE

Trial not yet launched

- Inpatient, Master Protocol
- 1 Protease Inhibitor
  - S-217622 (Shionogi)
- Leveraging ACTIV-1, ACTIV-3, ACTIV-5 Sites + 8 International Coordinating Centers (ICCs)

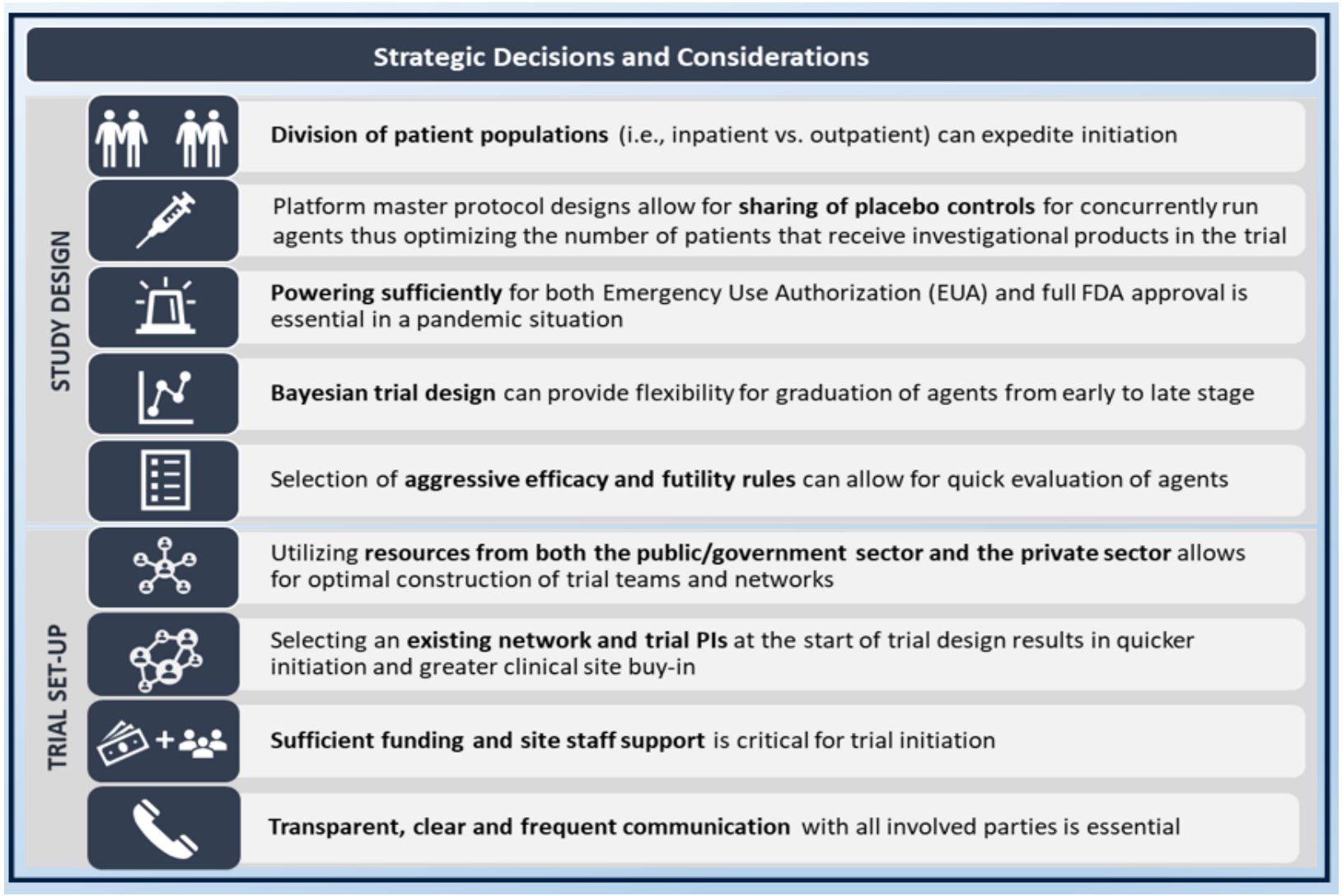
- AZ pulled out of trial to focus on BLA for AZD7442 for prevention
- Formal submission to the FDA occurred week of Jun 6
- **FDA Safe to Proceed was received on Jul 7**
- **FPI expected Oct 2022;** team is awaiting contracts
- Team continues to draft materials for Trial #2 and has ongoing discussions with potential agents

Design Decisions for ACTIV Master Protocols



ACTIV: Designing master protocols for evaluation of candidate Covid-19 therapeutics. *Annals of Internal Medicine*, Sep 2021

Lessons Learned for Future Protocols



ACTIV: Designing master protocols for evaluation of candidate Covid-19 therapeutics. *Annals of Internal Medicine*, Sep 2021

Preparing for the Next Pandemic

- Challenge of obtaining regulatory acceptance of trial innovations strategic for addressing a pandemic
  - Off-the shelf protocol and study design with regulatory pre-consultation can help (REMAP-CAP Covid appendix as example)
- Trial networks and infrastructure need to be in place, but how to support until needed?
- Ability to move to light-touch study procedures as pandemic worsens (and clinics may need to shut down) will be essential
- Need to work towards acceptance of better decision-making tools, ideally incorporating risk and benefit

CONCLUSION

Conclusion

- Effective leadership skills are needed to move from a statistical consulting role to a truly collaborative experience
- The importance of communication (2-way!) cannot be over-stated
- The benefits of a more collaborative environment include better, more efficient decision-making and greater adoption and acceptance of innovation
- Caution: Traditional statistical thinking/consulting could work against statistical innovation
- We have not yet landed on a good working model for leadership training in our discipline(s)
- ASA Institute can help

THANK YOU!