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Single Day Event

Suresh Chenji, Eli Lilly

Master Protocols and Adaptive Design Approaches for COVID-19 Treatment and Vaccine Development and for Other Ongoing Clinical Trials Impacted by COVID-19

Objective :

To briefly summarize platform trials with adaptive design planning requirement for COVID therapeutics and vaccine development during this public health emergency

Disclaimer

All the slide content are from published source for brief education purpose

The views and opinions presented here represent those of the speaker and not necessarily represent the views or practices of my employer

Adaptive Design Trials

A clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the study

Types of adaptive designs

- Adaptations to statistical aspects of design (primary estimand typically does not change)
  - Group sequential designs
  - Adaptations to sample size / statistical information, analysis schedule, decision criteria randomization ratio
- Adaptations to scientific aspects of design (primary estimand does change)
  - Adaptations to patient population, treatment arm selection, endpoint selection

- **Advantages** in statistical efficiency – e.g., a greater chance of detecting a drug effect at a given expected sample size
- Ethical **advantages** – e.g., stop trial if data not consistent with an effective drug (futility) or if persuasive evidence of important effect (efficacy)
- Methodology **challenges** in ensuring control of chance of erroneous conclusion, reliability in estimation (e.g., bias, CI coverage)
- Operational **challenges** in maintaining confidentiality and trial integrity
- Potential **challenges** in interpretability due to changes in estimand of interest
- **E.g.**,Complex multiple adaptive design, PREVAIL II (to evaluate ZMapp for Ebola virus disease)

Master Protocols

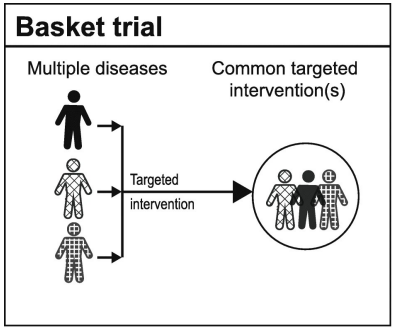
Types of Master Protocols

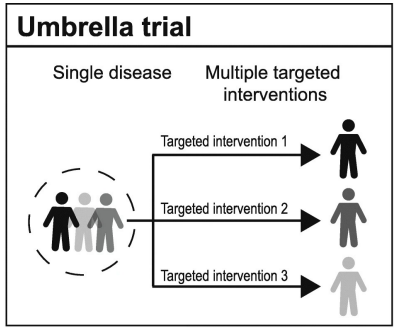
Basket Trial – To study a single targeted therapy in the context of multiple disease or disease subtypes
E.g., BRAFV600, to evaluate vemurafenib in nonmelanoma cancers

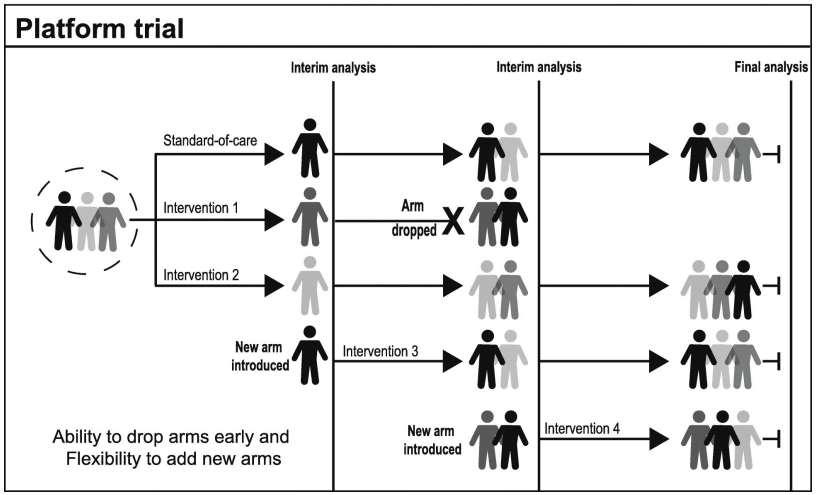
Umbrella Trial – To study multiple targeted therapies in the context of a single disease
E.g., Lung-MAP, to evaluate biomarker-matched therapies in rare squamous-cell subsets of NSCLC

Platform Trial – To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm
E.g., For COVID therapeutics REMAP-CAP(Tocilizumab), RECOVERY(Dexamethasone) trials

Master protocol approaches for clinical trial design can be combined with adaptive features to bring new medicines faster to patients







Woodcock J, LaVange LM. N Engl J Med ;377:62-70
Park, JJH et al. (2020)

Type of COVID-19 Treatment Being Studied

Antiviral drugs keep viruses from multiplying and are used to treat many viral infections (such as HIV, Herpes, Hepatitis C, and influenza).

Immunomodulators are aimed at tamping down the body's own immune reaction to the virus, in cases where the body's reaction basically goes overboard and starts attacking the patient's own organs.

Neutralizing antibody therapies may help individuals fight the virus and include manufactured antibodies, animal-sourced antibody therapies, and blood-derived products such as convalescent plasma and hyperimmune globulin, which contain antibodies taken from people who have previously had COVID-19.

Cell therapy products include cellular immunotherapies and other types of both autologous and allogeneic cells, such as stem cells, and related products.

Gene therapy products seek to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.

The diversity of therapeutic approaches being investigated is important because it rapidly expands our understanding of the effect of different categories of potential treatments.

COVID Therapeutics -Clinically Meaningful Endpoints (Standardised)

Based on patients disease severity at baseline

- SARS-CoV-2 infection without symptoms; Mild COVID-19; Moderate COVID-19; Severe COVID-19; Critical COVID-19

The choice, time frame, and interpretation of endpoints may differ depending on the population evaluated in the trial.
For example, In a trial in **severe and/or critically ill patients**, examples of appropriate endpoints could be

- All-cause mortality at an appropriate time point (e.g., at least 28 days for hospitalized noncritically ill patients, 60 days for critically ill patients)

- Proportion of patients alive and free of respiratory failure at an appropriate time point (e.g., at least 28 days for hospitalized noncritically ill patients, 60 days for critically ill patients)

- Clinical status using an ordinal scale that incorporates multiple clinical outcomes of interest (e.g., death, mechanical ventilation) ordered by their clinical importance at an appropriate time point (e.g., at least 28 days for hospitalized noncritically ill patients, 60 days for critically ill patients)

- First occurrence of any component of a composite endpoint of symptomatic deepvein thrombosis, pulmonary embolism, other venous thromboembolism, ischemic stroke, myocardial infarction, other arterial thromboembolism, and all-cause mortality by an appropriate time point

- Time to sustained recovery assessed over an appropriate duration

Master Protocols for COVID Therapeutics

Examples of COVID-19 confirmatory master protocols

Trials	Therapeutics Type	Patient Population	Innovative Design Elements
Solidarity	Antiviral/Antiinflammatory/ Vaccine	Hospitalized COVID-19 patients	Endpoint modification; Sample size reestimation; Interim analyses for early dropping or graduating an arm; Adding new arms
Recovery[a]	Antiviral/Anti-inflammatory/ Antibiotic/ Antibody	Hospitalized COVID-19 patients	Factorial design; Subsequent randomization for progressive COVID-19 patients; Interim analyses to amend the arms and for early results; Adding new arms
Principle	Anti-inflammatory/ Antibiotic/	Elderly COVID-19 patients: 1) aged 50–64 with comorbidity; or 2) aged 65 and over	Interim analyses to allow stopping, replacing or adding arms
I-SPY COVID[b]	Treatment of acute respiratory distress syndrome (ARDS)	Moderate to severe COVID-19 patients	Biomarker integration; Interim analyses for early dropping or graduating an arm; Adding new arms; Combining treatments
Remap-Cap	Antibiotic/ Antiviral/ Steroid	Community-acquired pneumonia patients	Multifactorial design; Continuously monitoring and updating the optimal set of treatments
ACTIV 1[c]	Immune modulators	Hospitalized COVID-19 patients	Master protocol with a single control arm; Adaptive features to allow rapid removal, identification and addition of experimental drugs; Leveraging existing networks

[a] ACCORD platform trial is an early stage exploratory master protocol aiming to feed potential drugs into confirmatory COVID-19 studies, such as Recovery trial.
[b] I-SPY COVID is currently at the exploratory phase and the treatments graduate this phase will remain in the trial for the confirmatory phase.
[c] Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) is a public-private partnership coordinated by the Foundation for the National Institutes of Health (FNIH). ACTIV 1-5 have been planned and ACTIV 1-4 have been initiated. Each master protocol has different type of therapeutics and/or patient populations.

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

Working in an unprecedented timeframe, the ACTIV public-private partnership has evaluated hundreds of available therapeutic agents with potential application for COVID-19, prioritized the most promising candidates, designed and harmonized **adaptive master protocols** for ACTIV clinical trials, and selected numerous **NIH-supported networks** to launch these clinical trials to test prioritized therapeutic candidates

ACTIV-1 Immune Modulators
ACTIV-2 Outpatient Monoclonal Antibodies and Other Therapies
ACTIV-3 Inpatient Monoclonal Antibodies and Other Therapies
ACTIV-4 Antithrombotics
ACTIV-5 Big Effect Trial
ACTIV-6 Outpatient Repurposed Drugs

ACTIV-3 protocols are Phase 3 randomized, placebo-controlled trials testing multiple therapies, beginning with monoclonal antibodies but including other types of therapeutics.

The **ACTIV-3 inpatient protocol** is designed with two stages of testing, allowing for quick analysis of compounds for effectiveness in Stage 1 and then a seamless progression to Stage 2 to validate the compound for broader use in patients. This protocol will enroll hospitalized patients with COVID-19 to evaluate investigational treatments for safety and efficacy in reducing time to recovery and effects on extrapulmonary complications and respiratory dysfunction.

ACTIV-3 Inpatient Master Protocol Example

Agent	Trial Phase	Description
LY-CoV555 **This sub-study has closed.**	Phase 3	An investigational antibody developed by Eli Lilly and Co. in partnership with AbCellera Biologics. AbCellera collaborated with NIAID's Vaccine Research Center to identify and isolate the antibody from a blood sample from a person who recovered from COVID-19. This sub-study closed because the Data Safety Monitoring Board determined low likelihood that the intervention would be of clinical value in this hospitalized patient population.
VIR-7831 **This sub-study has closed.**	Phase 3	A monoclonal antibody developed through a partnership between Glaxo-SmithKline plc and Vir Biotechnology, Inc. The Data Safety Monitoring Board recommended that recruitment in the sub-study should cease, due to futility.
BRII-196 and BRII-198 **This sub-study has closed.**	Phase 3	Two monoclonal antibodies developed by Brii Biosciences. The Data Safety Monitoring Board determined that the therapeutics did not meet the inclusion for criteria for further enrollment in the trial, due to futility.
AZD7442	Phase 3	An investigational long-acting antibody combination developed by AstraZeneca.

The Adaptive COVID-19 Treatment Trial (ACTT)

The Adaptive COVID-19 Treatment Trial (ACTT) is evaluating the safety and efficacy of the investigational antiviral Veklury® (remdesivir), developed by Gilead Sciences Inc., alone and in combination with other therapeutics. The patient population is hospitalized adults with COVID-19 and evidence of lung involvement, including rattling sounds when breathing (rales) with a need for supplemental oxygen or abnormal chest X-rays, or illness requiring mechanical ventilation.

These trials are other NIH-funded flagship COVID-19 therapeutic trials of ACTIV-prioritized agents using protocols informed or endorsed by the ACTIV partnership.

Example, Important ACTT Studies

Agent	Trial Phase	Description
Veklury® (remdesivir) *This study has closed.*	Phase 3	ACTT-1 evaluated remdesivir alone against placebo. Remdesivir has been approved by the FDA for the treatment of hospitalized people 12 years and older with COVID-19.
Veklury® (remdesivir) and Olumiant® (baricitinib) *This study has closed.*	Phase 3	ACTT-2 evaluated remdesivir plus baricitinib, an anti-inflammatory drug licensed to Eli Lilly and Company by Incyte, against remdesivir and placebo. Baricitinib is approved in the U.S. and ~65 other countries as a treatment for adults with moderate to severe rheumatoid arthritis. Baricitinib received emergency use authorization in combination with remdesivir, for hospitalized COVID-19 adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)

Example: ACTT-1 Trial Selected Details

Primary Clinical Efficacy Endpoint: Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale:

- Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
- Not hospitalized, limitation on activities and/or requiring home oxygen;
- Not hospitalized, no limitations on activities.

Recovery is evaluated up until Day 29.

A blinded sample size re-estimation will be conducted after approximately 115 patients to evaluate the proportion of subjects who have recovered by Day 29, which will provide important information about the number of patients needed to achieve 400 recoveries. Additionally, the number of deaths will be evaluated.

Interim Efficacy Review: The Lan-DeMets spending function analog of the O'Brien-Fleming boundaries will be used to monitor the primary endpoint as a guide for the DSMB for an overall two-sided type-I error rate of 0.05. Interim efficacy analyses will be conducted after the blinded sample size re-estimation of the primary efficacy endpoint at approximately 33%, 67%, and 100% of total information.

Results: A total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo). Those who received remdesivir had a median recovery time of **10** days (95% confidence interval [CI], 9 to 11), as compared with **15** days (95% CI, 13 to 18) among those who received placebo (**rate ratio for recovery**, **1.29**; 95% CI, 1.12 to 1.49;P<0.001, by a log-rank test). The Kaplan–Meier estimates of **mortality** were **6.7%** with remdesivir and 11.9% with placebo by day 15 and **11.4%** with remdesivir and **15.2%** with placebo by **day 29** (hazard ratio, **0.73**; 95% CI, 0.52 to 1.03).

https://clinicaltrials.gov/ *Remdesivir for the Treatment of Covid-19 — Final Report, N Engl J Med 2020;383:1813-26*

Example: ACTT-2 Trial Selected Details

Primary Clinical Efficacy Endpoint: Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale:

- Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
- Not hospitalized, limitation on activities and/or requiring home oxygen;
- Not hospitalized, no limitations on activities.

Recovery is evaluated up until Day 29.

Interim Efficacy Review: The Lan-DeMets spending function analog of the O'Brien-Fleming boundaries will be used to monitor the primary endpoint as a guide for the DSMB for an overall two-sided type-I error rate of 0.05. Interim efficacy analyses will be conducted at approximately 33%, and 100% of total information.

Results: A total of 1033 patients underwent randomization (with 515 assigned to combination treatment and 518 to control). Patients receiving baricitinib had a median **time to recovery** of **7** days (95% confidence interval [CI], 6 to 8), as compared with **8** days (95% CI, 7 to 9) with control (rate ratio for recovery, **1.16**; 95% CI, 1.01 to 1.32; **P=0.03**), and a 30% higher odds of improvement in clinical status at **day 15** (odds ratio, **1.3**; 95% CI, 1.0 to 1.6).
Patients receiving **high-flow oxygen or noninvasive ventilation** at enrollment had a time to recovery of **10 days** with combination treatment and **18 days** with control (rate ratio for recovery, **1.51**; 95% CI, 1.10 to 2.08).
The **28-day mortality** was 5.1% in the combination group and 7.8% in the control group (hazard ratio for death, **0.65**; 95% CI, 0.39 to 1.09).

https://clinicaltrials.gov/ *Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19, N Engl J Med 2021;384:795-807*

Preventive Vaccines for COVID-19

FDA Guidance for phase 3 preventive vaccine studies

Primary efficacy endpoint:

- The incidence of laboratory-confirmed symptomatic COVID-19

Statistical success criteria:

- point estimate of vaccine efficacy at least 50%
- the lower bound of the alpha-adjusted confidence interval at least 30%

Vaccine Efficacy(VE)= [(COVID-19 incidence rate in the unvaccinated group - COVID-19 incidence rate in the vaccinated group) / COVID-19 incidence rate in the unvaccinated group]*100%

VE=1-RR,

Relative risk or risk ratio (RR)= incidence of COVID-19 cases in vaccinated group/incidence of COVID-19 cases in the unvaccinated group

Ex. after post-vaccination follow-up, 100 cases confirmed COVID in unvaccinated group and 50 cases confirmed in vaccinated group

VE=(100-50)/100*100% = 50%

Preventive Vaccines for COVID-19

Patient-year follow-up period will be similar in both unvaccinated and vaccinated group and included in calculation of incidence rate

VE point estimate not depend on sample size, and for sample size calculation the lower bound of alpha-adjusted confidence interval around the primary efficacy endpoint point estimate needs to be greater than 30%

Important parameter for sample size calculation the incidence of laboratory-confirmed symptomatic COVID-19 cases in unvaccincated group

- difficult to predict, it shifts with time and geographical region
- impacted by COVID prevention strategies and policies

Lower incidence cases require large sample size is needed for phase 3 study to demonstrate vaccine efficacy

During Jun2020, vaccine experts want the FDA to commit to 30,000 people in COVID-19 vaccine trials

Sample Size Calculations

Example, with efficacy lower bound=0.3, power=80%, pre-specified alpha level=0.05

Incidence Rate in Control arm	True VE	Total number of cases	Expected Sample size (approx..)
0.01	0.6	99	14144
0.008	0.6	99	17680
0.01	0.5	254	33868
0.008	0.5	254	42334

Ivan S.F. Chan & Norman R. Bohidar (1998) Exact power and sample size for vaccine efficacy studies, Communications in Statistics - Theory and Methods, 27:6, 1305-1322

COVID Vaccine Studies Summary

Study Design Characteristics	BNT162b2 (mRNA vaccine)	ChAdOx1 nCoV-19	mRNA-1273	Ad26.COV2.S
Placebo Rate (6-month)	1.3%	0.8%	0.75%	1.4%
Target VE	0.6	0.6	0.6	0.6
Interim Design	Bayesian Sequential	Group Sequential	Group Sequential	sequential probability ratio test (SPRT)
Statistical Methods	Binomial (Even Split)	Poisson Regression	Cox PH Regression	Binomial (Event Split)
Interim Cases	32, 62, 92, 120 (P(VE>30%)>0.995)	75 (0.00155)	53, 106 (0.0002, 0.0073)	Weekly (after 20 events)
Total cases at final analysis	164	150	151	154
Sample Size (TRT vs PCB)	44000(1:1)	30000(2:1)	30000 (1:1)	60000 (1:1)

Covid-19 vaccine trial protocols released A rare opportunity for public scrutiny of these key trials, Peter Doshi: 21 October 2020 http://dx.doi.org/10.1136/bmj.m4058

COVID Impact on Ongoing Trials

For each trial, examine whether trial objectives can still be evaluated
- if not, modification may be needed (e.g. change of estimand) and discuss with health authorities

Assess the risk impact of
- (i) COVID-19 potentially affecting trial participants directly and
- (ii) COVID-19 related measures affecting clinical trial conduct

on trial integrity and interpretability is recommended

Plan/perform additional analyses (include in the Statistical Analysis Plan) to investigate the impact of the three phases (pre, during, and post COVID-19) to understand the treatment effect as estimated in the trial

Potential impact of COVID-19 pandemic on statistical analysis, including handling missing data
- develop procedures to capture additional COVID-19 info (e.g. new IEs, PDs, missing information, censoring rules)
- consider alternative strategies to collect data
- provide extra summaries (e.g. COVID-19 related or not)
- characterize type and amount of missing data, perform sensitivity analyses
- stratification by pre-, during- and post-COVID-19 pandemic
  - Challenge: different calendar times/intensities by regions/countries
  - Alternative: subgroup analyses by phase/country or region
- explore supplementary analyses

Summary

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) across worldwide posed public health emergency which led industry, regulatory and academia come together to expeditiously evaluate the safety and efficacy of potential treatments for COVID-19 and preventive vaccines through innovative clinical study designs like platform trials with adaptive design setting

COVID Pandemic continued to have major impact on planned and ongoing trials, number of strategies and recommendations to consider to address issues related to missing data, estimands, meeting protocol specified procedures, participant's safety need for additional exploratory analysis for overall study data evaluation and interpretability

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ICH E20 EWG Adaptive Clinical Trials

https://www.covid19-trials.com

FDA guidance, Conduct of clinical trials of medical products during COVID-19 public health emergency, latest update Jan 2021

EMA guidance, Points to consider on implications of Coronavirus disease(COVID-19) on methodological aspects of ongoing clinical trials

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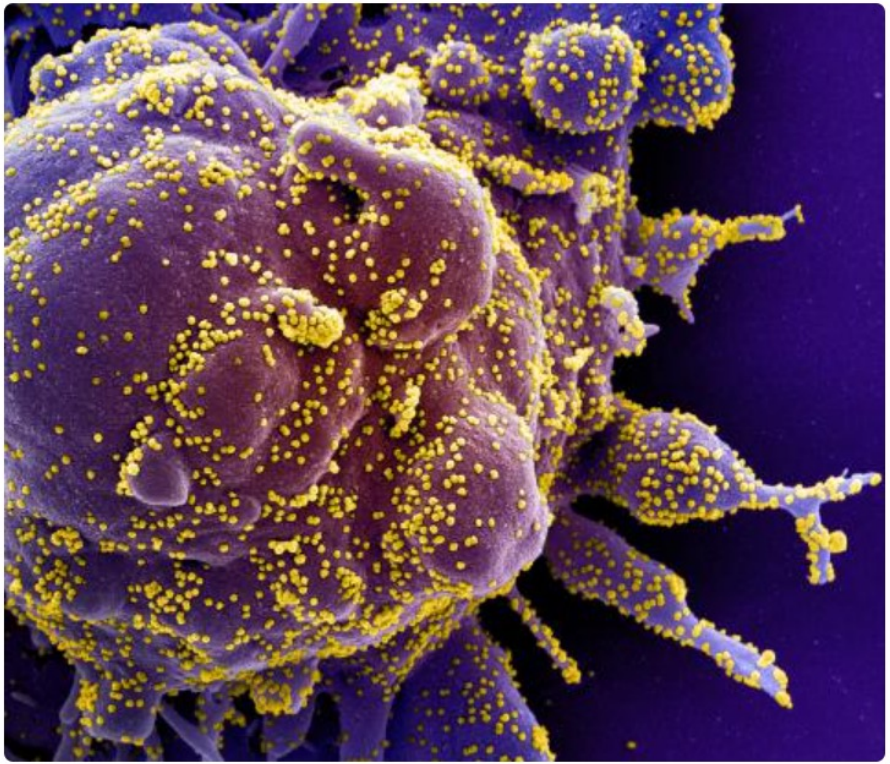

Colorized scanning electron micrograph of an apoptotic cell (purple) heavily infected with SARS-COV-2 virus particles (yellow), isolated from a patient sample. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland.

Credit: NIAID

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The Global Healthcare Data Science Community

Contact Channels

UK +44 1843 609600
USA +1 609 514 5105
office@phuse.global
phuse.global

Social Media

@phusetwitta
/phusebook
/phusetube
/company/phuse