CHOICE OF ENDPOINTS IN COVID-19 TRIALS

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Structure of this Webinar

Other considerations
- Estimands
- Design issues
- Analysis issues

COVID-19 endpoints
- The disease
- Landscape
- Regulatory guidance

Endpoints in clinical trials
- What is an endpoint
- Types of endpoints
- 3 dimensions

What we’ll not cover: Endpoints in early phase trials, safety endpoints
The Food and Drug Administration will refuse to approve the NDA under section 505(d) of the Federal Food, Drug, and Cosmetic Act if:

“**There is a lack of substantial evidence** consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling” [21CFR314.125]

**“Substantial Evidence”** of what?

Ans: Clinically meaningful **something**.
Clinically meaningful **something direct** that the patient can/will relate to.

- **Surives**
  - Can be used as an individual or a composite
- **Functions**
- **Feels**
  - Can be objective/subjective
Validated surrogate endpoint

- A surrogate endpoint is a laboratory measure or a physical sign that is intended to be used as a substitute for a clinical outcome
- Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinical outcome
- This expectation must be supported by strong data ("validation")
- Ideally, the surrogate should exist within the therapeutic pathway between the drug and meaningful benefit
  - i.e. the drug results in the therapeutic benefit by virtue of its effect on the surrogate
## Surrogate Endpoints Examples

<table>
<thead>
<tr>
<th>Disease area</th>
<th>Endpoint</th>
<th>Surrogate for</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Viral load</td>
<td>Complications of HIV</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>IOP</td>
<td>Loss of vision</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Cholesterol levels</td>
<td>Atherosclerotic disease</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Arterial blood pressure</td>
<td>CVA, MI, heart failure</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Blood glucose/hemoglobin A1c</td>
<td>Complications</td>
</tr>
</tbody>
</table>
Surrogate endpoints can be used for drug approval:

- if well validated, or
- under Subpart H (21 CFR 314.500-560; “accelerated approval” for serious and life-threatening illnesses; 1992)
  
  - requires adequate and well controlled trials
  - requires demonstrated effect on surrogate endpoint that is “reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit”
  - requires that the Applicant carry out, with due diligence, further adequate and well controlled studies to verify and describe the clinical benefit of the surrogate (where there is uncertainty as to the relation of the surrogate to the clinical benefit)
Types of Endpoints

• **Quantitative/Numerical** endpoint
  – Continuous [e.g. VAS]
  – Discrete [e.g. scores, patient reported outcomes, quality of life]
  – Time to event [e.g. time to death, time to discharge from hospital]

• **Qualitative** endpoint
  – Categorical [e.g. success/failure]
  – Ordinal [e.g. degree of impairment]
3 Dimensions of Endpoints

Endpoints in clinical trials
COVID-19 Endpoints
Context/Issues

What is measured
- Survival
- Feel
- Function
- Surrogate

What type
- Continuous
- Categorical
- Ordinal
- Time-to-event

How important
- Primary
- Secondary
- Exploratory
Prioritization of Endpoints

• Primary endpoint:
  – Success of the trial depends on it
  – Trial must be adequately powered for this endpoint
  – Multiple endpoints may be used, but co-primary endpoints usually means both must be met.
  – If at least one must be proven, then multiplicity concerns must be addressed.

• Secondary endpoint:
  – These are included in labeling claims
  – Multiple endpoints will require control of Family-wise-error (FWE) rate
  – For the above reason, usually these need to be prioritized

• Exploratory endpoint:
  – These cannot be included in labeling claims
  – Useful for future trials
  – Multiplicity is not a concern
COVID-19
COVID-19: The Disease

- **Respiratory disease** COVID-19 = Coronavirus Disease 2019 a name chosen by WHO on 11 Feb 2020

- ... caused by a novel coronavirus (= SARS-CoV-2)

- COVID-19 can range from mild to severe disease, the latter including pneumonia, severe acute respiratory syndrome, multi-organ failure, and death

- The incubation period ~14 days, with a median time for symptom onset ~4 to 5 days from exposure
Therapy for COVID-19: Drugs

- There are **no drugs or other therapeutics** presently approved by the FDA to prevent or treat COVID-19.

- **Clinical management** includes symptomatic and supportive care

- The most assessed drugs in the intervention arm
  - Hydroxychloroquine
  - Azithromycin
  - Remdesivir
  - Sarilumab
  - Tocilizumab

- Ventilation
Therapy for COVID-19: Ventilation

1. Non-invasive ventilation

   Face mask fitted over nose and mouth, no tube for airway

2. Mechanical ventilation

   1. Mechanical ventilation
   
   Ventilator unit contains air pressure system and controls
   
   Used air (carbon dioxide) flow from patient
   
   Air (oxygen) flow to patient
   
   Tube inserted into airway
   
   Lungs
   
   Humidifier to match air to body temperature and add moisture
   
   All ventilation needs close supervision by trained staff

3. Extracorporeal membrane oxygenation (ECMO)

   Return cannula
   
   Oxygenator
   
   Superior vena cava
   
   Ascending aorta
   
   Inferior vena cava
   
   Descending aorta
   
   Left femoral artery
   
   Drainage cannula
   
   Right femoral vein

Endpoints in clinical trials
COVID-19 Endpoints
Context/Issues
Landscape: Current Trials

Colors indicate the number of studies with location in that region.

Labels give the exact number of studies.
Regulatory Guidance on COVID-19 trials

- **ICMRA:** *International Coalition of Medicines Regulatory Authorities: Workshop* [July ’20]
- **FDA:** *Development and Licensure of Vaccines to Prevent COVID-19* [June ’20]
- **FDA:** *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention - Guidance for Industry* [May ’20]
Primary endpoint must be either

- **COVID-19** (virologically confirmed)
- **SARS-CoV-2 infection** (virologically or serologically confirmed)

Sponsors should collect clinical outcome data (e.g., hospitalization) and data on symptoms

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- etc.

Also important: whether COVID-19 is milder in persons receiving prophylaxis compared to the ones who are on placebo.
The guidance covers what needs to be shown for a superiority trial over placebo

- **Primary endpoint**: Point estimate of treatment difference > 50% with lower bound of 95% Confidence interval > 30%

- **Secondary endpoint**: A lower bound of > 0% is acceptable

For non-inferiority trials over an approved vaccine

- Lower bound > -10%

Surrogate endpoints may be acceptable (same requirements as in non-COVID-19 trials)
• **Phase 2 trials**: a virologic measure may be acceptable as a primary endpoint.

• **Phase 3 trials**: virologic endpoints may be assessed as secondary endpoints.
  – Collection of virologic data and evaluation of antiviral resistance are important components of drug development for COVID-19.

This basically means that virologic measure is not considered a surrogate endpoint!
The choice, time frame, and interpretation of endpoints depend on the population evaluated. For example,

- **In a trial in severe and/or critical patients**, examples of appropriate endpoints could be
  - Proportion of patients alive and free of respiratory failure [A COMPOSITE ENDPOINT]
  - Time to sustained recovery assessed over an appropriate duration
  - All-cause mortality at an appropriate time point (e.g., at least 28 days)
  - Clinical status at an appropriate time point assessed using an ordinal scale that incorporates multiple outcomes of interest (e.g., death, mechanical ventilation) ordered by their clinical importance [A COMPOSITE ENDPOINT]

- **In an outpatient treatment trial**, examples of appropriate endpoints could be
  - Proportion of patients hospitalized by an appropriate time point (e.g., at least 28 days)
  - Time to sustained clinical recovery assessed over an appropriate duration
The relevance and appropriateness of measures may depend on the
- Mechanism of action
- population studied
- baseline disease severity

Examples of important clinical outcome measures in treatment trials include the following:
- All-cause mortality
- Respiratory failure (i.e., need for mechanical ventilation, ECMO, noninvasive ventilation, or high-flow nasal cannula oxygen delivery)
- Need for invasive mechanical ventilation
- Need for intensive care unit (ICU) level care based on clear definitions and specific clinical criteria
- Need for hospitalization based on clear definitions and specific clinical criteria
- Objective measures of sustained improvement (e.g., return to room air or baseline oxygen requirement)
- Sustained clinical recovery (e.g., resolution of symptoms)

“Analyses of all-cause mortality will be important regardless of the selected primary endpoint.”
COVID-19 Trial: Other Considerations
Other Considerations

- Trials must be **placebo-controlled**

- The primary efficacy analysis should be based on **intention-to-treat** population
  - all randomized subjects, assigned to the planned treatment

- For endpoints defined by events through or at a prespecified time point, the time point should be defined as **number of days after randomization**

- Prespecify prognostic **baseline covariates** (e.g., age, baseline severity, comorbidities) in the primary efficacy analysis
  - Prespecify methods of covariate adjustment in protocol
  - With a mixture of patients with different baseline severity levels, sponsors should conduct subgroup or interaction analyses by baseline severity to assess for differential treatment effects.
Other Issues: Analyses of Endpoints

- Examples of analytic approaches for the primary efficacy analysis include:
  - **Binary outcome analysis**: each person is classified as having a successful or an unsuccessful outcome, with a difference in proportions used to compare treatment arms.
  - **Time-to-event analysis**: use of a proportional hazards model or log-rank test should be supplemented by a display of Kaplan-Meier curves in each treatment group.
  - **Composite Ordinal outcome analysis**: options include
    - proportional odds model approach
    - rank-based approach, and
    - score and weight-based approach
    - Multi-state models
    - But they are all more complicated – especially while designing a study

- Mortality can be included in all 3 above. However, for single endpoint consider the binary assessment since the COVID trials are shorter in length and time-to-event endpoint can be problematic.
Ordinal Endpoints: Multistate Analysis

• Severe Case:

• Mild and Moderate Case:

Ref: Cube et al, 2020
Ordinal endpoints: Rank-Based Approach

- Rank the clinical outcomes of interest in a specific order
  - Mortality first
  - Ventilation next
  - Hospital stay next

- That is, mortality > ventilation > hospital stay

- Can do a rank-based test to see if active treatment is better than placebo.
Same as confirmatory studies for other diseases

- **Multiplicity**
  - Must be addressed. “There is no free lunch.”

- **Missing data**
  - All patients must be followed up whether or not they have discontinued treatment.
  - Be conservative when data is missing.

- **Sample-size/power calculation**
  - Can be tricky in COVID-19 studies, especially with composite endpoints.

- **Define estimands**
  - A relatively new concept. ICH E9 Addendum.
• Endpoints/variables are one part of the **estimand**. Must be explained in the Statistical Analysis Plan.

• The other 3 parts are
  – Population
    ➢ E.g. Intention-to-Treat
  – Summary measure
    ➢ E.g. Mean change from baseline
  – Intercurrent events
    ➢ E.g. Rescue medication

Ref: Chrissie Fletcher, PSI Meeting Sept 2017
In Summary 1/2

• Follow the general framework on endpoints

• Only clinical outcomes are of interest unless there is a surrogate endpoint

• At this moment there’s no surrogate endpoint for COVID-19

• Virologic endpoint can be used as a primary endpoint in
  — Vaccine trials
  — Phase 2 or earlier-stage trials with drugs/biologics

• COVID-19 trials should be **placebo-controlled** (for now)

• Collect **baseline covariates** (age, severity, medical history)

• Use **day as unit of time**.
For vaccine trials

- Either COVID-19 or Coronavirus infection can be used as primary endpoint.
- Secondary endpoints can include symptoms

For drug/biologic trials

- Two common clinically relevant endpoints are mortality and a composite of ordinal responses
  - Mortality should always be evaluated (may or may not be primary)
  - If mortality is used, use proportion of deaths (and not time to death)
  - If ordinal/composite endpoint is chosen pay attention to the design of the trial.

- Consult regulators if in doubt.
A Few References

- Clinical Trial Endpoints – Eugene J. Sullivan [https://www.fda.gov/media/84987]
- COVID-19: Developing Drugs and Biological Products for Treatment or Prevention - Guidance for Industry [https://www.fda.gov/media/137926/download]
- Sample Size Calculations for Ordered Categorical Data – Whitehead, *Statistics in Medicine, 1993, Vol 12*
- A simulation study for Power Calculation in Large Cohort Studies based on Multistate Models, *Bestian et al. 2018*,