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Balancing Evidence and Speed in COVID-19 Therapeutics and Vaccines

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FDA oversight of drugs and vaccines

- Statutory standards for drug/vaccine approval
  - Substantial evidence of efficacy from adequate and well-controlled trials
  - Adequate tests by all methods reasonably applicable to show whether or not a drug safe for use
- FDA scientists review data, determine whether benefits appear to outweigh risks
- Why?
  - Protect consumers
  - Advance knowledge
  - Promote well-functioning markets/useful innovation

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Important principles

- No minimum efficacy thresholds (other than zero)
- Efficacy can be demonstrated based on changes to surrogate measures or actual clinical endpoints (how a patient feels, functions, or survives)
- Efficacy as measured in clinical trials may not predict effectiveness in routine care, owing to differences in real-world patient characteristics
- Not all adverse reactions can be detected during pre-approval clinical trials, even if the trials are large
  - Phase 4 studies, spontaneous adverse event reports, Sentinel/PRISM systems for prospective monitoring

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COVID19 Vaccine Trial Guidance

- Either laboratory-confirmed COVID19 disease or laboratory-confirmed infection is acceptable primary endpoint
  - If use infection, prefer + at least 1 symptom
- Expect approved vaccine would reduce the occurrence or severity of disease in at least 50% of recipients, a standard similar to that for annual influenza vaccines
  - 95% confidence that it is effective in at least 30% of the recipients
  - 2007 FDA guidance: vaccine for pandemic influenza should be supported by evidence showing that the lower bound of the 95% CI of the percent of subjects achieving seroconversion was at least 40%
- Safety considerations
  - Solicited adverse events within 7 days
  - Unsolicited adverse events within 21-28 days
  - Monitor serious events for at least 6 months
  - Expect at least 3,000 patients to get vaccine

FDA, Development and licensure of vaccines to prevent COVID-19: guidance for industry. June 2020

Shortcuts Relevant to COVID19

- 1. Accelerated approval
  - Endpoint: surrogate measure "reasonably related" to actual clinical endpoint
  - Post-approval confirmatory study required

- COVID19 guidance: *allow "accelerated approval" of a vaccine based only on antibody levels or another biochemical marker rather than actual clinical outcomes. This could occur if "additional understanding of SARS-CoV-2 immunology, and specifically vaccine immune responses that might be reasonably likely to predict protection against COVID-19, is acquired"*

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AA confirmatory studies

- 22 drugs (24 indications) marketed via AA pathway 2009-2013
  - **38** post-approval studies required
- By April 2017 (minimum 3 yrs of follow-up), 20 complete and 18 published
  - 10 randomized, 8 single-arm
  - 17 surrogate measures as endpoints
    - Disease response (n=9, 50%), progression-free survival (n=6, 33%), pharmacokinetic measures (n=2, 11%)
  - 15 were positive

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Shortcuts Relevant to COVID19

- 1. Accelerated approval

- 2. Expanded access
  - Authorize use of investigational product outside clinical trials
    - Criteria: potential benefit justified the risks ***AND*** treating physician determined that probable risk from drug not greater than risk from disease (individual pts) or at least preliminary clinical evidence of effectiveness (larger patient populations)
  - "Right to Try" (2018)

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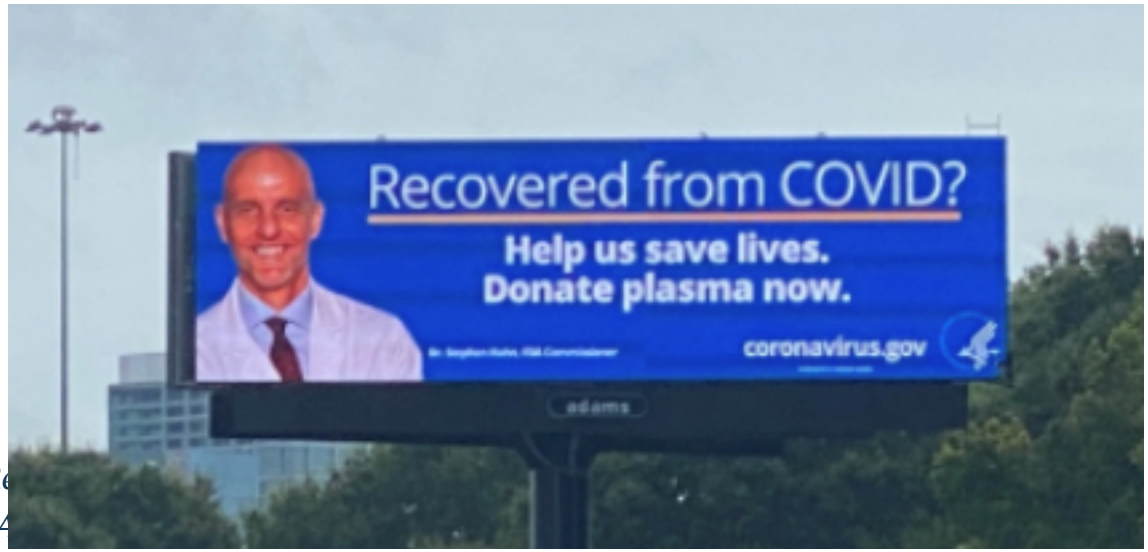
Convalescent Plasma

- National Expanded Access Treatment Protocol run by Mayo Clinic
  - Est 4/20, enrolled >90,000 by 8/13/20
  - Primary goal: provide access in hospitalized subjects with severe or life-threatening COVID-19 or judged by the treating provider to be at high risk of progression to severe or life-threatening disease



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Remdesivir

- Expanded access program managed by Gilead
  - Access to >1000 patients before March 2020
  - Switch to group expanded access at 46 sites in US, FR, IT, SP, SW, UK
    - Exceptions for pregnant women and children under 18
- 4/20 (NEJM): Case series of 61 pts with severe Covid19
  - 36 (68%) of 53 patients improved
    - 56% of intubated patients did well
  - 23% of patients had serious adverse events
- What conclude?
  - Unclear how many patients in original denominator
  - Administered median 12 days after symptom onset
  - 8 patients excluded from analysis

Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *N Engl J Med*. April 2020. [Epub ahead of print].

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- 3. Emergency Use Authorization

Emergency Use Authorization (EUA)

- Project Bioshield Act of 2004: FDCA s564
  - Secretary of HHS power to authorize emergency use of drugs, devices, and biological products that (a) **have not yet been** approved, cleared, or licensed by FDA or (b) that have been approved, cleared, or licensed for **certain uses but not others**
  - FDA can then permit public health authorities, health care providers, and others to **distribute and administer products needed to respond to emergency**, potentially on a mass scale
- "Medical countermeasures" against CBRN threats
  - Drugs
  - Biologic products (blood plasma, vaccines)
  - Devices (PPE, in vitro diagnostics)
- NOT an approval – cannot claim that product is now FDA-approved for the condition

Criteria for issuing EUA

1. The specified agent can cause a **serious or life-threatening disease or condition**;
2. Based on the *totality of available scientific evidence*, it is reasonable to believe that (a) the product **may be effective** in diagnosing, treating, or preventing the disease or condition, or a serious or life-threatening disease or condition caused by an EUA product or an approved, cleared, or licensed product for diagnosing, treating, or preventing the disease or condition, and (b) the **known and potential benefits of the product outweigh the known and potential risks**; and
3. There is **no adequate, approved, available alternative** to the product for diagnosing, preventing, or treating the disease or condition

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First Drug EUA

- Mar 28: Chloroquine and Hydroxychloroquine
  - Already approved for RA, lupus, malaria
- "Limited in-vitro and anecdotal clinical data in case series" = small trial conducted in France available online Mar 20
  - Non-randomized
    - many controls refused treatment
    - Intervention group was from large center in Marseilles while control group was from other centers
    - limited data, big differences on baseline characteristics (no adjustment)
    - Not significant if comparison between azithro group and Hcq/azithro
  - Primary endpoint of unclear relevance: **virus clearance at day 6** (clinical endpoints and side effects not reported)
  - Differential loss to follow up: 26 pts in intervention group (6 lost: 3 to ICU, 1 died); 16 controls (none)
- ***Withdrawn 6 wks later***

Rome & Avorn, NEJM, 2020

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Second Drug EUA

- May 1: Remdesivir
- 3 studies reviewed and determined that known and potential benefits outweigh known and potential risks and that may be effective for hospitalized patients with COVID-19
- Double-blinded, placebo-controlled NIAID trial
  - 1063 patients randomized
    - Median recovery time 11 vs 15 days for placebo (P<0.001)
    - Non-sig change in HR for death: 0.70 (95% CI: 0.47-1.04)
    - SAE: 21.1% vs 27.0% for placebo

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Another drug

- March 2020: RECOVERY RCT initiated to test a range of potential treatments for COVID-19
  - Over 11,500 patients enrolled from over 175 NHS hospitals in UK
- June 8 2020: analysis halted enrollment to the dexamethasone arm
  - "Sufficient patients had been enrolled to establish whether or not the drug had a meaningful benefit"
- 2104 pts randomized receive dexamethasone 6 mg qd vs. 4321 randomized to receive usual care
  - 33% of the steroid-treated patients had died, compared to 41% of the patients on usual care or a placebo
- ***No EUA***

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Third Drug EUA

- Aug 23: Convalescent plasma
- History, preclinical evidence, other trials, Mayo EAP results
  - Open-label, non-randomized
  - Post-hoc subgroup analysis
    - In patients transfused within 3 days of diagnosis, mortality 8.7% (95% CI 8.3%-0.2%) vs. 11.9% [CI 11.4%-12.2%] in patients transfused 4 or more days after diagnosis ($p<0.0001$)
- NIH panel: "insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19"

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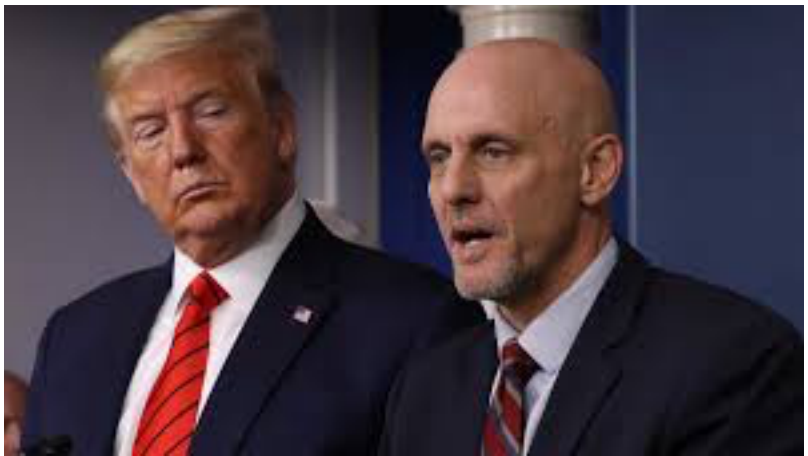
Next steps: Vaccine EUA?

- What will be the efficacy outcome used?
- What are safety outcomes?
  - What kinds of patients are enrolled, how long did the trial last, and how were adverse events ascertained?
- Will government encourage FDA to issue EUA for a product that has antibody data that only seem promising, even over objections of internal FDA scientists?
  - Or even without formal request of manufacturer?
  - Use Defense Production Act to require production?



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If EUA issued…

- What is the post-EUA data gathering plan?
  - What are the criteria for revoking EUA or 'graduating' to full approval?
- What price will vaccine be made available for?
  - Remdesivir at $3,120 per patient
  - Substantial taxpayer investment in vaccine development
- How will vaccine EUA be received by public given growing patient skepticism about political influence on the process?