What Makes this Difficult?

- Data are evolving. Initial EUA given for small studies with few endpoints.
- Recent impressive results are not available in peer-reviewed literature or reviewed by FDA
- Logistics are difficult--requires early identification of high-risk patient before they become sick enough to require 02 or hospitalization
    - Complex dynamics with patients and families
        - Absorb diagnosis and risk
        - Consider getting infusion--raises fears
- Antibodies are given by infusion requiring expertise and attention to details of supply chain, clinical care and documentation
- **Conclusion: Best to have a clear institutional protocol that unambiguously sets criteria for treatment and specifies granular details of treatment pathway**

Importance of Continued Evidence Generation

- Variants are developing with increased transmission
- Some of these variants “escape” the therapeutic antibody (antibody doesn’t recognize the virus)
- This causes diminished or lost efficacy of the therapeutic antibody
- Critical to institute a system of evidence generation
    - Genetic epidemiology of the virus (looking for variants)
    - Registries of antibody infusion outcomes (looking for variation in treatment related outcomes)
    - Randomized trial capability to rapidly test modified antibody cocktails designed to recognize and neutralize variants

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The basic approach for efficiently treating patients with the mAb supply available, maximizing the impact of that supply, and generating further evidence to inform use should include several steps:

- **Prioritize access based on risk** of serious consequences of COVID-19 infection, utilizing risk models where available and appropriate to more accurately predict and further define patients who may benefit most
- **Establish or augment existing COVID-19 registries** to include data on treated and

- **Track key endpoints**, including allergic/other reactions, emergency room visits, hospitalization, mechanical ventilation (if available), and death (if available)
- **Conduct real-world analyses of key questions** related to use, safety, and effectiveness
- **Characterize the utility and limitations of such rapid observational analysis,** particularly for generating actionable insights that could help to refine clinical practice while additional randomized trials continue to add to the larger mAb evidence base
- **Explore the feasibility of conducting practical real-world randomized studies through health care organizations participating in the registries**, focusing on questions that reflect current standards of care and where placebo controls are not needed – for example, studies of alternative doses of mAbs

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Appendix: Snapshot of Select Ongoing mAb Trials

mAb	Sponsors	Setting	Phase	Enrollment Progress	Study Sites	Status	Completion Milestone
bamlanivimab	Eli Lilly + AbCellera	Inpatient	1	24 Actual	11	Completed	8/26/20
	Eli Lilly + NIAID + AbCellera	Nursing Home + Outpatient	3	Part 1: 1175 Actual Part 2: 2000 Target Part 3: 500 Target	26	Recruiting Part 3	Part 1: week 8 public disclosure 1/20/21
	NIAID + Others	Inpatient	3	314 Actual	61	Halted - Not Recruiting	
	NIAID + Eli Lilly + AIDS Clinical Trials Group	Outpatient	2/3	2000 Target	84	Lilly Arms Completed Recruiting	
bamlanivimab + etesevimab	Eli Lilly + AbCellera + Shanghai Junshi	Outpatient	2/3	2370 Actual / 3300 Target	131	Recruiting	Mono Ph2: public disclosure 9/16/20 Combo Ph2: public disclosure 10/7/21 Combo Ph3 (2800/2800 mg): public disclosure 1/26/21 Estimated completion 5/31/21
		Outpatient	2	700 Target	107	Recruiting	
casirivimab + imdevimab	Regeneron	Outpatient	1/2/3	275 Actual / 6240 Target	97	Recruiting	
		Inpatient	1/2/3	2970 Target	97	Recruiting	
		Outpatient	3	2000 Target	127	Recruiting	
		Outpatient	1	974 Actual	7	Halted – Not Recruiting	
sotrovimab	Vir + GSK	Outpatient	2/3	1360 Target	91	Recruiting	

A successful effort that efficiently establishes a registry or linked registry could contribute even more to our understanding of the most effective approaches to provide access to mAbs, and of mAb impct, including a number of key topics where real-world evidence could be helpful:

- Characterizing events related to safety and effectiveness in subgroups of high-risk COVID-19 patients
- Identifying and assessing approaches to address disparities in access across demographic, geographic, and risk groups, as well as understanding the ability of alternative strategies to increase access to address these disparities
- Improving operational efficiency of rapid treatment programs and processes
- Assessing comparative effectiveness of mAbs, including in subgroups of patients infected with new genetic variant strains