Clinically relevant endpoints for COVID-19 and influenza: a clinician perspective

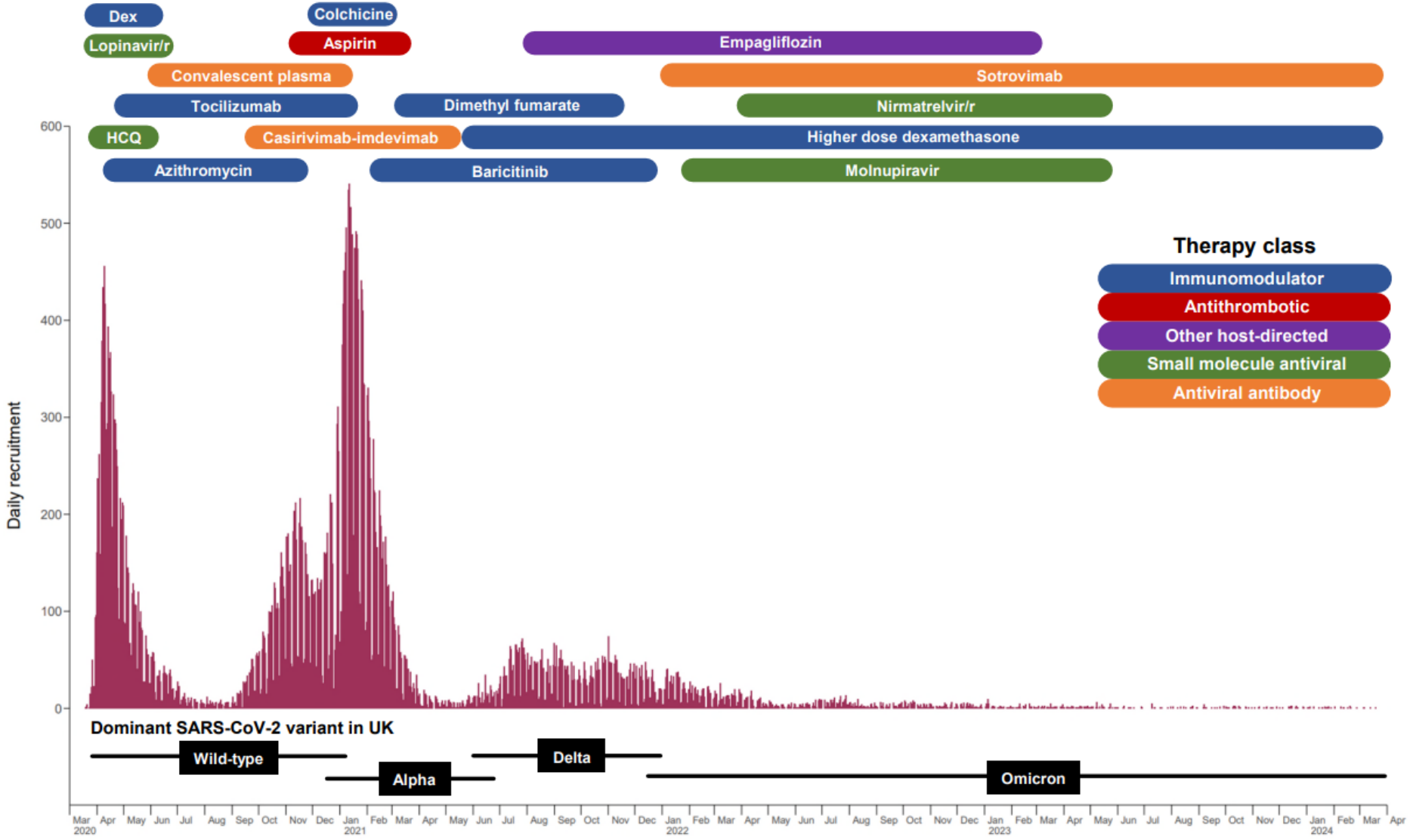
EMA workshop on primary efficacy endpoints for antivirals and monoclonal antibodies intended to treat COVID-19 and Influenza – 5-6 June 2025

Leon Peto

Clinical Co-ordinator for the RECOVERY trial - University of Oxford

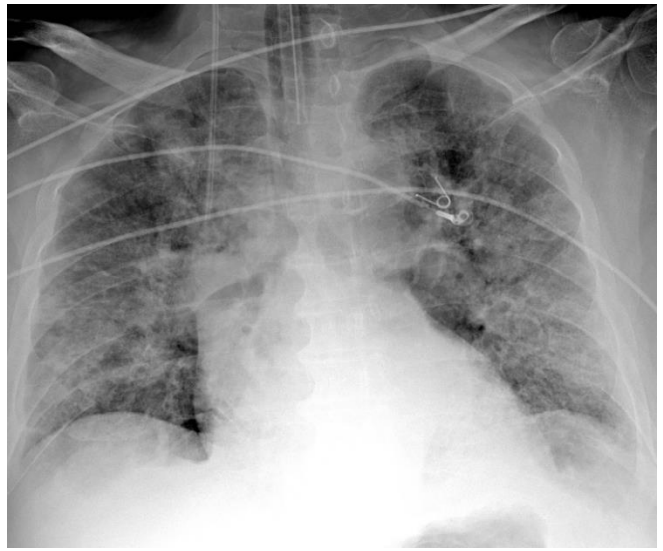
Consultant in Infectious Diseases & Microbiology - Oxford University Hospitals NHS Trust

RECOVERY COVID-19 comparisons

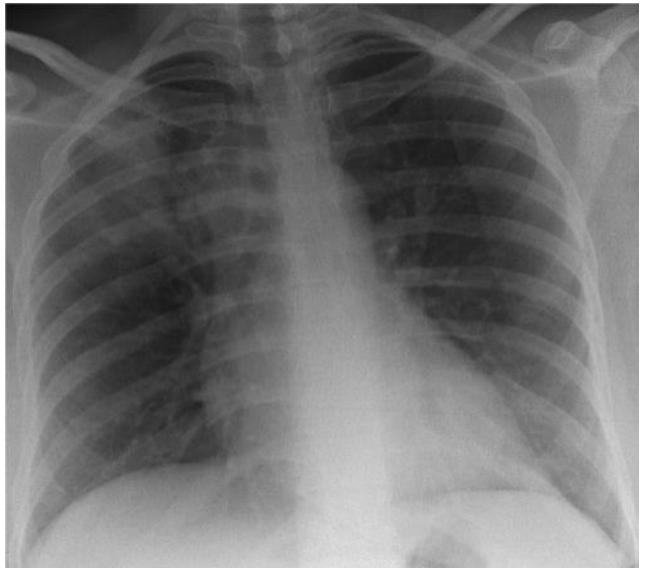


Pandemic vs post-pandemic infection

- Pandemic COVID-19 (2020-2022)
  - Severe viral pneumonia common, especially in older adults
  - Hospitalisation common in high risk outpatients (~5%)
  - Death & ventilation common in hospitalised patients (~10-30%)



- Post-pandemic COVID-19 and influenza
  - Disease less severe and more heterogeneous:
    - 1° pneumonia (esp. immunocompromised)
    - 2° bacterial infection
    - Decompensation of chronic disease (esp. lung disease)
  - Hospitalisation rare in most outpatients (<1%)
  - Death & ventilation uncommon in hospitalised patients (~2-10%)



Efficacy endpoints

- Clinical priority is to reduce the risk of death & major complications
- Symptom improvement important, but secondary
- Additional public health focus on reducing transmission & health service pressure
- Ideal trial would accurately quantify the effect of treatment on important & easily understandable clinical endpoints, and influence global practice
- But this is hard to achieve, particularly in post-pandemic setting
  - Can observational ('real world') data supplement or replace RCTs?
  - Are effects on 'softer' clinical or virological endpoints sufficient to inform practice?

Observational vs randomised data

Convalescent plasma associates with reduced mortality and improved clinical trajectory in patients hospitalized with COVID-19

METHODS. The multicenter, electronic health records–based, retrospective study included 44,770 patients hospitalized with COVID-19 in one of 176 HCA Healthcare–affiliated community hospitals. Coarsened exact matching (1:k) was employed, resulting in a sample of 3774 CP and 10,687 comparison patients.

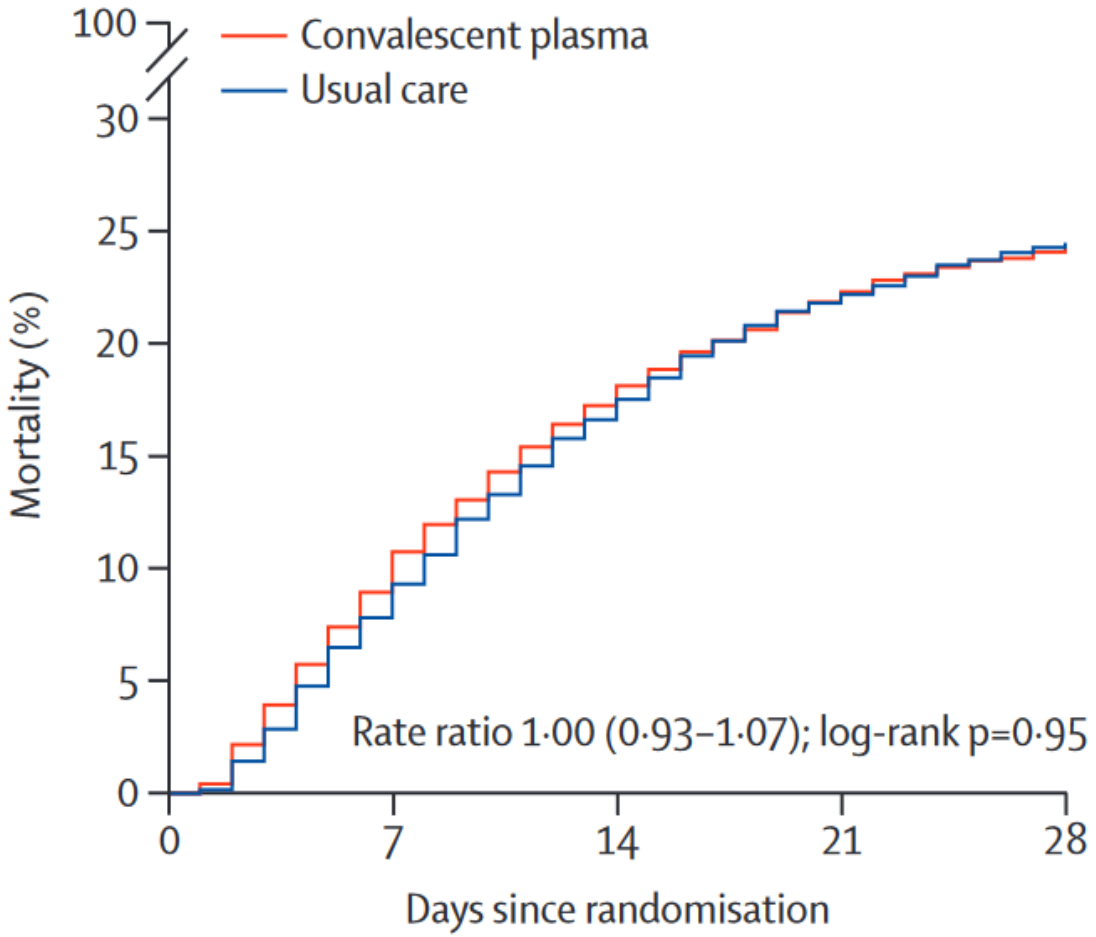
RESULTS. Examination of mortality using a shared frailty model, controlling for concomitant medications, date of admission, and days from admission to transfusion, demonstrated a significant association of CP with lower mortality risk relative to the comparison group (adjusted hazard ratio [aHR] = 0.71; 95% CI, 0.59–0.86; $P < 0.001$).

	aHR	LLCI	ULCI
RTRM matched (n_{events} = 417)			
CP	**0.71**	0.59	0.86
Date of admission	**1.01**	1.00	1.01
Days to transfusion	**1.03**	1.01	1.05
Anticoagulants	0.85	0.57	1.28
Tocilizumab	**1.89**	1.45	2.45
Azithromycin	0.92	0.74	1.15
Statins/ACEi	**1.20**	1.02	1.40
Steroids	**2.05**	1.50	2.80

Arnold Egloff SA, et al. J Clin Invest. 2021 Oct PMID34464352

Observational vs randomised data

- 11,558 hospitalised patients randomised in RECOVERY
- 1399 vs 1408 deaths
- Inconsistent with observational studies of CP in this setting
- Observational data cannot reliably assess treatment effects unless these are extreme, and gave misleading results for COVID-19 treatments



RECOVERY Collaborative Group. Lancet. 2021 May PMID34000257

Outpatient efficacy endpoints

Table 1 Potential primary endpoints in COVID-19 outpatient clinical trials.

Outcome	Strength(s)	Weakness(es)
Death	Objective Top patient priority Easy to capture	Very low proportion in outpatient setting Lower in high income country with well-resourced healthcare settings Decreasing in frequency with vaccination and less severe variants Not a feasible outcome in non-severe patients
Hospital admission	Important to patients in itself Important for the effect on healthcare system Indicative of follow-on effects Easy to capture	Between-setting variation in practice Decreasing in frequency with vaccination and less severe variants In vaccinated settings, has decreased to an extent that may no longer be a feasible outcome
Recovery (including time to recovery)	Important to patients Measurable in every patient, and thus requiring many fewer patients to detect treatment effects	Subjective, raising measurement challenges and markedly increasing importance of blinding to reduce bias
SpO_2	Objective, standardized measurement Easy implementation	Inconsistent readings with cold digits. A surrogate, not itself important to patients.
Viral Load	Objective, standardized measurement	A surrogate, not itself important to patients Poor correlation to severe outcomes and patient experience

Thorlund K, et al. Commun Med (Lond). 2023 Apr PMID37069219

Inpatient efficacy endpoints

Potential primary endpoints for COVID-19 or influenza phase 3 inpatient trials		
Outcome	**Strength(s)**	**Weakness(es)**
Death	Most important, clear & objective Routinely captured	Relatively rare – very large sample needed
Need for organ support (NIV, IMV, ICU admission)	Important, clear & objective Routinely captured	Uncommon – large sample needed Variation in practice Possibly influenced by trial allocation
Organ support score (e.g. days on IMV, WHO ordinal scale)	Important & objective More power than binary death/organ support	Composite scores may be of unclear relevance Possibly influenced by trial allocation Additional data collection may be needed
Time to discharge	Important, clear & objective Routinely captured More power than binary death/organ support	May not correspond to major endpoints Possibly influenced by trial allocation
Recovery time, Symptom severity score	Important to patient More power than binary death/organ support	Subjective – need for blinding Unclear importance & relation to major endpoints Additional data collection
Virological measures, Clinical observation scores (e.g. fever, HR, SpO2)	Objective Well-powered	Surrogate – unclear relationship to important endpoints Absence of effect may not exclude benefit Additional data collection

Experience from pandemic COVID-19

- Where adjusted and unadjusted trial results differ, the adjusted results are more reliable, e.g. dexamethasone in RECOVERY, remdesivir in ACTT-1

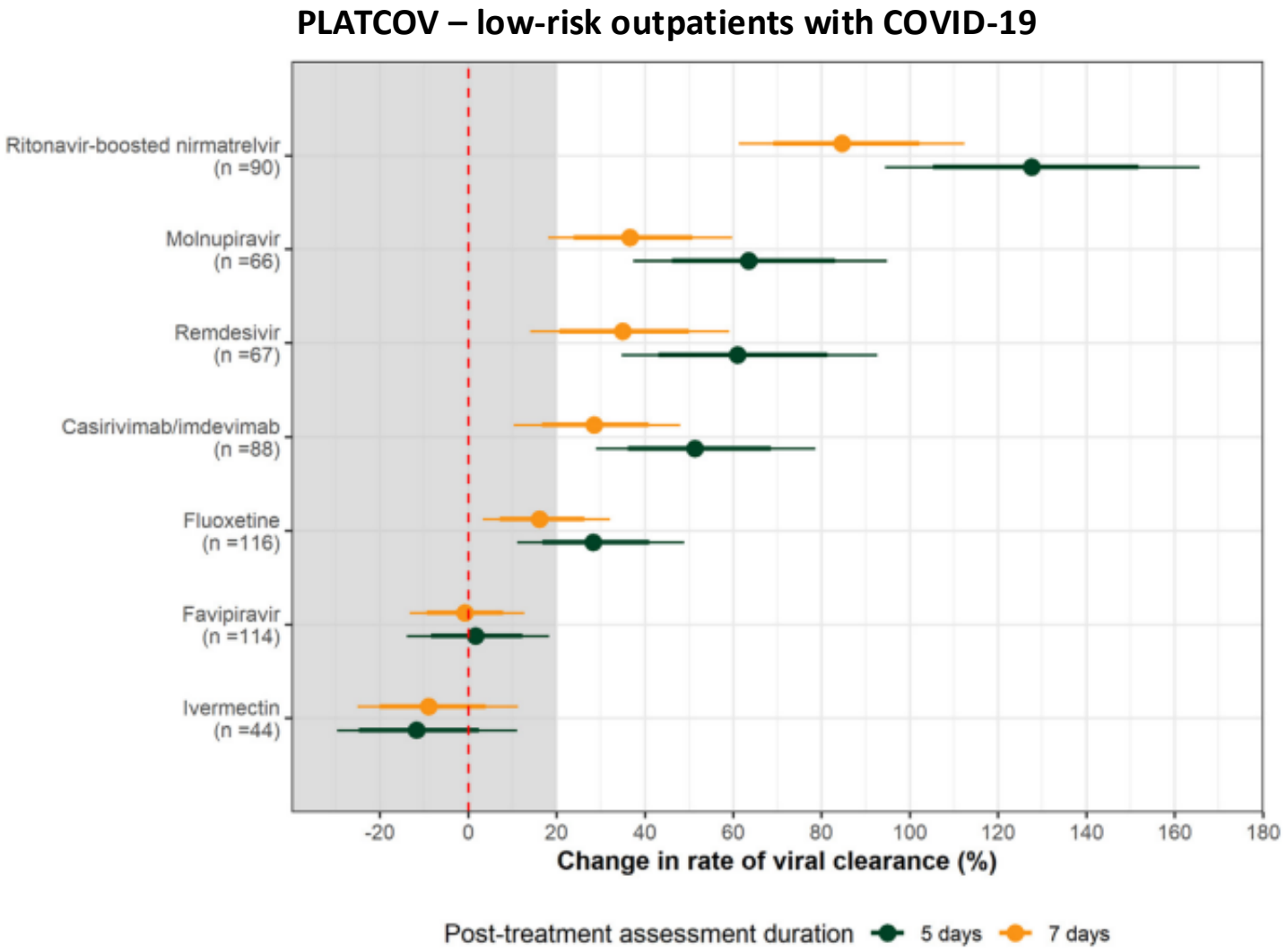
- The benefit of antivirals (& immunomodulators) depended strongly on disease severity, e.g. remdesivir:
  - Outpatients – hospitalisation HR 0.13 (0.03-0.59)
  - Inpatients, oxygen only – mortality RR 0.85 (0.75-0.96)
  - Inpatients, ventilatory support – mortality RR 1.11 (0.92 – 1.35)

- Most randomised evidence for influenza antivirals is in very early infection, <2d from symptom onset

- Patients typically hospitalised much later than this (median symptom duration 5 days in RECOVERY)

Gottlieb RL et al. N Engl J Med. 2022 Jan. PMID 34937145
WHO Solidarity Trial Consortium. Lancet. 2022 May PMID 35512728

Virological endpoints



- Virological endpoints most useful in <u>early phase trials</u>, or in the context of <u>well-established clinical efficacy</u> of similar agents in other studies (e.g. anti-spike mAbs)
- Difference in virological efficacy clear in PLATCOV, which should inform clinical studies

Jittamala P, et al. EClinicalMedicine. 2025 Jan PMID 39896880

Virological endpoints

- However without concordant evidence of clinical efficacy the relevance of virological outcomes is uncertain & insufficient to justify treament

RECOVERY – molnupiravir for inpatients with COVID-19

	Molnupiravir vs usual care			
	Molnupiravir (n=445)	Usual care (n=478)	HR, RR, or MD (95% CI)	p value
28-day mortality (primary outcome)	74 (17%)	79 (17%)	HR 0·93 (0·68 to 1·28)	0·66
Median time to discharge alive, days (secondary outcome)	10 (6 to >28)	9 (5 to >28)	..	..
Discharged from hospital within 28 days (secondary outcome)	319 (72%)	354 (74%)	HR 0·96 (0·82 to 1·12)	0·60
Mean baseline-adjusted viral RNA copy number on day 5 (log copies/mL)	3·57 (0·11)	4·02 (0·10)	MD –0·45 (–0·74 to –0·16)	0·0024

RECOVERY Collaborative Group. Lancet Infect Dis. 2025 May PMID 40383127

Conclusions

- For the next pandemic - some trials needed that rapidly recruit many thousand patients and focus on major clinical endpoints (esp. death or need for ventilatory support)
  - Streamlined regulatory approval and trial procedures are essential for their success

- Outside a pandemic - clear results for these endpoints would need large trials, e.g. 5-10,000 patients
  - This is common in some diseases, like acute MI, but not in acute infection
  - Such trials are possible, and may have the greatest impact on clinical practice

- More sensitive clinical endpoints (e.g. time to discharge or clinical ordinal scale) allow lower recruitment, but the importance & impact of these is less certain

- Virological endpoints can complement, but not replace, clinical endpoints