Designing efficient clinical trials during a pandemic

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Background

- A new disease brings many uncertainties
- Trials must start rapidly to identify treatments that
  - help patients
  - can be used as part of the outbreak response
- COVID-19 presentation is heterogeneous – can improve within days or last weeks or lead to death.

The 2014 Ebola experience

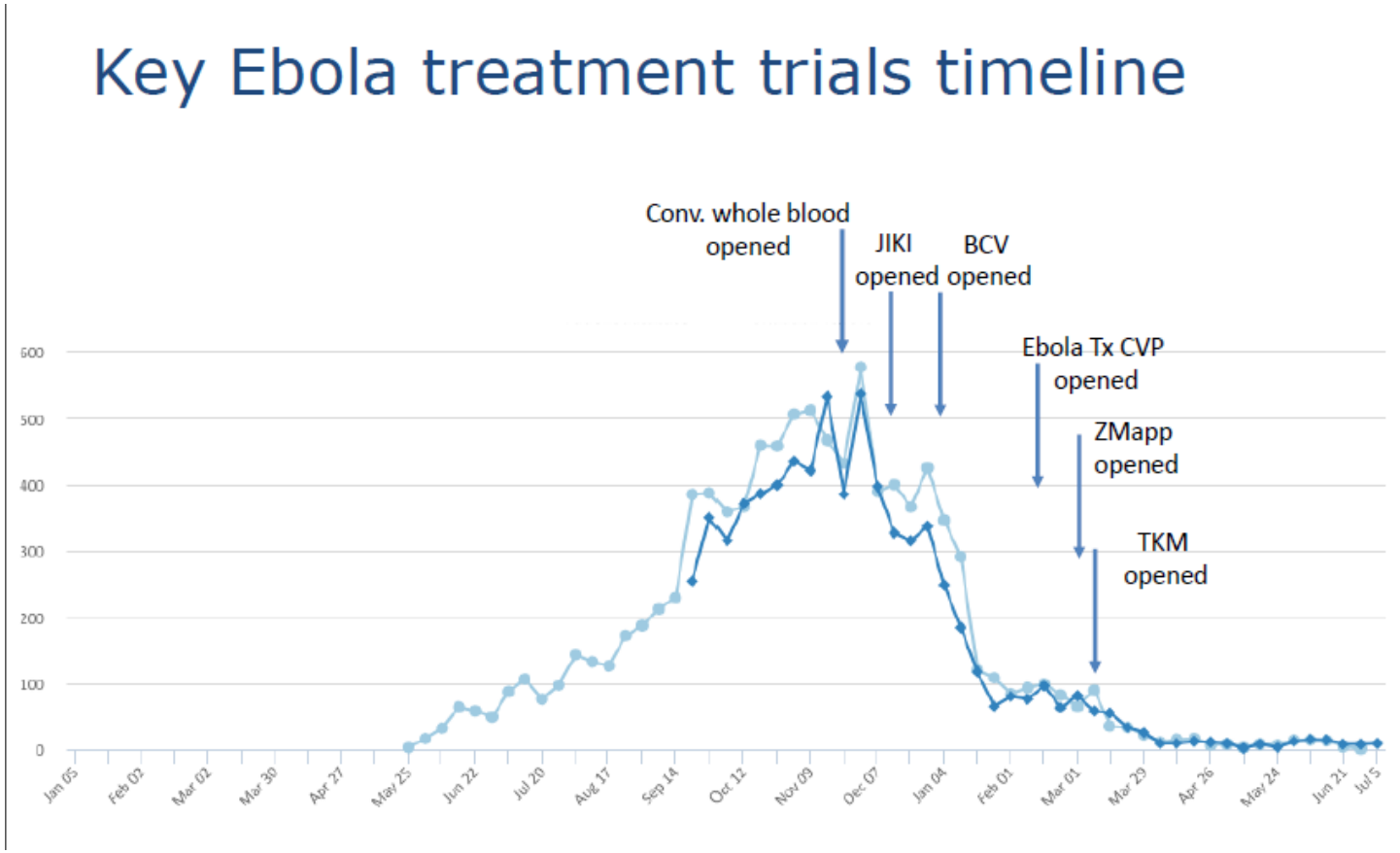


Figure: Number of new Ebola cases over time (courtesy of Peter Horby).

LOTUS trial (Cao et al, 2020)

- Trial started on 18 January 2020
- Open-label trial of Loptinavir/Ritonavir
- Endpoint: time to 2-point improvement on 7-point scale or hospital discharge

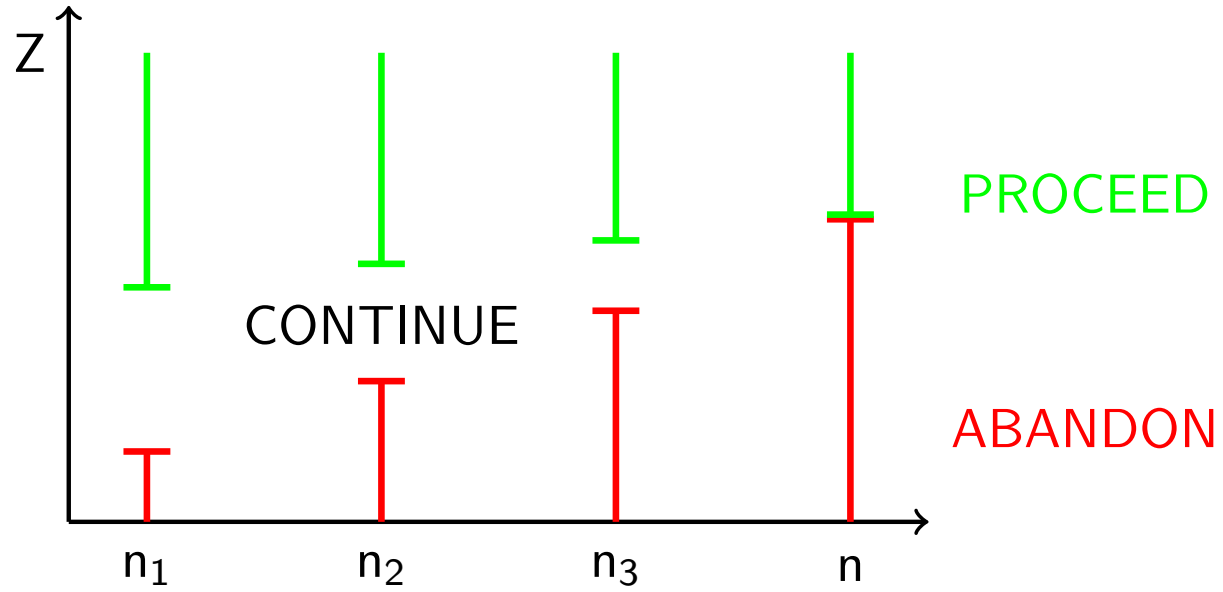
7	Death
6	ICU, requiring ECMO and/or IMV
5	ICU/hospitalization, requiring NIV/HFNC therapy
4	hospitalization, requiring supplemental oxygen
3	hospitalization, not requiring supplemental oxygen
2	Not hospitalised, but unable to resume normal activities
1	Not hospitalised with resumption of normal activities

IMV, invasive mechanical ventilation; NIV, non-invasive mechanical ventilation.

- Trial started without formal design

Remdesivir trials (Wang et al, 2020)

- Trial of remdesivir
- Group-sequential design (1 interim analysis at half-way point)



- Primary endpoint: time to 2-point improvement on 6-point scale.
  - Collapsed category 1 and 2 from previous endpoint

The perfect trial during a pandemic

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- Uses meaningful and efficient endpoint
- Discards poor treatments quickly
- Can cope with multiple treatments
- Minimizes burden on frontline staff
- ...

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$\Rightarrow$ is ADAPTIVE[1]

[1] Stallard et al (2020) for an overview of adaptive methodology

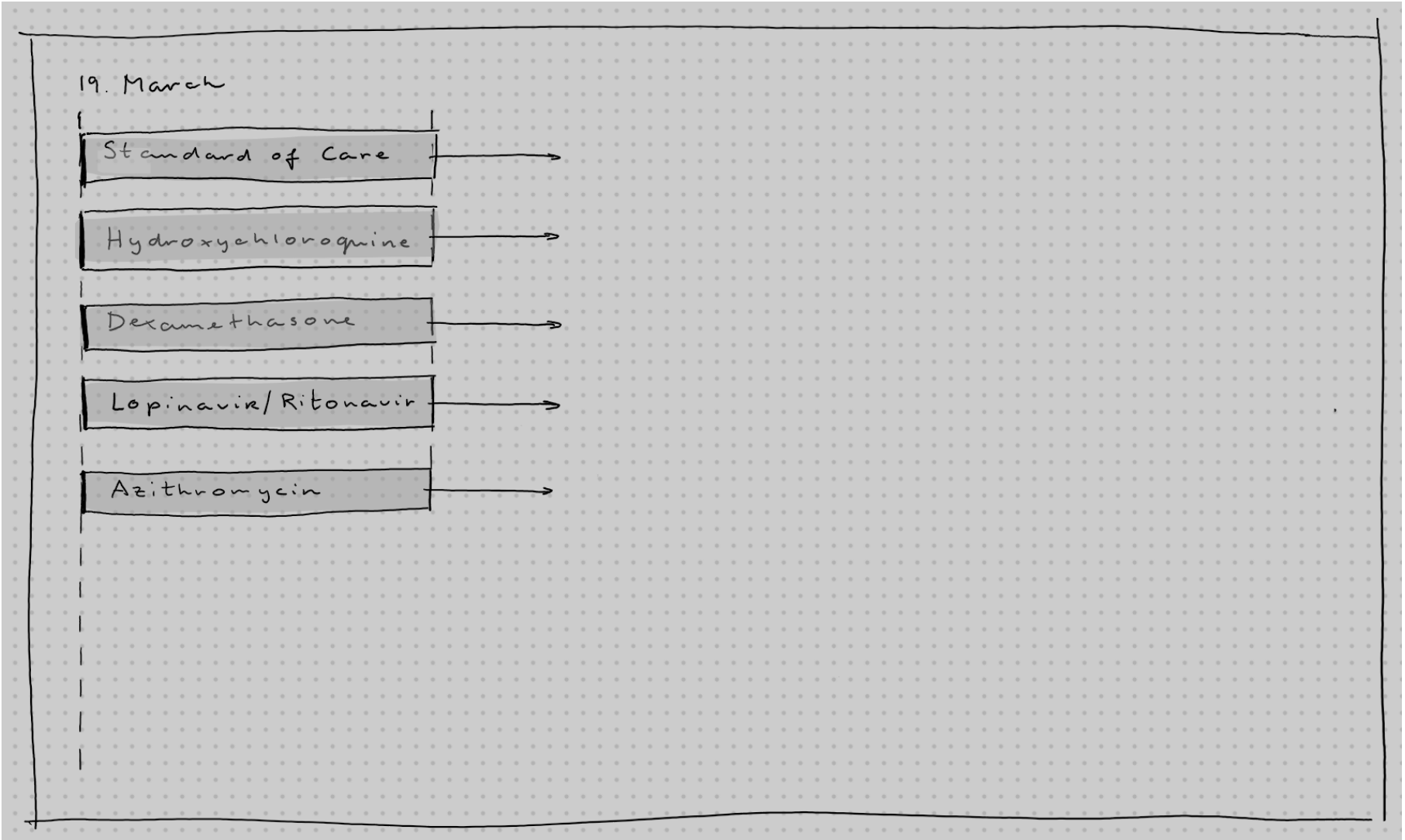
RECOVERY (www.recoverytrial.net)

- Multi-arm platform trial
  - Initially 4 treatments
- Endpoint: Mortality at 28 days
- Minimal data collection - data linkage

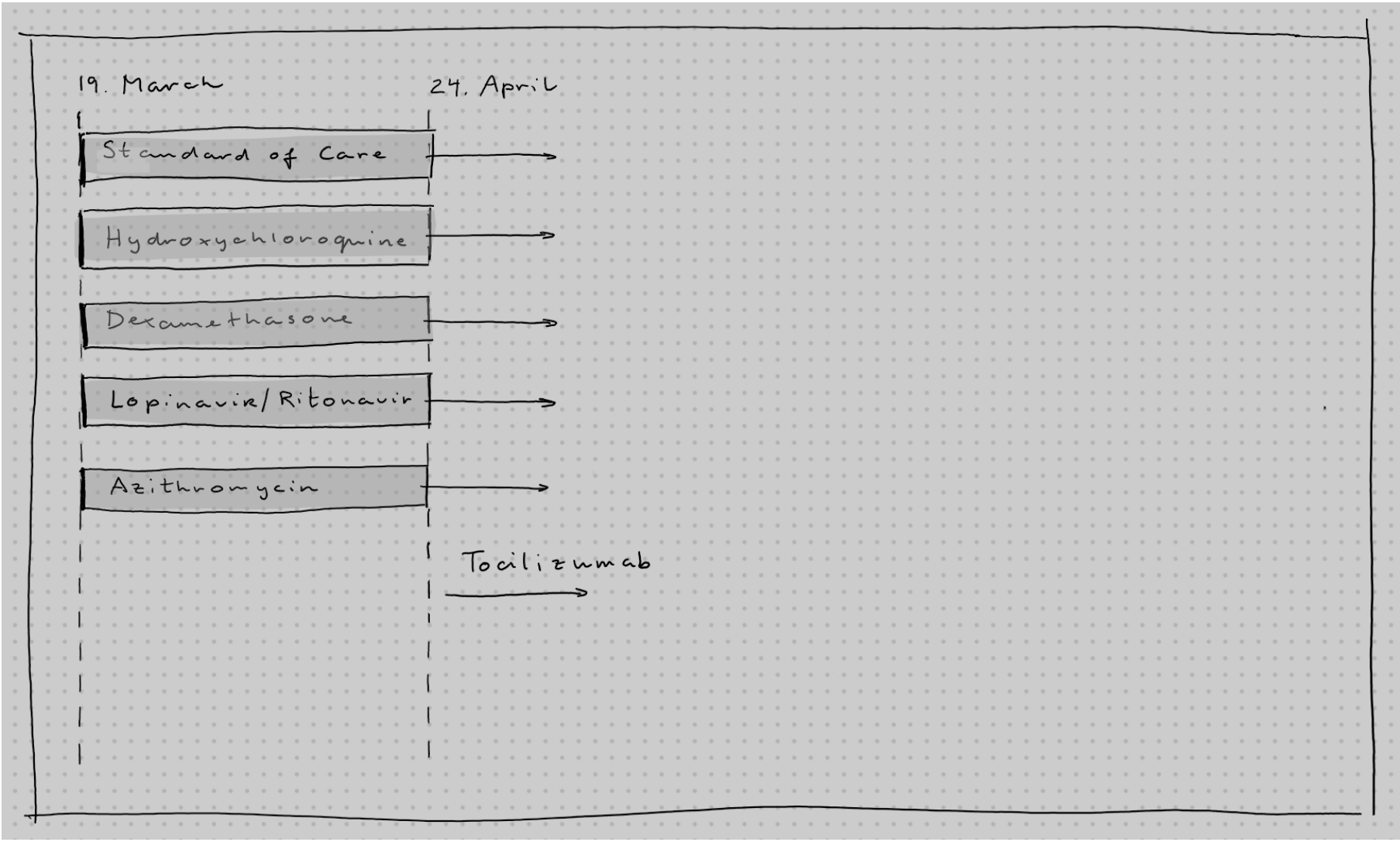
A great story . . .

- $\sim$ 11,500 patients recruited in 90 days and over 17,000 to date
- 175 centers
- open to all ages
- 9 days from funding to first patient
- . . .

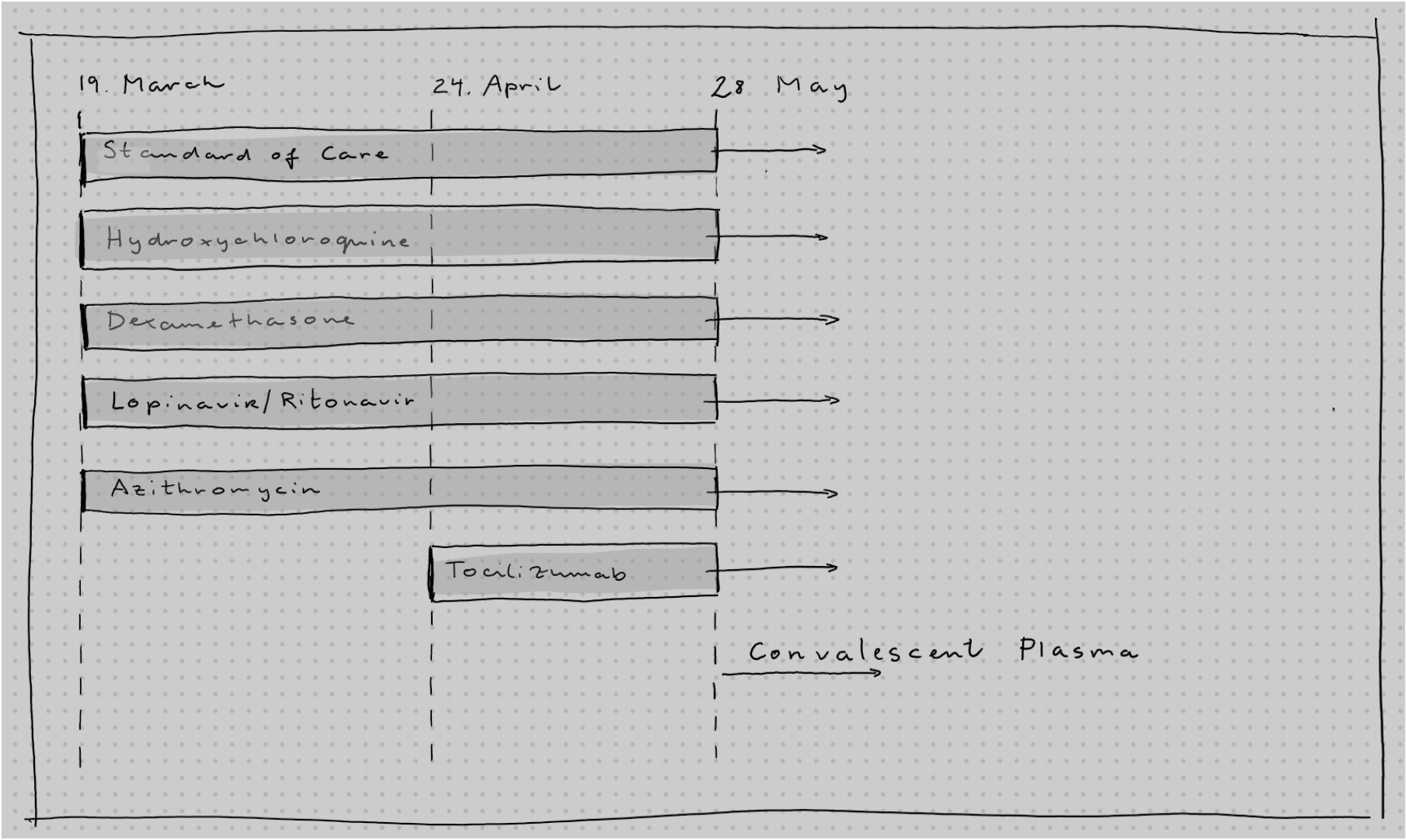
RECOVERY


19. March
Standard of Care
Hydroxychloroquine
Dexamethasone
Lopinavir/Ritonavir
Azithromycin

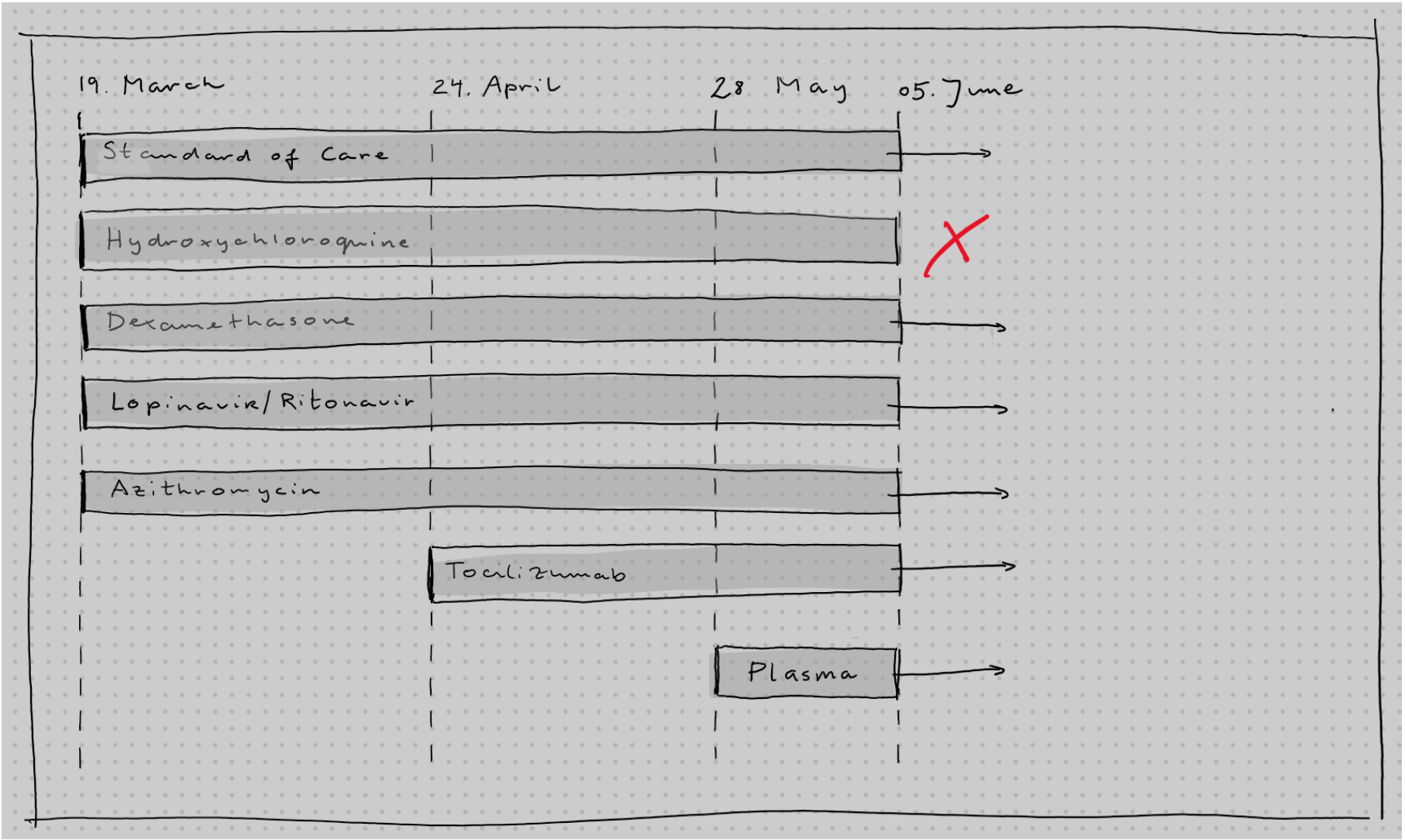
RECOVERY


19. March
24. April
Standard of Care
Hydroxychloroquine
Dexamethasone
Lopinavir/Ritonavir
Azithromycin
Tocilizumab

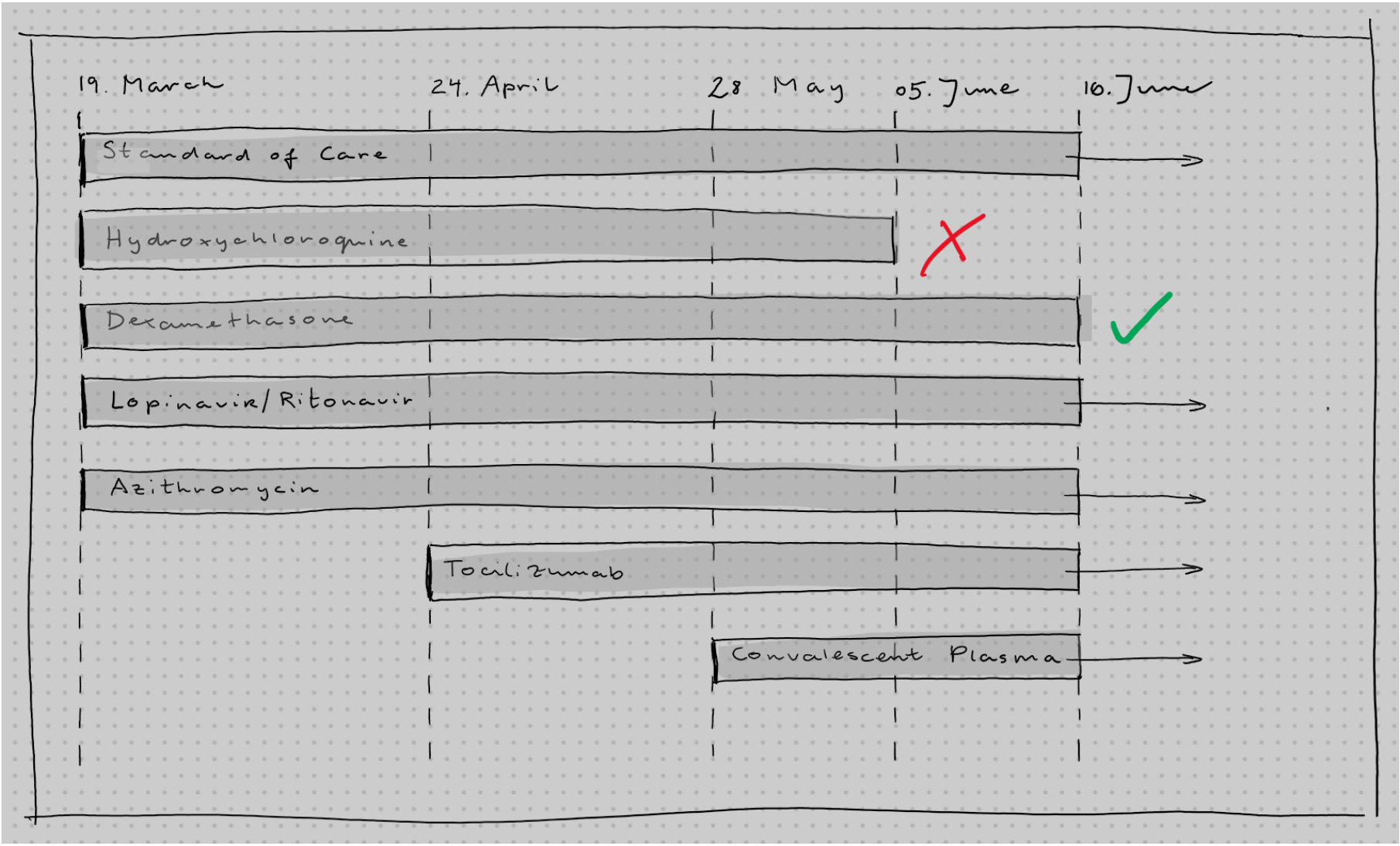
RECOVERY


19. March
24. April
28 May
Standard of Care
Hydroxychloroquine
Dexamethasone
Lopinavir/Ritonavir
Azithromycin
Tocilizumab
Convalescent Plasma

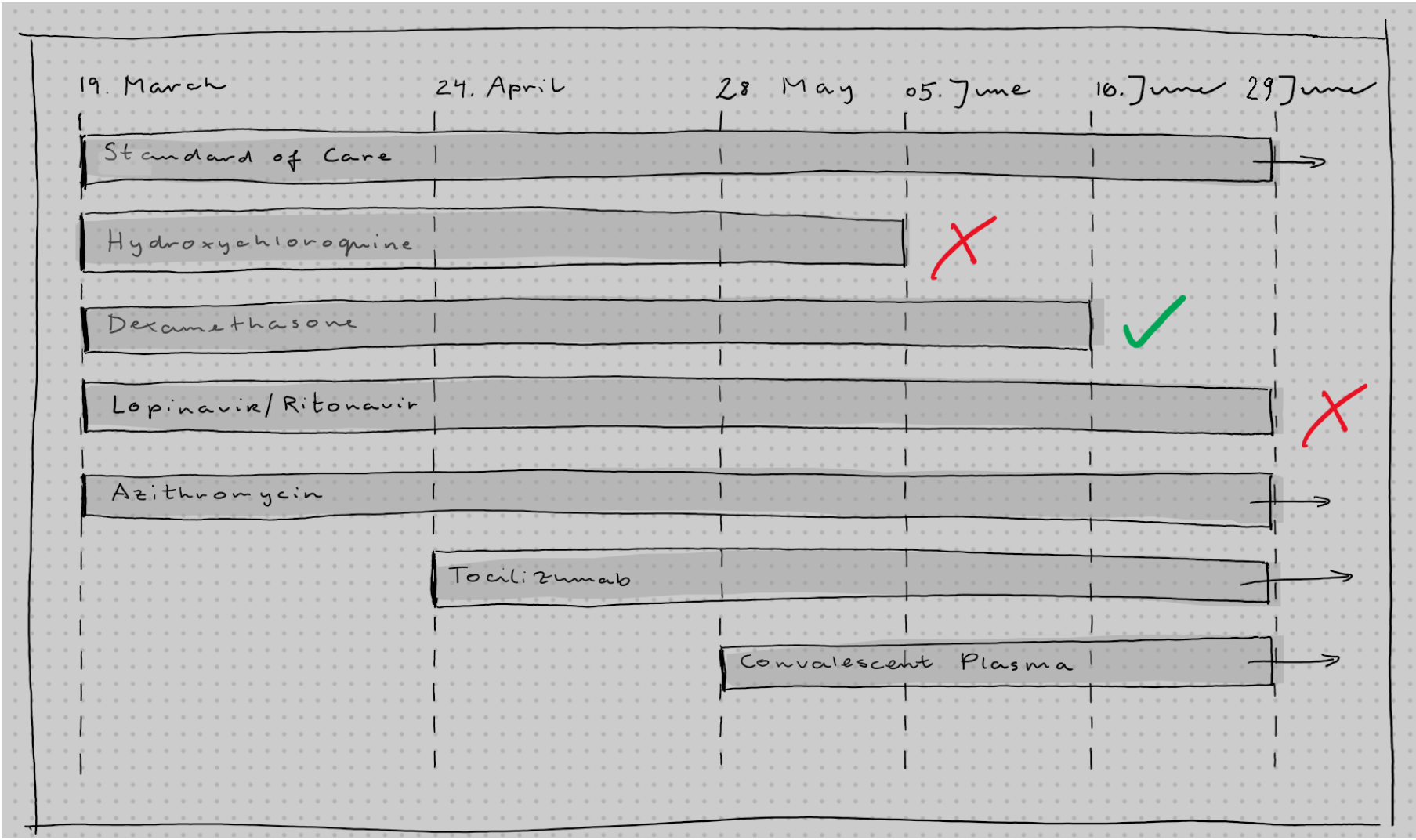
RECOVERY (Horby et al.; 2020a)



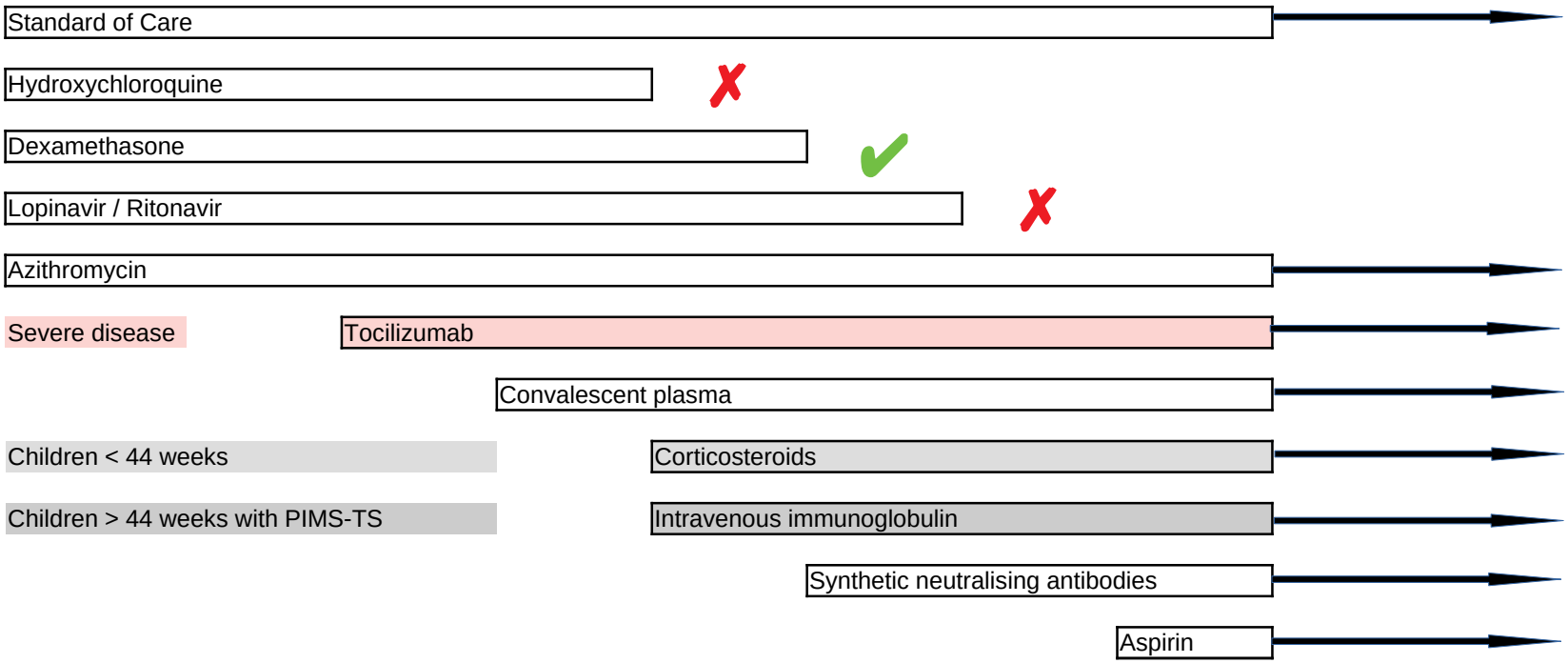
RECOVERY (Horby et al.; 2020b)



RECOVERY (Horby et al.; 2020c)



RECOVERY


Standard of Care
Hydroxychloroquine
Dexamethasone
Lopinavir / Ritonavir
Azithromycin
Severe disease
Tocilizumab
Convalescent plasma
Children < 44 weeks
Corticosteroids
Children > 44 weeks with PIMS-TS
Intravenous immunoglobulin
Synthetic neutralising antibodies
Aspirin

Discussion

- Well conducted randomized clinical trials are the gold standard for evidence gathering, also during a pandemic

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- Trials in a new disease should be adaptive
- ADWG designed several COVID-19 trials (e.g. early phase platform AGILE, DECISIVE, ...) and is otherwise involved
- Collaboration is crucial (Dean et al, 2020)

References

Cao B et al. (2020) A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine*.

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Horby P et al. (2020a) Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. *New England Journal of Medicine*.

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Dean NE et al. (2020) Accumulating Evidence from Randomized Clinical Trials across Outbreaks. *New England Journal of Medicine*. 382(14):1366-1369.