Designing efficient clinical trials during a pandemic

Some personal lessons from the RECOVERY trial

Thomas Jaki

Lancaster University
t.jaki@lancaster.ac.uk

University of Cambridge
thomas.jaki@mrc-bsu.cam.ac.uk

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

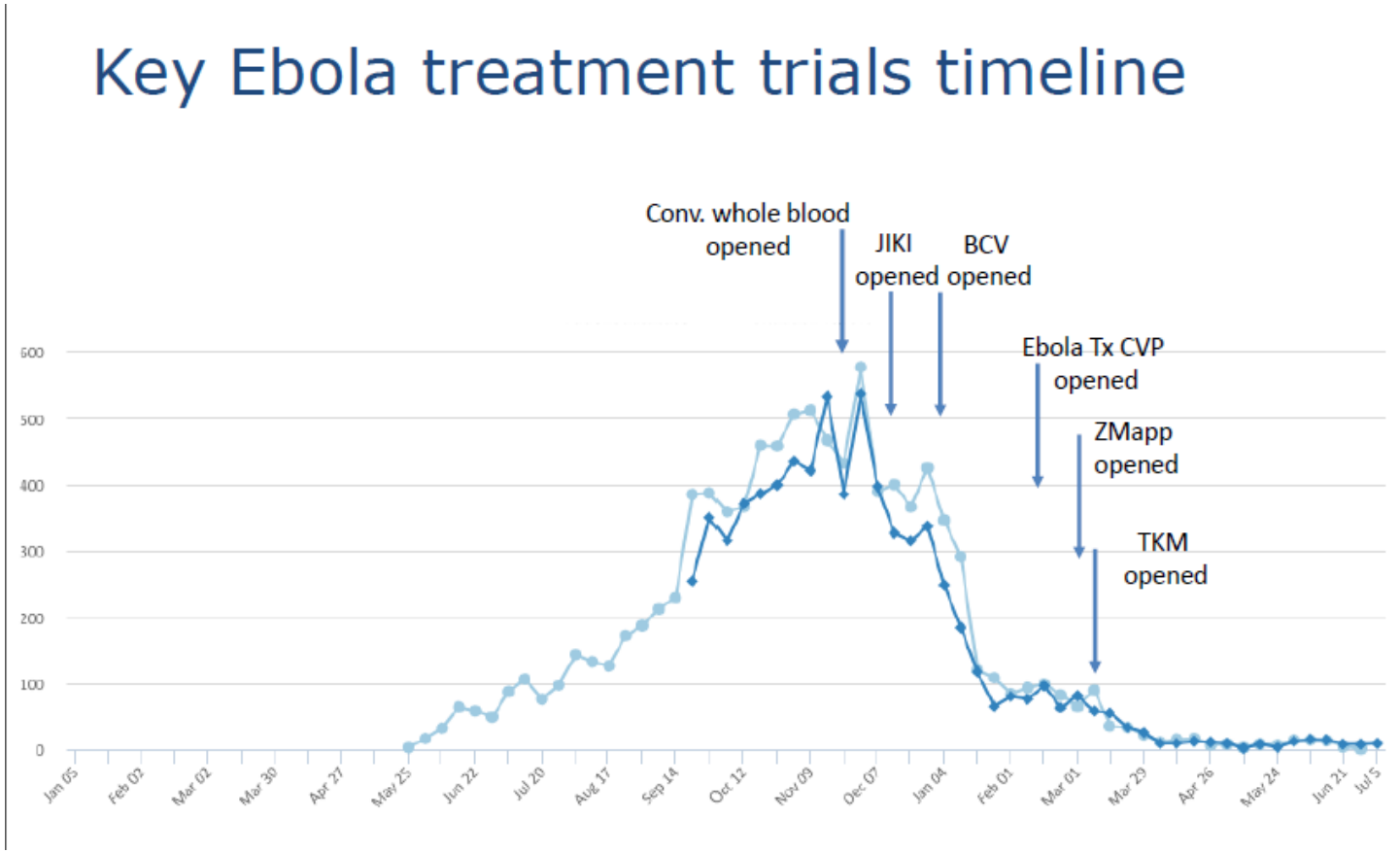


Figure: Number of new Ebola cases over time (courtesy of Peter Horby).

LOTUS trial (Cao et al, 2020)

- Trial started on 18 January 2020
- Open-label trial of Loptinavir/Ritonavir
- Endpoint: rate of clinical 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.

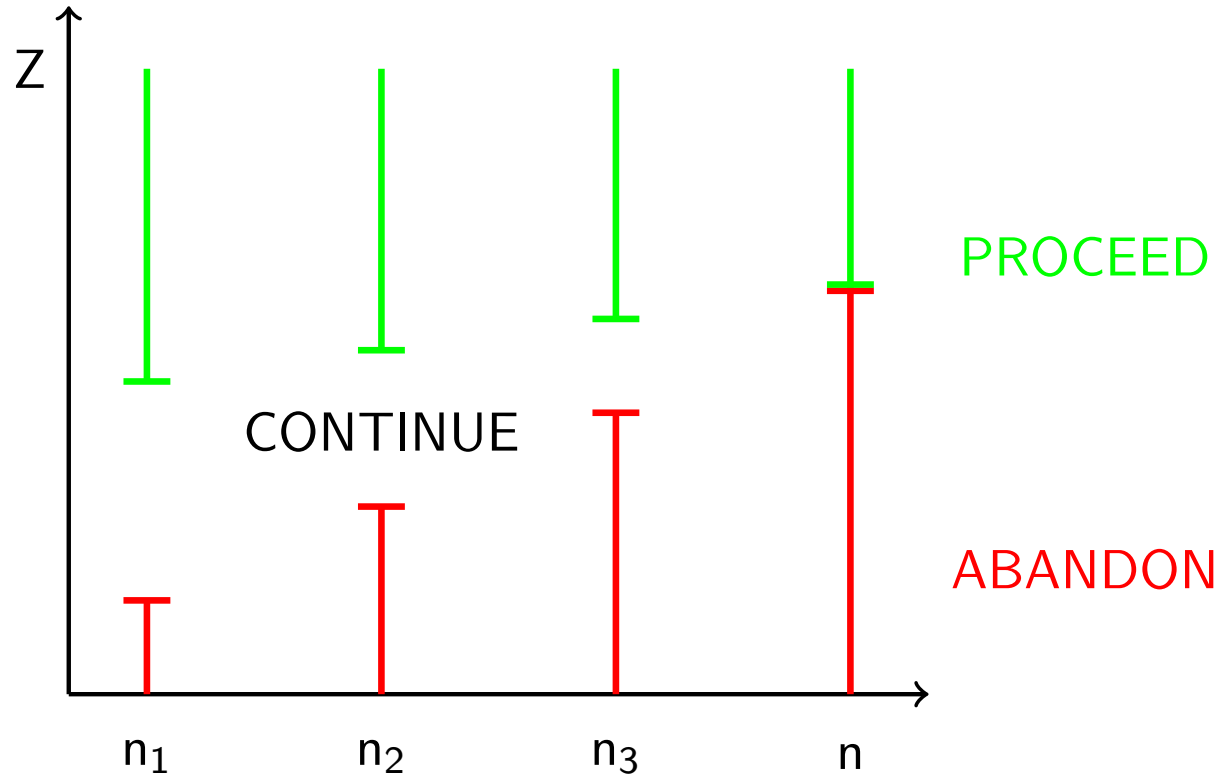
- Trial started without formal design

Adapting the design

- Primary endpoint - informed by Influenza trials
  - changed to time to clinical improvement
- Formal sample size calculation
- Discussed group-sequential and multi-arm design options

Remdesivir trials (Wang et al, 2020)

- Two trials - mild/moderate and severe cases
- Group-sequential design



Remdesivir trials (Wang et al, 2020)

- 1 interim analysis planned at half-way point
- Primary endpoint: time to 2-point improvement on 6-point scale.
  - Collapsed category 1 and 2 from previous endpoint
- Recruitment within 10 days of symptom onset

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

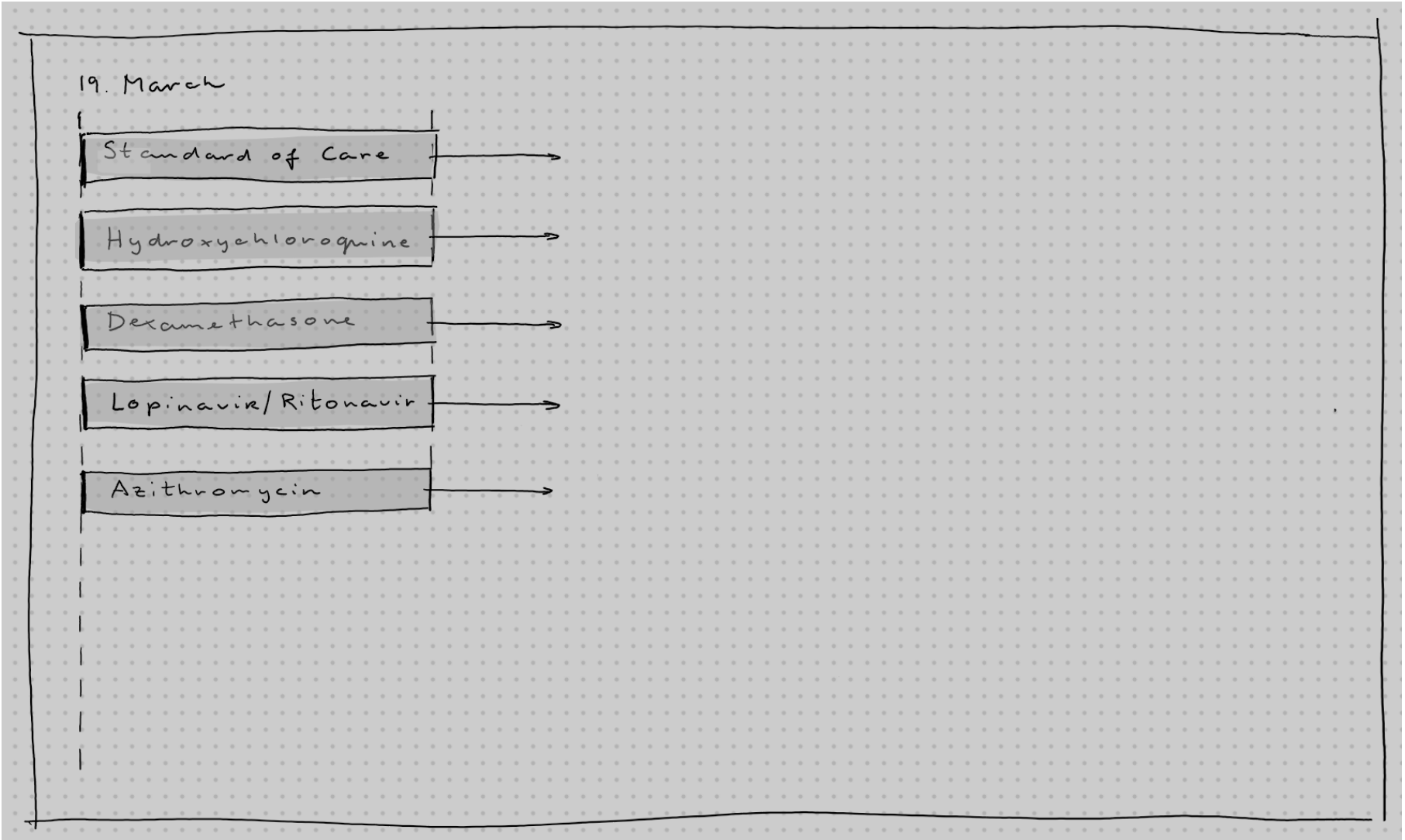
RECOVERY (www.recoverytrial.net)

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

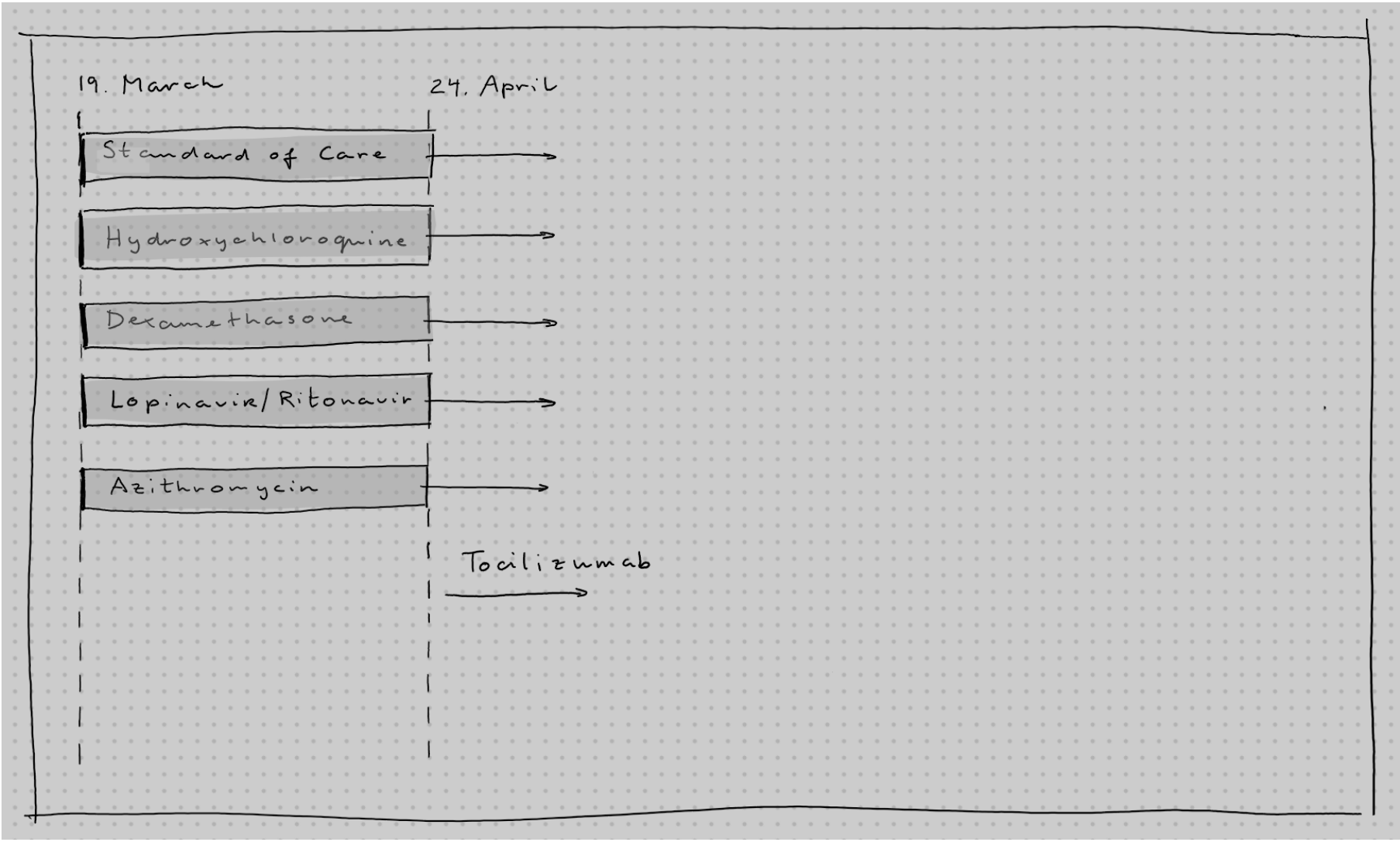
A great story . . .

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

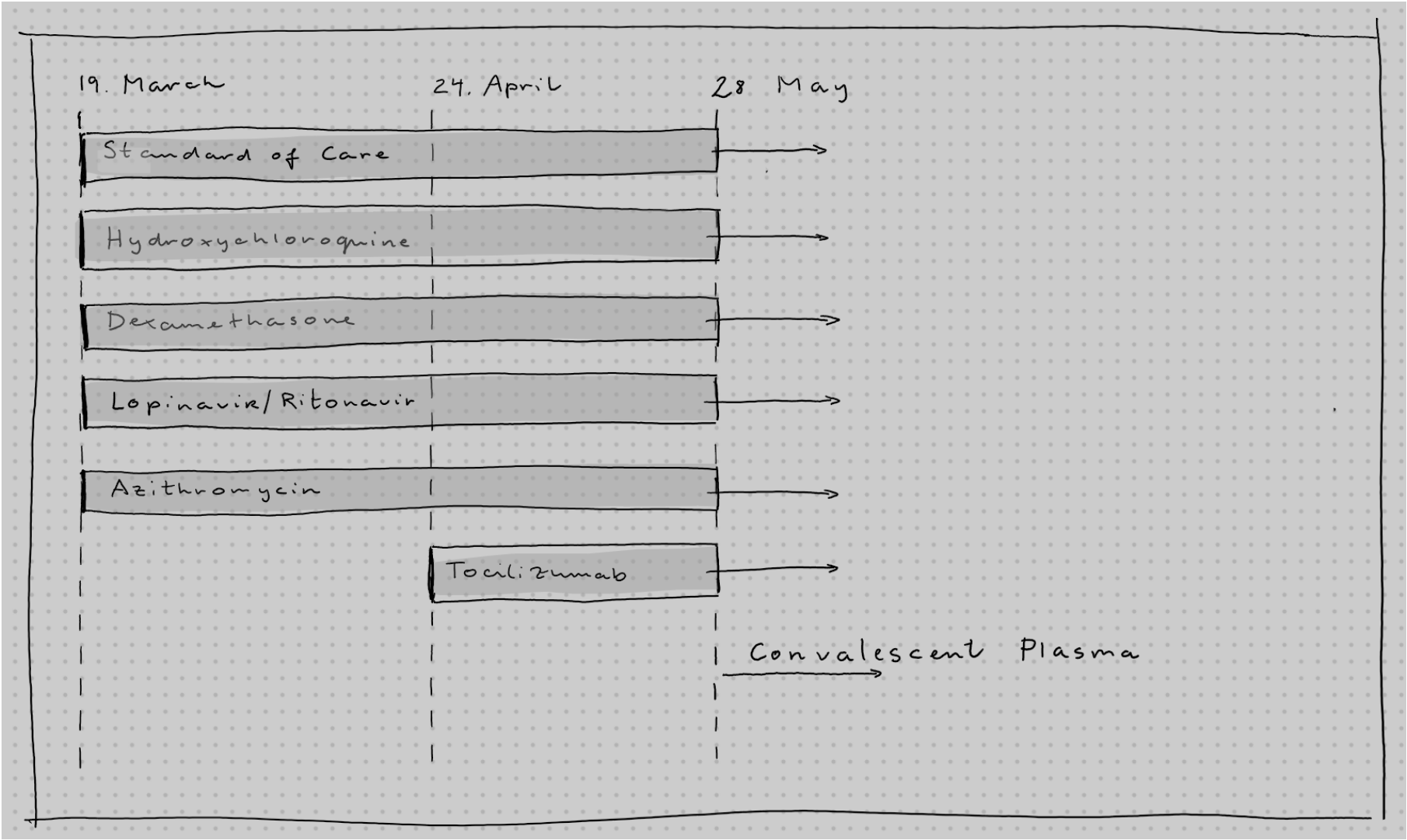
RECOVERY


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

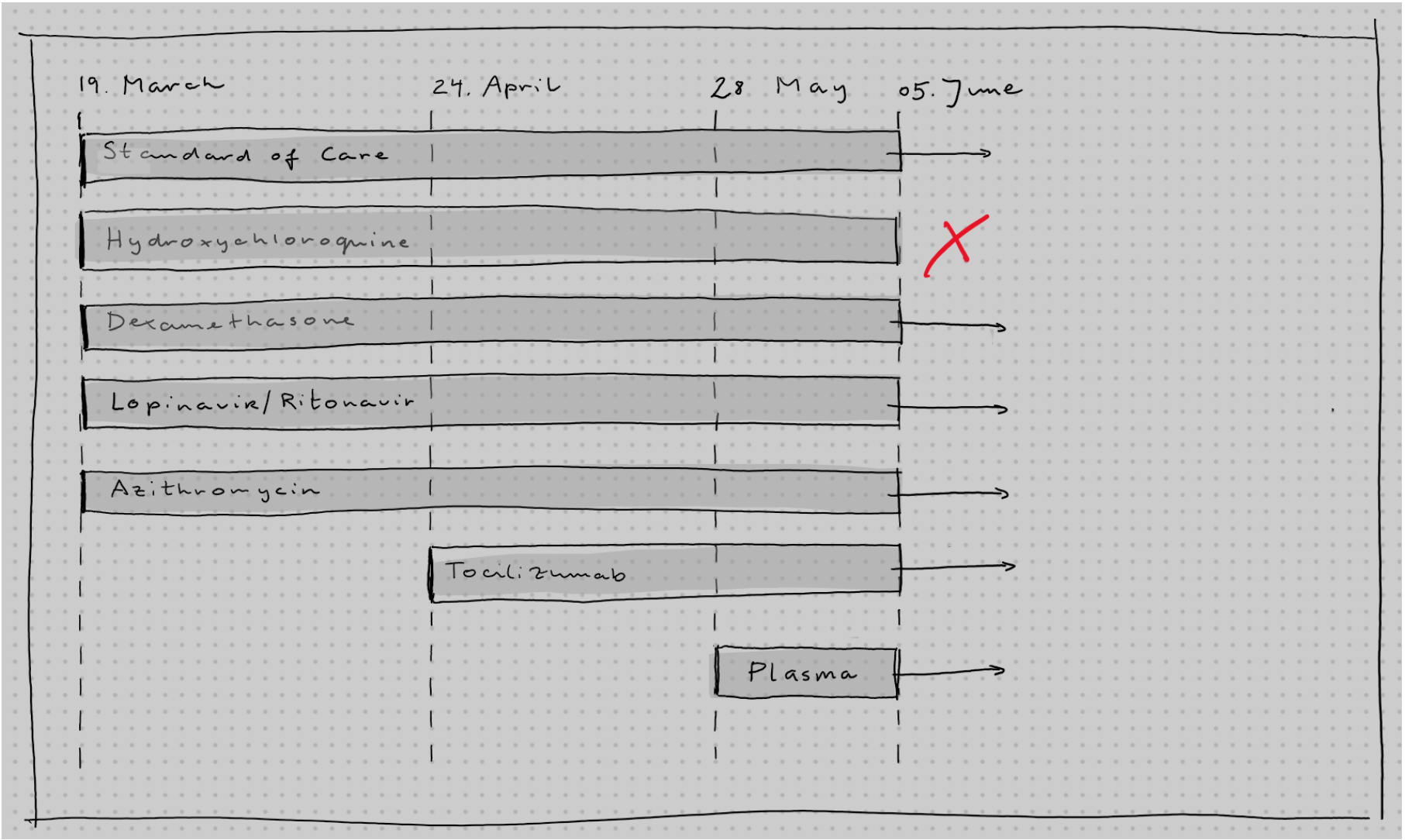
RECOVERY


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

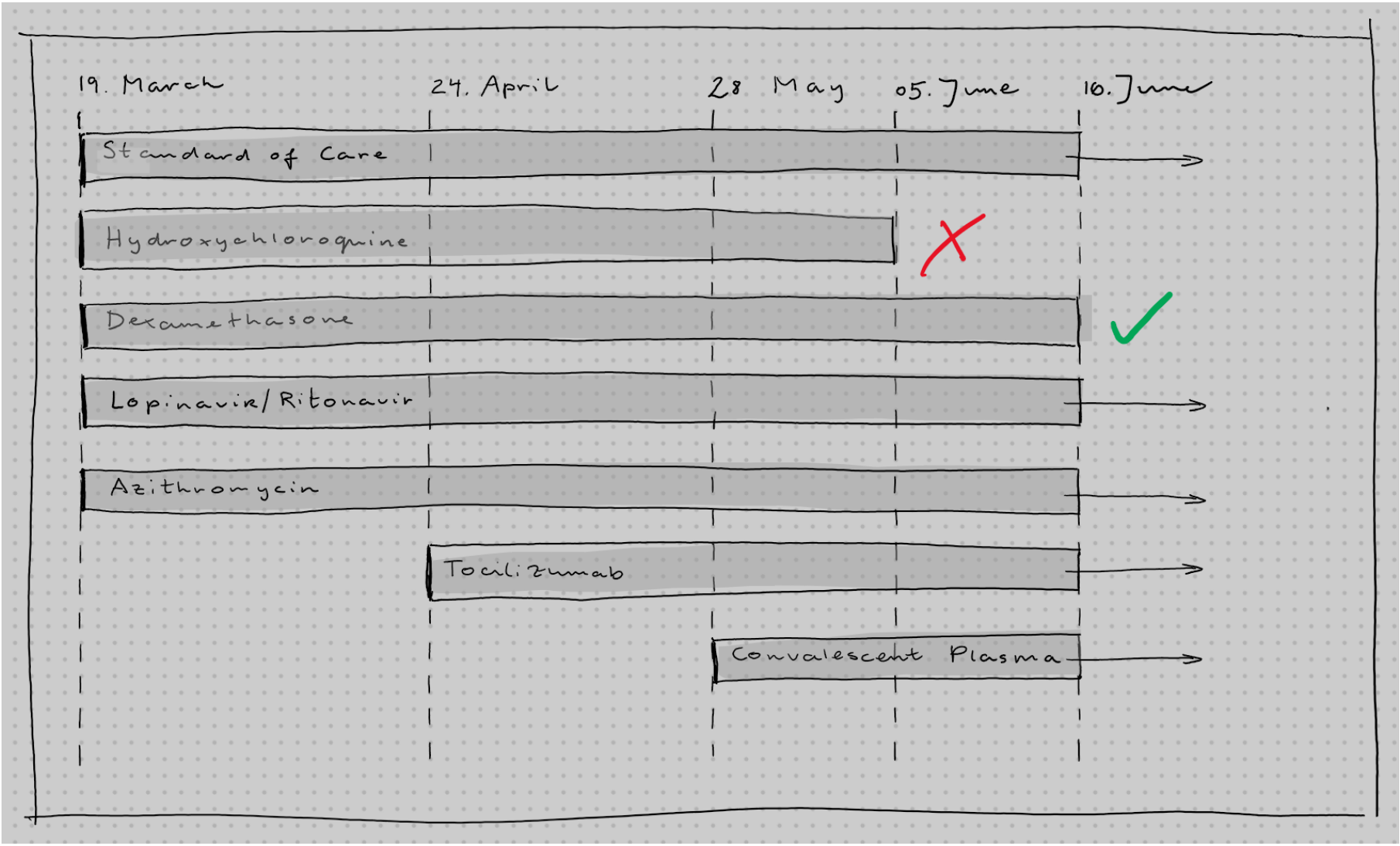
RECOVERY


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

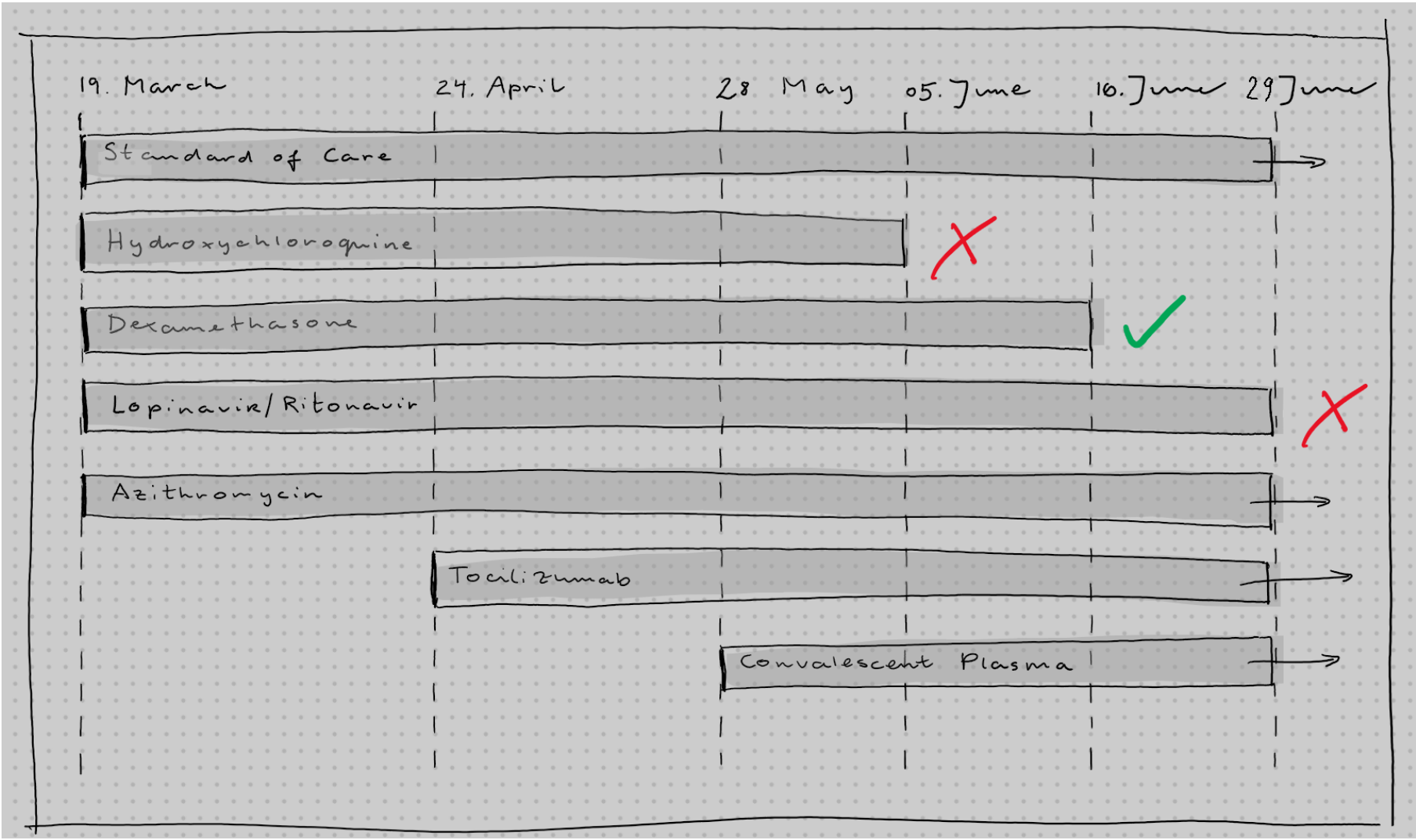
RECOVERY (Horby et al.; 2020a)



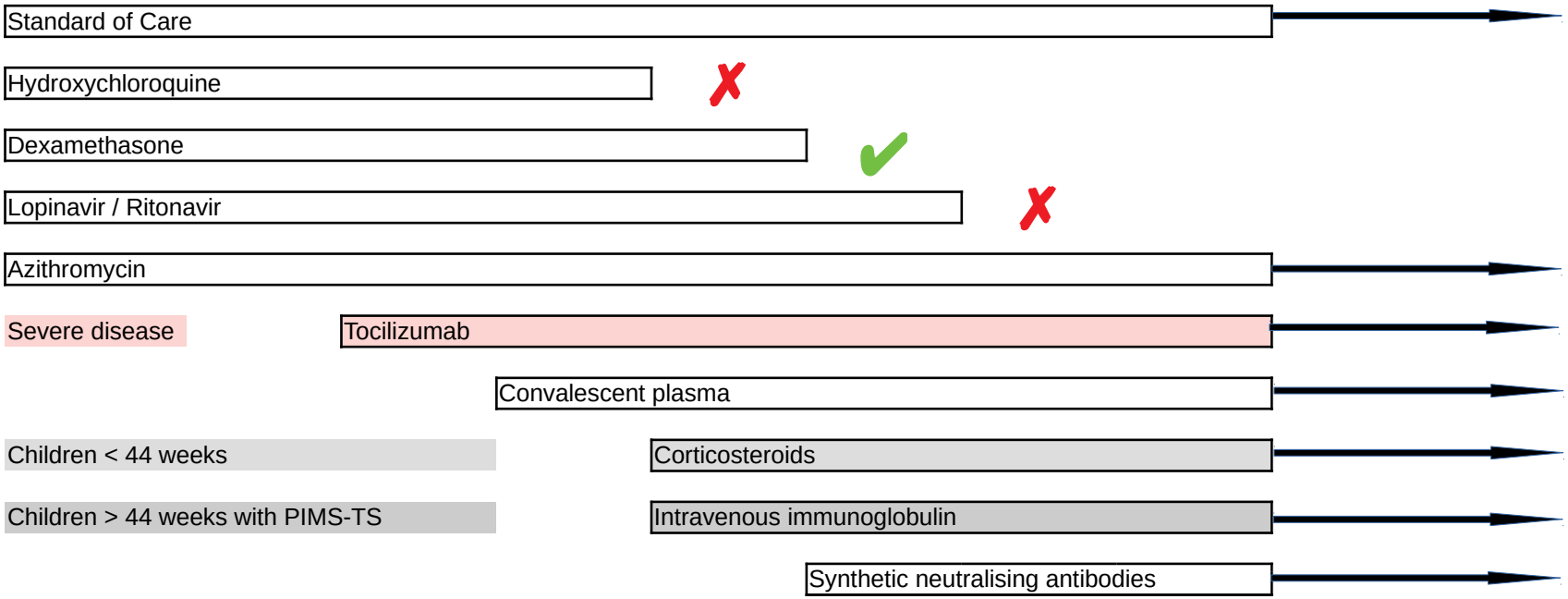
RECOVERY (Horby et al.; 2020b)



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

. . . not all perfect

- how, when and what do you include in the study?
  - e.g. Convalescent plasma added in a factorial manner[2]
- no formal stopping rules
  - DMC decides on stopping
- . . .

[2] How to add an arm while controlling FWER: Burnett et al. (2020)

. . . not all perfect

- how, when and what do you include in the study?
  - e.g. Convalescent plasma added in a factorial manner[2]
- no formal stopping rules
  - DMC decides on stopping
- . . .
- huge sample sizes

[2] How to add an arm while controlling FWER: Burnett et al. (2020)

Choice of primary endpoint (Dodd et al., 2020)

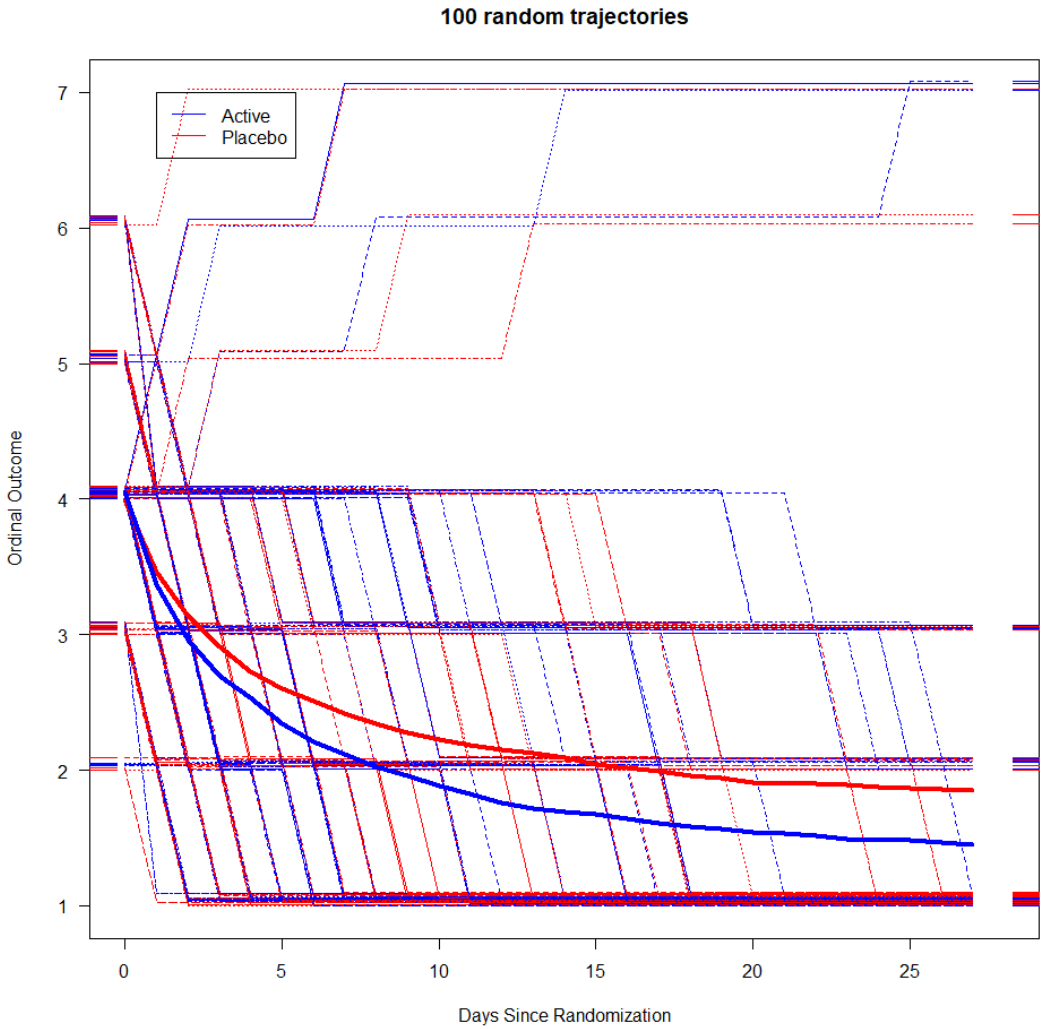
- Recovered vs not recovered almost always of interest (Whitehead & Horby, 2017)

- Ordinal scales (e.g. WHO clinical severity score)

0	Uninfected
1	Ambulatory, no limitation on activities
2	Ambulatory, limitation on activities
3	Hospitalized, no oxygen therapy
4	Hospitalized, oxygen by mask or nasal prongs
5	Hospitalized, non-invasive ventilation or high-flow oxygen
6	Hospitalized, intubation and mechanical ventilation
7	Hospitalized, ventilation + organ support - pressors, RRT, ECMO
8	Death

- Biomarkers (e.g. SpO2/FiO2 ratio, viral load)

A simulation study



Scenarios

	Proportional Odds					Time-to-event			Proportion
Scenario	**Day 1**	**Day 7**	**Day 14**	**Day 28**	**Mean Score**	**Time to 2-point improvement**	**Time to Recovery**	**Time to Death**	**28 Day Mortality**
Reference	0.05	0.76	0.85	0.88	0.80	0.81	0.82	0.63	0.58
Lagged treatment effect	0.05	0.05	0.76	0.86	0.66	0.82	0.78	0.58	0.73
Faster recoveries	0.05	0.86	0.93	0.93	0.87	0.87	0.89	0.65	0.59
Higher mortality rate	0.05	0.76	0.85	0.88	0.80	0.81	0.82	0.75	0.71
Mortality differences only	0.05	0.23	0.26	0.32	0.24	0.31	0.28	0.51	0.46

Discussion

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

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- Well conducted randomized clinical trials are the gold standard for evidence gathering, also during a pandemic
- Trials in a new disease should be adaptive
- Mortality is a desirable primary endpoint, but may be difficult in practice
- Time-to-improvement/recovery endpoints are useful alternatives
- Focus should not only be on repurposed treatments
- Collaboration is crucial (Dean et al, 2020)

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