A hybrid design approach using matched historical controls in the context of a randomised controlled study to evaluate a repurposed treatment in patients with severe COVID-19.

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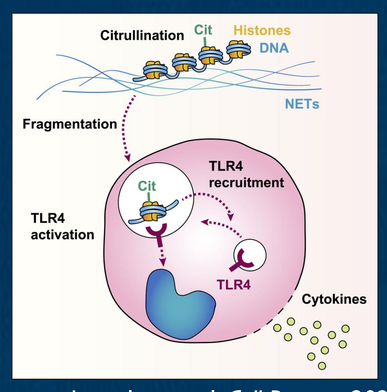
Scientific Rationale

COVID-19 associated with:
- Lung damage.
- Build up of Neutrophil Extracellular Traps (NETs).
- Hyperinflammation.

Dornase alpha:
- Existing treatment for Cystic fibrosis.
- Clears NETs.
- Reduces hyperinflammation.



Tsourouktsoglou et. al. *Cell Reports* 2020

Challenges

Very little known about COVID-19 at the time

Limited information to inform study design

Urgent need to meet unmet medical emergency

Appropriate outcome variable?

What is the variability of the outcome?

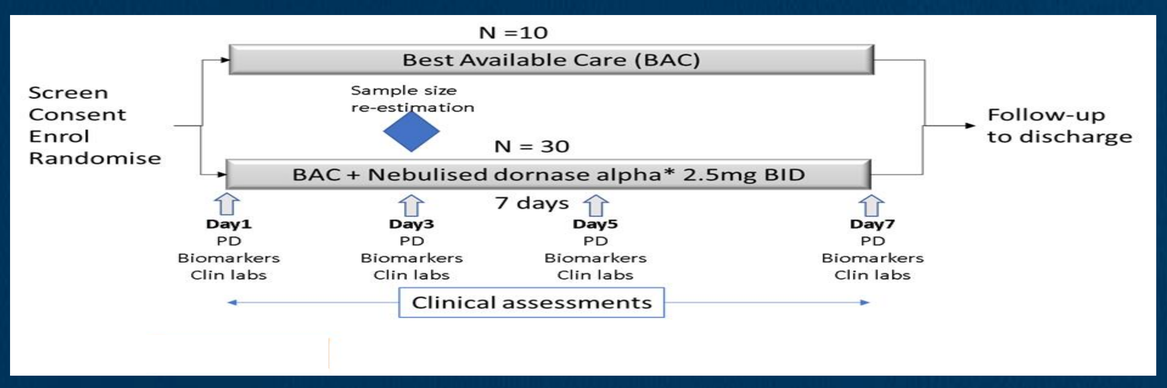
Limited time

Numerous competing clinical studies and platforms

Rapidly changing situation: case numbers, vaccines.

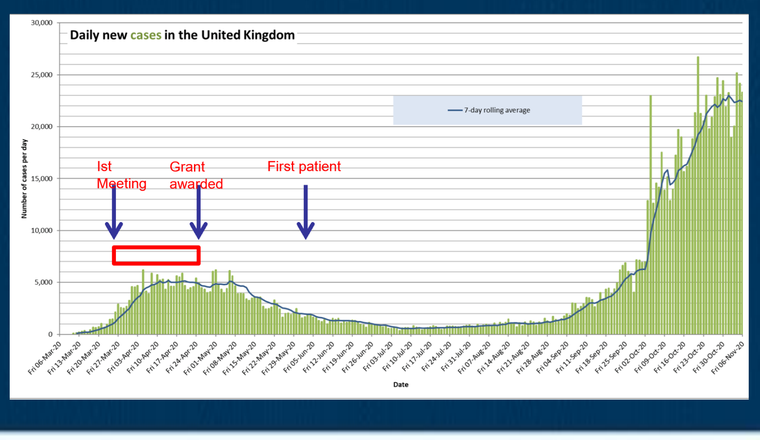
Approach

- Randomise 3:1 Dornase alpha + best available care: best available care (BAC).
- Supplement BAC arm with 60 historical controls using electronic health records.
  - Accelerates study timeline
  - Motivates participants to enroll into study
  - Selected using propensity score matching
- CRP chosen as primary endpoint:
  - Variability well understood
  - Collected routinely in electronic health records
  - Clinically important marker of inflammation
  - Early data from China and Italy supporting the role of CRP in COVID-19



Inclusion criteria:
- Over 18 years
- Hospitalised
- Hypoxic, not on ventilator
- CRP ≥ 30mg/L

Rapid initiation of COVASE trial:



Results: propensity score matching

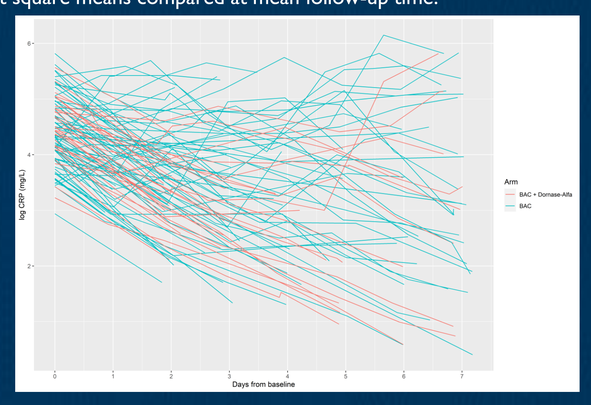
	Randomised to Dornase alpha + BAC (N=30)	Randomised to BAC (N=9)	Historical controls (N=60)	All BAC (N=69)	Total (N=99)
Age (years)					
N	30	9	60	69	99
Mean	56.8	53.3	57.3	56.8	56.8
SD	12.5	13.7	14.5	14.3	13.7
Median	58.0	53.0	57.0	57.0	57.0
Gender					
Male N (%)	23 (76.7)	7 (77.8)	45 (75.0)	52 (75.4)	75 (75.8)
BMI (kg/m^2)					
N	30	9	60	69	99
Mean	27.8	30.8	27.8	28.2	28.0
SD	4.7	7.8	5.6	6.0	5.6
Median	26.5	28.9	27.9	28.2	27.7
Baseline CRP (mg/L)					
N	30	9	60	69	99
Mean	101.9	91.9	100.7	99.5	100.2
SD	52.2	68.1	68.3	67.8	63.3
Median	86.3	74.6	75.8	75.3	79.6
Key Comorbidity					
Yes N (%)	14 (46.7)	6 (66.7)	32 (53.3)	38 (55.1)	52 (52.5)

Results: primary analysis

CRP (mg/L)	Randomised to Dornase alpha + BAC (N=30)	All BAC (N=69)	Ratio Dornase alpha + BAC : BAC	p-value*
N	30	69		
Least-square mean CRP (95% CI)*	23.23 (17.71, 30.46)	34.82 (28.55, 42.47)	0.67 (0.49, 0.91)	0.010

*Modelled on log scale. Linear mixed model. Least square means compared at mean follow-up time.

Log CRP decline approximately linear over 7 days follow-up. Statistically significant (2 sided alpha 0.05) difference in least squared mean log(CRP) at the mean follow-up time between arms.



Results: sensitivity analyses

CRP (mg/L)	Randomised to Dornase alpha + BAC	All BAC	Ratio Dornase alpha + BAC : BAC	p-value*
Per-protocol population				
N	29	68		
Least-square mean CRP (95% CI)*	22.64 (17.35, 29.54)	34.82 (28.70, 42.24)	0.65 (0.48, 0.88)	0.006
Randomised participants only				
Per-protocol population				
N	30	9		
Least-square mean CRP (95% CI)*	22.12 (17.16, 28.50)	36.34 (22.79, 57.94)	0.61 (0.38, 0.98)	0.041

*Modelled on log scale. Linear mixed model. Least square means compared at mean follow-up time.

Conclusions

- Dornase alpha shown to be safe and effective in hospitalized COVID-19 patients.
- Multiple sensitivity analyses provided further supportive evidence of efficacy.
- Use of historical controls worked well in this context because they were contemporaneous and relevant data on primary and secondary endpoints and were routinely collected in clinical practice.
- However, a lot of data cleaning and preparation was required.
- The rapidly changing environment posed particular problems for the study with regards to recruitment and the concept of best available care.

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References

Tsourouktsoglou et. al. *Cell Reports* 2020

Porter et. al. *MedRxiv* 2022

Acknowledgements

We are grateful to all trial participants and to LifeArc for funding

unlocking the value in data