Large, simple, “platform” RCTs of treatments in pandemics

Need for reliable assessment of MODERATE effects on mortality

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Some examples of successful “platform” trials

PALM trial in Ebola showed 2 particular antibodies produced better survival than 2 other treatments

Recovery, Solidarity, REMAP-CAP and ACTT trials in COVID evaluated several inpatient treatments, showing some to be effective and some not
One key need is reliable assessment of MODERATE effects on mortality
Requirements for reliable assessment of **MODERATE** effects: **NEGLIGIBLE** biases, and **SMALL** random errors

Avoidance of **MODERATE** biases: **RANDOMISE** properly
Non-randomised ‘real-world’ evidence can have moderate biases

To achieve **SMALL** random errors, enter **LARGE** numbers
Make everything as simple as possible & get wide collaboration
Two particular pandemic problems:
(1) Need to move FAST to initiate trials

Make the questions **practicable** and make the study **simple**

Seek **wide** collaboration (if this doesn’t unduly delay start-up)

Avoid undue delay in ethical and regulatory approval (**How??**)
Two particular pandemic problems:
(2) May well need to evaluate MORE THAN ONE treatment

To evaluate more than one drug, factorial (2x2) trials may help as they are more efficient than multi-way randomisation (if they don’t unduly delay trial start-up, or slow recruitment)

“Platform” trials aim to move smoothly from one drug to another, (reducing the disruption of re-establishing the trial machinery from scratch as soon as a new question has to be answered)

But, neither must be at the expense of inadequate sample sizes!
Assessment of MODERATE differences in mortality

• Need all the main trial results, to avoid undue emphasis on particular studies

<table>
<thead>
<tr>
<th>Drug and trial</th>
<th>ClinicalTrials.gov identifier</th>
<th>Initial dose and administration</th>
<th>No. of deaths/total No. of patients Steroids No steroids</th>
<th>Odds ratio (95% CI)</th>
<th>Favors steroids</th>
<th>Favors no steroids</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>DEXA-COVID 19 NCT04325061</td>
<td>High: 20 mg/d intravenously</td>
<td>2/7 2/12</td>
<td>2.00 (0.21-18.69)</td>
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<td>0.92</td>
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<tr>
<td>CoDEX</td>
<td>NCT04327401</td>
<td>High: 20 mg/d intravenously</td>
<td>69/128 76/128</td>
<td>0.80 (0.49-1.31)</td>
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<td>18.69</td>
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<tr>
<td>RECOVERY</td>
<td>NCT04381936</td>
<td>Low: 6 mg/d orally or intravenously</td>
<td>95/324 283/683</td>
<td>0.59 (0.44-0.78)</td>
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<td>57.00</td>
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<tr>
<td>Subgroup fixed effect</td>
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<td></td>
<td>166/459 361/823</td>
<td>0.64 (0.50-0.82)</td>
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<td>76.60</td>
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<tr>
<td>Hydrocortisone</td>
<td>CAPE COVID NCT02517489</td>
<td>Low: 200 mg/d intravenously</td>
<td>11/75 20/73</td>
<td>0.46 (0.20-1.04)</td>
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<td>6.80</td>
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<td>COVID STEROID</td>
<td>NCT04348305</td>
<td>Low: 200 mg/d intravenously</td>
<td>6/15 2/14</td>
<td>4.00 (0.65-24.66)</td>
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<td>1.39</td>
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<td>REMAP-CAP</td>
<td>NCT02735707</td>
<td>Low: 50 mg every 6 h intravenously</td>
<td>26/105 29/92</td>
<td>0.71 (0.38-1.33)</td>
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<td>11.75</td>
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<tr>
<td>Subgroup fixed effect</td>
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<td>43/195 51/179</td>
<td>0.69 (0.43-1.12)</td>
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<td>19.94</td>
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<tr>
<td>Methylprednisolone</td>
<td>Steroids-SARI NCT04244591</td>
<td>High: 40 mg every 12 h intravenously</td>
<td>13/24 13/23</td>
<td>0.91 (0.29-2.87)</td>
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<td>3.46</td>
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<tr>
<td>Overall (fixed effect)</td>
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<td>222/678 425/1025</td>
<td>0.66 (0.53-0.82)</td>
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<td>100.0</td>
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</tbody>
</table>

Weighted average of all trial results reliably demonstrates definite benefit
Meta-analyses should use assumption-free weighted averages

A weighted average of all trial results gives similar weight to each death, no matter what size trial it is in, but it does NOT assume true RR is the same in all trials (so it should NOT be called “the fixed-effect method”)

Where there seems to be substantial heterogeneity between the results of different trials, “random-effects methods” give substantially greater weight to the deaths in the smaller trials, which is not appropriate – and, if there is only one large trial, each death in it may be virtually ignored

Weighted average of all trial results reliably demonstrates definite benefit

“Random effects” method misleadingly suggests uncertain benefit
Assessment of MODERATE differences in mortality

• Need **all** the main trial results, to avoid undue emphasis on particular studies*

* Don’t give events in smaller trials much greater weight than those in larger trials (ie, avoid using “random effects” methods)
Main need: bigger numbers randomised

To discover how best to treat many millions, many thousands should be randomised with respect to many different treatments,

and many tens of thousands should be randomised with respect to many different vaccination questions.

Simplicity, multi-centricity, platforms, and meta-analyses are all means to big numbers