**In epidemics or in pandemics,
consider randomizing 3 ways:**

A vs B vs AB

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consider randomizing 3 ways:**

A vs B vs AB
(eg, A=monoclonal antibody, B=small-molecule drug)

AB vs B evaluates A

AB vs A evaluates B

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Assumes that neither drug nullifies the other drug's effects.

Does not assume independence of effects of A and of B.

NB It is likely that the combination AB has not been tested for safety,
but it may still be appropriate to proceed with a trial that includes AB.

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In epidemics or in pandemics,
consider randomizing 3 ways:

Acceptability: in a trial of A vs B vs AB,
all participants will get at least one drug

In contrast, a control group given no active treatment
(eg, in a 2-way trial of A vs no active drug, or in
a 4-way [2x2] trial of A vs B vs both vs neither)

may prove to be wholly unacceptable,
or may greatly delay the trial starting,
or may greatly limit recruitment rate.

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A 3-way trial of A vs B vs AB is
better than a 2-way trial of A vs B

In A vs B, a null result may mean both drugs work,
or may mean neither drug works.

In A vs B, even if A is definitely better than B,
AB might be shown to be better than A alone

(eg, PALM trial of A=antibody vs B=remdesivir in Ebola)

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Why randomise at all?
Why not just try giving new drugs,
and observe whether they seem to work?

Observation failed in the West African Ebola outbreak (30,000 cases),
but randomization succeeded in the Eastern DRC outbreak (3000 cases)

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Why randomise at all?
Why not just try giving new drugs,
and observe whether they seem to work?

(now aided by complex computer models of "historical controls"
or "propensity-score matching" or "*in silico* twin patients" or
"Bayesian probability calculations" [as for Z-Mapp in W Africa])

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In epidemics or in pandemics,
consider randomizing 3 ways:

A vs B vs AB: Sensitivity depends on numbers

IF 600 patients would be randomized, then

a 3-way trial (A vs B vs AB)
would compare only 200 A vs 200 not-A,

but a 2-way trial (A vs not-A)
or a 2x2 trial (A vs B vs both vs neither)
would compare 300 A vs 300 not-A.

But, if a 3-way trial is much larger than a 2x2 trial would have been then it may well be much more sensitive.

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