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# Mitigation of the Ethical Dilemma in Ebola Drug Effectiveness Testing

In the News Feature "A Dose of Reality" (*Science*, 21 November, p. 908), J. Cohen and K. Kupferschmidt report on an intense debate at the World Health Organization (WHO) meeting in early November. Summarizing this debate, two drugs (Brincidofovir and Favipiravir) appear to be ready for efficacy trials using randomized controlled trials (RCTs), but a crucial NGO (Doctors Without Borders or MSF) is strongly opposed, on the ethical ground that such trials would wrongly deny some participants a treatment which is agreed to be of possible value.

This is a false dichotomy in a way – and no ethical dilemma need necessarily exist – because there is no inherent statistical need for an RCT to deny *any* participant at least some level of treatment. For example, the $i^{th}$ participant could be treated from his/her own numbered vial of medication containing, say, Brincidofovir at a concentration level randomly chosen between the largest value deemed reasonably safe ("$B_i = B_{max}$") and a smaller concentration ("$B_i = B_{min}$") still deemed to have some chance of being clinically useful. One could argue, however, that a truly ethical value of $B_{min}$ might typically be larger than that chosen by an experimenter focused on generating data with sufficient sample variation in $B_i$ as to yield a usefully precise estimate of the mortality impact coefficient on $B_i$ with an economically feasible number of participants. Indeed, many experimenters would argue for setting $B_{min}$ to zero for this reason, whereas this is clearly a choice which raises ethical issues. My first point, then, is that a reasonable and expeditious way forward is to compromise by setting $B_{min}$ notably in excess of zero and to explicitly pay for ethical improvement by increasing the sample size sufficiently as to compensate for the resulting diminution in statistical precision.

Secondly – noting that a separate study is planned, to evaluate the effectiveness of Favipiravir – I suggest that a better way to substantially mitigate the ethical dilemma is to, in essence, combine the two efficacy studies into one and to take the trouble of uniformly distributing the concentrations of both drugs over their 'allowed' intervals, rather than providing only one drug and at only two possible concentration values. The treatment vial for subject *i* in such a combination study would thus contain *both* drugs: Brincidofovir in a concentration randomly chosen from within – i.e., uniformly distributed over – the interval $[B_{min}, B_{max}]$ and Favipiravir in a concentration randomly chosen in a similar manner from within the interval $[F_{min}, F_{max}]$, where $F_{min}$ and $F_{max}$ are analogously defined. There being no *a priori* reason to believe that these two drugs are antagonists, ethical values for $B_{min}$ and $F_{min}$ can be smaller in this combination study, since the unluckiest participant will now be receiving (at worst) the minimal value of both drugs. Indeed, most participants receiving a relatively small amount of one drug will be receiving at least an intermediate amount of the other. Thus, this combination study increases the statistical variation in both drug concentration variables – enhancing estimation precision – while notably mitigating the ethical dilemma. Of course, for such a study one would need to harmonize both the professional incentives of the two experimental groups and, possibly, the financial incentives of the two drug makers; one can hope that these obstacles could be readily overcome. Note, in this context, that what is most crucially being combined here is the

efficacy testing of the two drugs: the trials could still be conducted in two separate countries at two different times. The cost, of course, is the increased complexity involved in preparing the treatment vials.

The 'cost' in terms of the statistical analysis is only minimal, as the data can (and should) still be analyzed using quite standard regression methods: probit regression or the linear probability model (if one is a frequentist), or else the analogous Bayesian latent variable regression methods.[1] At least one additional mortality impact coefficient would need to be estimated in a such a combination study – on the concentration of the second drug – but this would be more than compensated for by the fact that the single sample for such a study could be larger and by the fact that (if $B_{min}$ and $F_{min}$ are reduced) then the sample could feature more sample variation in both of the drug concentrations.[2] Both of these aspects would increase parameter estimation precision, regardless of whether one analyzes the data using frequentist or Bayesian methods. Importantly, a study of both drugs at once could use a straightforward interaction term to evaluate possible synergy between the effectiveness of the two drugs, speeding up the process of designing possible combination therapies, as have been found useful in other contexts, such as treating HIV.[3]

In principle, the same idea would also be applicable when, in time, additional Ebola treatments – e.g., $ZM_{app}$ – become available. The statistical analysis for a study using regression techniques remains straightforward with more than two treatments, but it is worth noting that a graphical analysis of the data has its own unique strengths – e.g., in spotting threshold effects, etc. – and a two-drug study has the notable advantage that a plot of actual or expected mortality values versus the drug concentrations is interpretably three-dimensional.

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[1]These are all standard techniques, already (in the case of the two frequentist methods) implemented in commercial software, such as Stata. Technical descriptions of these frequentist methods are given in a number of graduate-level textbooks (e.g., William H. Greene, *Econometric Analysis*, 2011); very accessible descriptions can be found in my textbook: Ashley *Fundamentals of Applied Econometrics*, 2012, Chapters 9 and 19. Cohen and Kupferschmidt note that Bayesian statistical analysis is already being planned by several analysts. Modern Bayesian analysis is not so amenable to implementation in canned statistical software, but it is very well suited to the analysis of latent variable models, such as are needed in the present context. (One observes whether subject *i* survives or not, but one wants to model a latent – i.e., unobserved – variable: the probability that subject *i* will survive.) All three of these regression methods will likely produce similar results; indeed a failure to do so raises a valuable red flag with regard to all.

[2]A few additional coefficients would need to be estimated in a combined study, however, so as to allow for nonlinearities and so as to evaluate how mortality itself and the mortality impact coefficient for each drug might vary with the values of other observable explanatory variables, such as the participant's initial sickness level and the availability of supportive care. The data from two separate studies – i.e., conducted in two distinct locations – could be easily combined also, but one would then want to include additional explanatory variables to explicitly allow/test for the possibility that the intercept (and other coefficients) might differ across the two data sources.

[3]Such an interaction term simply amounts to including the product $B_iV_i$ as an additional explanatory variable in the model for the mortality rate of subject *i*. If its coefficient in the estimated model is positive, then there is synergy in the two treatments, which suggests that a combination therapy will be valuable.

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