Personal View

Are adaptive randomised trials or non-randomised studies the best way to address the Ebola outbreak in west Africa?

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The Ebola outbreak that has devastated parts of west Africa represents an unprecedented challenge for research and ethics. Estimates from the past three decades emphasise that the present effort to contain the epidemic in the three most affected countries (Guinea, Liberia, and Sierra Leone) has been insufficient, with more than 24 900 cases and about 10 300 deaths, as of March 25, 2015. Faced with such an exceptional event and the urgent response it demands, the use of randomised controlled trials (RCT) for Ebola-related research might be both unethical and infeasible and that potential interventions should be assessed in non-randomised studies on the basis of compassionate use. However, non-randomised studies might not yield valid conclusions, leading to large residual uncertainty about how to interpret the results, and can also waste scarce intervention-related resources, making them profoundly unethical. Scientifically sound and rigorous study designs, such as adaptive RCTs, could provide the best way to reduce the time needed to develop new interventions and to obtain valid results on their efficacy and safety while preserving the application of ethical precepts. We present an overview of clinical studies registered at present at the four main international trial registries and provide a simulation on how adaptive RCTs can behave in this context, when mortality varies simultaneously in either the control or the experimental group.

Introduction

The crushing Ebola virus disease outbreak that has devastated parts of west Africa is the largest recorded in history and represents an unprecedented challenge for health policy, research, and ethics.[1]

Although Ebola has affected people of all ages and both sexes, many of the people affected by the epidemic are young adults (aged 15–44 years)[2] who represent the social and economic backbone of already fragile local communities. The best available figures to estimate the size of the outbreak are chilling and underline a strong geographical inequity that shows the uneven capability of different countries to afford interventions, to contain transmission, and to care for infected people.[2,3] In the three most affected countries (Guinea, Liberia, and Sierra Leone), the effort to contain human-to-human transmission has been grossly insufficient. As of March 25, 2014, WHO[4] reported 24 907 Ebola virus disease cases and 10 326 deaths (41% mortality): 3429 cases from Guinea (2263 deaths), 9602 cases from Liberia (4301 deaths), and 11 841 cases from Sierra Leone (3747 deaths). Other cases have been reported from Mali (eight cases, six deaths), Nigeria (20 cases, eight deaths), Senegal (one case), Spain (one case), UK (one case), and USA (four cases, one death).[4]

Faced with such an exceptional event, WHO declared that it "is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention".[5] Although this is a reasonable statement under the circumstances, some experts argued that well designed randomised controlled trials (RCTs) are both unethical and infeasible in the present circumstances and that researchers should first try to ascertain which intervention is efficacious by doing observational or non-comparative studies.[6] We argue that this represents an inferior strategy and that instead, RCTs should be used from the early stages of human experimentation of candidate Ebola interventions.[7,8]

What has been done until now

The most sensible, and ethically acceptable, strategy for planning interventions during the largest Ebola virus disease outbreak ever recorded should have been to favour clinical studies located in the most affected areas to assess whether new therapeutic options could help those who are in the greatest need—ie, patients with acute Ebola virus disease—although little was done in this vein.

Of the 34 clinical studies submitted to the four main international registries (figure 1): 20 are enrolling healthy participants (only one is located in the main outbreak area), one is an observational study, two are studies launched to assess isolation measures in contacts, and only 11 (a third) are studies aimed to assess the efficacy of new interventions for patients with acute Ebola virus disease.

The analysis of these 11 studies is even more dissatisfying. Only two are RCTs and only one is located in the outbreak area but is not yet recruiting. The other nine studies are aimed at assessing efficacy against non-randomised controls—three of these studies are enrolling participants at present. Table 1 outlines the study design and enrolment status of each study, as of March 1, 2015, and table 2 reports present knowledge about the potential safety and efficacy of the experimental interventions under investigation.

14 months after the start of the outbreak—which has caused more than 10 300 deaths as of March 25, 2015,[4]—the best evidence base for Ebola virus disease treatment is a handful of anecdotal experiences in high-resource settings,[11,13,20,21] which are hardly reproducible in Africa. The unrealistic notion that three uncontrolled studies

(one of which is testing herbal remedies against supportive therapy) could succeed in showing an intervention to have substantial effectiveness against one of the deadliest human infections shows the exceptional scarcity of trial investments made so far in the face of the an outbreak that is still not under control. Even if somehow the present epidemic is eventually contained (something that is far from certain), the world will still be totally unprepared for the next epidemic that could strike again at any time in an equally explosive manner.

Ethical considerations on RCTs

RCTs are widely deemed to be the most important vehicle for generating evidence about the efficacy and safety of novel interventions. The ethical basis of RCTs relies on the principle of clinical equipoise (ie, no genuine evidence exists that an experimental treatment is better than the standard of care) and individual uncertainty (ie, clinical investigators and enrolled patients are substantially uncertain about the merits of the experimental treatment). By providing a virtually unbiased comparator, RCTs guarantee, at best, robustness of results about both the efficacy and safety of investigational drugs. Thus, since the inception of RCTs, researchers have acknowledged that until an intervention has been proven beneficial, randomisation is the most ethical approach and provides the best answer soonest.[7,22–26] The idea that RCTs are ethically unjustified in the present Ebola outbreak might be based on several widespread misconceptions.

The first is a somewhat fatalistic assumption that case fatality rates always exceed 70% because no standard of care exists that can substantially affect the clinical outcomes of patients with Ebola virus disease.[6] This assumption is incorrect because enough evidence exists from previous[27] and present Ebola outbreaks[2] that standard supportive therapy can significantly reduce mortality.[28,29] Remarkably, reported case fatality rates range widely between less than 50% to more than 70% according to the different countries where patients are treated.[2,7] This variability is probably because of the application of supportive therapy and other intangible differences across studies and settings.

The second is the overoptimistic assumption that drug efficacy in preclinical studies unequivocally translates into significant benefits towards the clinical outcomes of patients.[30]

The third is that in phase 1 and 2 research, non-randomised designs are preferable, merely because they are widely used[8] or easily accepted by local communities.

We believe that when ethical aspects of non-randomised studies are considered in the midst of the most terrifying Ebola virus outbreak ever recorded several topical answers arise.[31] First, how will non-randomised studies affect global capability to manage present and future Ebola outbreaks? Second, will non-randomised studies guarantee a reliable assessment of safety of new treatments? Third,
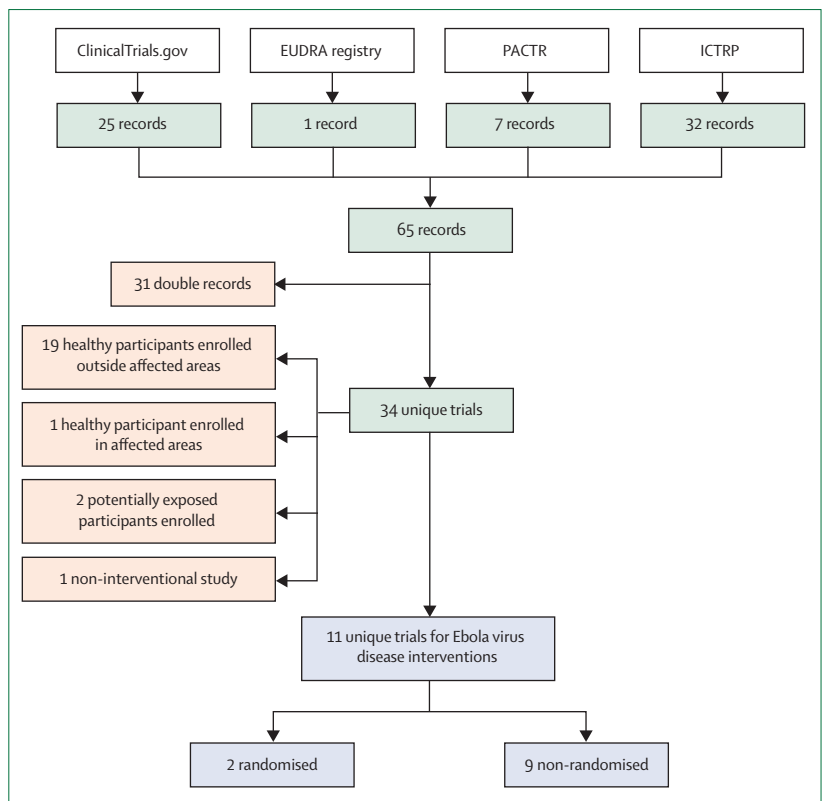

Figure 1: Flowchart for selection of clinical trials enrolling patients with acute Ebola virus disease to assess efficacy or safety, or both, of new interventions
Records or trial to be selected (green boxes); excluded records or trials (orange boxes); analysed trials (blue boxes). EUDRA=European Union Drug Regulatory Authorities. PACTR=Pan African Clinical Trial Registry. ICTRP=International Clinical Trials Registry Platform (WHO).

will non-randomised studies have an immediate effect of ameliorating health-care standards in the location where the study is set, when general improvements in patient care might be as important for reducing mortality as any experimental intervention? Fourth, are non-randomised trials ethical for testing treatments that still do not have a line of mass-scale production and thus can only be used for a few, selected patients? Finally, which kinds of so-called alternative study designs should be approved, which kinds should not be acceptable, and, most importantly, what will the selection criteria be for distinguishing between these choices?

Previous experiences with the severe acute respiratory syndrome outbreak and H1N1 pandemic influenza[32] suggest that these issues can be reasonably met by well designed RCTs, whereas no guarantee is provided by the possibly disorganised implementation of non-randomised studies based on subjective perceptions rather than scientifically sound and rigorous methods.

Randomised designs are better and safer than non-randomised studies

In the present situation of perceived impotence and absence of reliable estimates about the real efficacy of

	Ebola virus disease diagnosis	Location	Recruitment status	Sponsor	Main outcome	Size (design)*	Intervention model	Patent	First received	Anticipated completion date
Randomised										
NCT02307591; PACTR201501001014425	Laboratory confirmed	Sierra Leone	Not recruiting	Emergency Onlus	Safety, efficacy	Up to 132 in two groups (parallel assignment)†	Amiodarone + sSC vs sSC alone	Expired	Nov 21, 2014	August, 2015
NCT02363322	Laboratory confirmed	USA	On invitation	NIAID, USA	Safety, efficacy	Up to 1000 in two groups (parallel assignment)†	ZMapp + sSC vs sSC alone	Mapp Bio	Feb 13, 2015	December, 2016
Non-randomised										
PACTR201411000939962	Laboratory confirmed	Liberia	Withdrawn	University of Oxford	Safety, efficacy	140 (single arm)	140 brincidofovir vs HCC	Chimerix‡	Nov 14, 2014	June, 2015
NCT02342171	Laboratory confirmed	Guinea	Not recruiting	ITM, Belgium	Safety, efficacy	Up to 400 in two groups (convenient allocation)§	ECP + sSC vs sSC in HCC	NA	Jan 12, 2015	October, 2015
ChiCTR-OON-14005558	Clinical	Sierra Leone	Recruiting	China Army	Efficacy	Up to 60 in two groups (convenient allocation)¶	QBD + XBJ + ST vs western drugs||	NA	Nov 29, 2014	..
NCT02333578	Laboratory confirmed	Liberia	Recruiting	Clinical RM	Safety, efficacy	70 (single arm)	ECP vs HCC	NA	Jan 5, 2015	June, 2015
NCT02329054	Laboratory confirmed	Guinea	Recruiting	INSERM, France	Safety, efficacy	225 (single arm)†**	Favipiravir + sSC vs HCC	Toyama Chemical	Dec 16, 2014	June, 2015
NCT02295501	Laboratory confirmed	USA	Recruiting	Cerus Corporation	Safety, efficacy	12 (single arm)	INTERCEPT†† ECP	Cerus Corporation	Nov 4, 2015	January, 2016
NCT02271347; EUDRA-2014-004450-33	Laboratory confirmed	Europe, North America	Withdrawn	Chimerix UK Limited	Safety, efficacy	50 (single arm)	Brincidofovir	Chimerix‡	Oct 7, 2014	..
PACTR201501000997429	Laboratory confirmed	Sierra Leone	Not recruiting	University of Oxford	Safety, efficacy	100 (single arm)	TKM-Ebola	Tekmira	Jan 16, 2015	June, 2015
JPRN-UMIN000016101	Laboratory confirmed	Japan	Not recruiting	NCGHM, Japan	Safety, efficacy	5 (single arm)	Favipiravir	Toyama Chemical	Jan 2, 2015	..

sSC=standardised supportive care (ie, in comparative studies when standardised control treatment is reported). HCC=historical or concurrent controls (non-random). ECP=Ebola convalescent plasma. NA=not applicable. QBD=Qingwenbaidu decoction (herbal product). XBJ=Xuebijing injection (herbal product). ST=symptomatic therapy. *No study uses allocation concealment (masking). †Adaptive design (ie, any deign that uses interim analyses to modify study design). ‡On Feb 1, 2015, Chimerix said it would stop participation in clinical studies because of a substantial decrease in the number of new cases of Ebola virus disease. §No patient will be refused ECP; control will be patients with Ebola virus disease recruited during the period before ECP becomes available or for whom no compatible convalescent plasma is available. ¶Allocation on voluntary base. \|\|If western drug (ie, not traditional Chinese medicine) and ST are unspecified the study is reported as observational. **Final analysis will be done according to three different groups: (A1) adults with time between first symptoms and first dose of favipiravir (≤72 h); (A2) adults with time between first symptoms and first dose of favipiravir >72 h; and (C) all children. ††INTERCEPT is a US Food and Drug Administration approved system for ex-vivo preparation of plasma to reduce the risk of transfusion-transmitted infection during treatment of patients needing therapeutic plasma transfusion.

Table 1: Description of registered clinical trials that enrol participants with acute Ebola virus disease to assess efficacy or safety, or both, of new therapies by registration number

present medical interventions, no guarantee exists that the efficacy and safety of the new therapies can be assessed without a comparable control group—only random-isation can provide this guarantee.[7,33] Non-randomised studies will inevitably produce contrasting results with the risk of fostering uncertainty among experts while ultimately jeopardising the effort to produce clear and feasible clinical guidance.

Similar to other investigators,[34] we think that well designed RCTs with adaptive study design[35] should be endorsed in this crisis and preferred to non-randomised designs for several reasons.

First, no unequivocal data about the case fatality rates of Ebola virus disease exist. The most reliable estimates from WHO range between 46% in Nigeria (ie, the most affluent setting) to 72% in Liberia (ie, the least affluent setting).[2] In such circumstances, non-randomised studies will provide clinicians with no reliable means to assess promptly the safety and efficacy of new treatments, thus making room for larger ethical

dilemmas than those arising from random allocation of interventions.

Unless a new treatment has great effectiveness (eg, by decreasing mortality to close to 0% in series of hundreds of patients), we might continue to have substantial uncertainty about whether a treatment works at all for many years after the trial finishes. If a treatment does confer such great effectiveness, an RCT should be able to detect and document the effectiveness very quickly. However, if effectiveness is only slight, external comparators (both concurrent or historical) in observational series or non-comparative studies could be severely biased because of high and undocumented patient heterogeneity and will probably differ systematically between patients who received treatment and patients who did not. By contrast, interim analyses in RCTs can, at best, inform clinical investigators on whether to proceed with the same randomised allocation, either shifting all patients to an intervention group with an effective treatment or stopping the

	Present knowledge			Potential issues for large-scale use in Africa
	Mechanism of action	Safety	Efficacy	
Amiodarone	Inhibition of viral entry	Widespread human use for more than 30 years; toxic effects are mainly reported for long-lasting use; potential acute toxic effects in case of low potassium concentrations in blood	In-vitro data show significant suppression of viral replication and infectivity at the same plasma concentration reached for clinical management of arrhythmia;[9] unpublished data on case-by-case use has not provided clear evidence for or against efficacy so far	No available in-vivo evidence for efficacy; however, the drug is easy to administer (available in both intravenous and oral routes, and is thermostable); the drug is low cost and already available for large-scale use
ZMapp	Neutralising antibody	Data on human beings are very restricted	100% efficacy on NHP;[10] case-by-case experiences on human beings are very restricted but promising[11]	Difficult to administer, potentially very expensive, and no guarantee exists that production can be scaled for wide use
Brincidofovir	Unclear	Tested in a clinical trial for DNA viruses; generally better tolerated than the already approved cidofovir[12]	Unpublished data from Viral Special Pathogens Branch (USA) revealed that in-vitro activity of brincidofovir against the Ebola virus is similar to that reported against other viral diseases; no animal data;[13] was used on two occasions in human beings with Ebola virus disease (one died and one survived)	The manufacturer has recently decided to stop experimentation in human beings
ECP	Neutralising antibody	Mainly transfusion related	Whole blood and ECP have been already used as empirical treatments with promising results in a small group of cases of Ebola virus disease[12,14,15]	WHO has already developed a guidance for use of ECP;[15] potential limitations are related to availability and risk for transmission of infections other than Ebola virus disease
QBD + XBJ	Immunomodulators[16,17]	Not assessed according to stringent regulatory authority requirements; however, human use is presumed to be widespread in China; both drugs are sold online	No available data on patients with Ebola virus disease	..
Favipiravir	Inhibitor of viral RNA-dependent RNA polymerase	Well tolerated in patients without Ebola virus disease; evidence from large clinical trials; the drug is approved for human use in Japan at present; preliminary data exist on patients with Ebola virus disease[18]	Evidence from studies in vitro and in small animals for activity against Zaire ebolavirus;[19] preliminary data on human use (case-by-case use and early analysis of trials) has not provided evidence on efficacy so far	Favipiravir is conveniently formulated in oral thermostable tablets, but cost might be high as it is a patented drug; Toyama Chemical announced in October, 2014, that it had 20 000 courses of treatment in stock
TKM-Ebola	Cleaves Ebola RNA inside the cell	Increased cytokines in safety studies on human beings;[12] FDA suspended phase 1 in July, 2014; in August, 2014, the FDA changed the status to partial hold, allowing the drug to be used under expanded access in people infected with Ebola virus but with the phase 1 trial still suspended (NCT02041715)	Up to 100% efficacy in NHP[12]	Potentially very expensive and no guarantee exists that production for wide use can be scaled

NHP=non-human primates. ECP=Ebola convalescent plasma. QBD=Qingwenbaidu decoction (herbal product). XBJ=Xuebijing injection (herbal product). FDA=US Food and Drug Administration.

Table 2: Interventions for which a clinical trial has been proposed during the present outbreak

treatment with a potentially unsafe drug.[7] The focus of an interim analysis is to respond rapidly to high quality data emerging from an RCT, rather than in an RCT without an interim analysis wherein researchers blindly treat and hope for a positive outcome.

Second, non-randomised or compassionate use of various interventions might happen anyhow. The challenge is not to encourage additional compassionate use and so-called hints and guesses, but to put together a robust RCT agenda. In fact, for proposed interventions that do not have an established line of large-scale production, and whose availability is very restricted (eg, ZMapp), use in non-randomised studies, instead of RCTs, is not straightforward. Such use wastes the already small sample size of potential RCTs that could have been done with the restricted available stock and thus negates the chances of being able to understand whether these treatments are effective or are not.[33]

Third, as recommended by WHO,[5,34] well designed RCTs will ensure that all patients receive at least the best feasible care, which at present is standard supportive care,[28,29] and

that "investigational therapeutic or prophylactic options should not divert attention or resources from the public health measures that remain the main priority in outbreak control".[5] In this view, RCTs should be designed to have a control group with standard supportive care (as deemed feasible in the sites where the trials are done) and an experimental group, consisting of one or more new drugs in addition to the standard care. Moreover clinical centres should be able to implement infection control measures in advance to prevent health-care associated transmission of infection. The sponsors of such studies should provide the clinical facilities and adequate resources to ensure that the standard supportive care meets minimum requirements of good clinical practice. The rigorous implementation and monitoring of interventions that are agreed by consensus as being practicable in the context of local care, would help to set minimum ethically acceptable practices for treatment and infection control. By contrast, the deregulated scenario, where any new drugs with unproven efficacy can be used, provides no such guarantee. Of course, we do not advocate that resources for RCTs should be drawn from the restricted

Panel: Randomised controlled trial description

A priori assumption
Scenario 1: $\pi 1 = 50\%$ and $\pi 2 = 30\%$
Scenario 2: $\pi 1 = 60\%$ and $\pi 2 = 40\%$
Scenario 3: $\pi 1 = 70\%$ and $\pi 2 = 50\%$
Efficacy (as difference): $\pi 2 - \pi 1 = -20\%$
Efficacy (as ratio): odds ratio between 0·43 and 0·44—ie,

$$\left(\frac{\left[\frac{\pi 1}{(1-\pi 1)} \right]}{\left[\frac{\pi 2}{\left(\frac{1}{\pi 2} \right)} \right]} \right)$$

Minimum and maximum sample size
70–210 participants

Intervention and drugs
Control group: standard supportive care
Experimental group: standardised supportive care + experimental drug

Study design
Intervention model: parallel assignment
Allocation ratio: 1:1
Masking: open
Primary purpose: treatment
Early stopping for efficacy: sequential group design
Stopping for toxicity: establishment and operation of clinical trial data monitoring committee

Adaptive framework
Null hypothesis: $\pi 2 - \pi 1 = 0$
Conditional power: 80%
Test: two-sided χ^2 with continuity correction
Number of interim analyses: two (ie, three stage design)
Sample size per stage: 35 per group fixed (ie, no sample size recalculation)
Information rate per stage: 33·3% (uniform)
α spending model: O'Brien and Fleming design
α spending function: 0·0005 (stage 1); 0·0143 (stage 2); 0·0500 (stage 3)
Potential inflation in comparison with standard design: 1·7% (to accept H_0 with 80% power)

Follow-up (maximum)
14 days after enrolment

Approximate study duration
2–6 months; depending on:
· Study location
· Phase of outbreak and effective reproduction number
· True mortality in overall population (figure 2)
· True efficacy of the experimental drug (figure 2)

Simulator specification
Software: ADDPLAN™ 6.1.1 ADDPLAN (approved by FDA, EMA, and PMDA)

$\pi 1 =$ morality in control group. $\pi 2 =$ mortality in experimental group. FDA=US Food and Drug Administration. EMA=European Medicines Agency. PMDA=Pharmaceuticals and Medical Devices Agency, Japan.

health-care resources of Ebola-stricken sites. RCTs should bring along additional resources to this acute crisis.

Fourth, as also acknowledged by others,[36] some non-randomised clinical study designs could even undermine present thinking. Particularly, when scarcely available treatment is given to consecutive series of patients without them being randomly assigned to a treatment group; the patients selected might be systematically different from their historical or contemporary control groups and the selection rules might choose sicker patients than the population average who might have the worst probability of responding, thus potentially condemning to failure even treatments that could have been effective in earlier stages of the disease than were treated.

Finally, in the present context of emergency, much of the information about the outcome of patients who receive the so-called new treatment might not be systematically collected and analysed in the absence of a clear study framework.

Testing the feasibility of adaptive RCTs with a standard simulation approach

The major challenge in the present Ebola crisis is not whether RCTs should be used or not, but how their efficiency can be increased, producing the desirable answers faster.

In view of the idea that a scientifically sound and rigorous method does not compromise ethics but in fact is the prerequisite to implement ethical precepts by production of valid and reproducible results,[31] we propose that adequate and well controlled studies can be safely done in the present Ebola outbreak and argue that the adaptive RCT approach is better than approaches proposed at present (table 1). Adaptive RCTs, particularly, can reasonably overcome the main objections raised against randomisation in emergencies and related to the ethical issue that a substantial number of patients would not receive a treatment with potentially (extraordinary) effectiveness. As acknowledged by the European Medicines Agency, "adaptive design would be best utilised as a tool for planning clinical trials in areas where it is necessary to cope with difficult experimental situations".[37]

To lend support to our idea we tested the performance of an ideal two-arm adaptive RCT aimed at assessing the efficacy of the addition of a specific investigational drug to the present standard of care (ie, supportive therapy) by comparison with the standard of care

alone. The RCT design and simulation has been done according to requisites for "generally well understood adaptive designs with valid approaches to implementation".[38]

The proposed RCT will have a maximum sample size of 210 participants and two interim analyses, allowing early cessation for efficacy (group sequential design) and toxicity stopping rules (decided by an independent data monitoring committee). The simulation was done to show how the RCT will behave in response to the simultaneous variation of the reported mortality in either treatment or control group. The full description of the RCT is reported in the panel and the results of the simulations are reported in figure 2.

Consistent with our hypothesis, an extraordinary unexpected efficacy of the experimental treatment will result in a very early RCT cessation. For example, if mortality in the experimental group is only 10% the probability of stopping the RCT at the first interim analysis will be 98·1%, 87·6%, and 61·7% for mortality in the control equal to 70%, 60%, and 50%, respectively (see figure 2A). With such an extraordinary efficacy no RCT will go beyond the second interim analysis (see figure 2B). Moreover, if a priori hypotheses are confirmed the chance that a significant effect will be reported at the second interim analysis is still about 50% (see figure 2B). As the likelihood of the study cessation is positively associated with the mortality in the control group, very few patients (in absolute terms) who did not receive such an extraordinary intervention will actually die. In view of the availability of a reliable comparator, interim analyses in RCTs are much stronger than analyses in non-comparative studies to inform investigators about any unexpected toxic effects of the investigational drug.

A singular confirmation of our argument is provided by the preliminary results (interim analysis) of the JIKI trial (NCT02329054; table 1) presented at the last Conference on Retroviruses and Opportunistic Infections, held in Seattle in February, 2015.[18] JIKI is a non-comparative, proof-of-concept trial aimed to enrol 225 participants to assess the benefit of high-dose favipiravir in reducing mortality and decreasing Ebola viral load in patients with acute Ebola virus disease. At present JIKI is the most ambitious trial in progress and since the start of enrolment, on Dec 17, 2014, the investigators have enrolled 80 participants after just 36 days. The main results presented were that mortality was positively associated with Ebola viral load; that favipiravir was generally well tolerated; and that a non-significant trend for reduced mortality was reported in those with the lowest Ebola viral load who received the drug by comparison with historical controls, whereas an opposite trend was reported in those with the highest Ebola viral load who received the drug.

In view of the absence of an extraordinary efficacy or a reliable comparator, the analysis provided hardly any conclusive evidence. An association between mortality and Ebola viral load and the good tolerability of favipiravir are all expected findings, whereas researchers remain uninformed about the efficacy of favipiravir. These results leave ethical uncertainty for the researchers about whether to continue the study as it is, change the enrolment according to baseline viral load, or to interrupt the study and divert resources for tests of new experimental drugs. Should the JIKI trial have been designed within an adaptive framework, the maximum sample size would have been reduced (210 vs 225) and, having gone through an adaptation iteration, the researchers would have been able to discuss truly comparative evidence for this kind of treatment by the time 80 patients had been assessed.

In our opinion this trial exemplifies the idea that when considerations related to the urgency of actions are preferred over scientific hypotheses the efforts to obtain new evidence could be jeopardised without the realisation of any ethical advantage.

Potential limitations of the adaptive design

Adaptive study designs remain attractive because of their flexibility, which could provide several practical and ethical advantages compared with standard RCT design. The primary goal of adaptive trials is to minimise the harm to study participants by exposing fewer participants to the burden and risks of research, and to benefit more participants with the favourable treatment, by reducing time to obtain conclusive evidence compared with conventional RCTs. Nevertheless this flexibility comes at a cost. Several issues could hinder the implementation of adaptive RCTs and reduce the internal and external validity of these studies.[39]

First, adaptive trial designs are more complex to implement and analyse than standard RCTs.[34,37,38] Second, adaptive study designs seem most suitable for
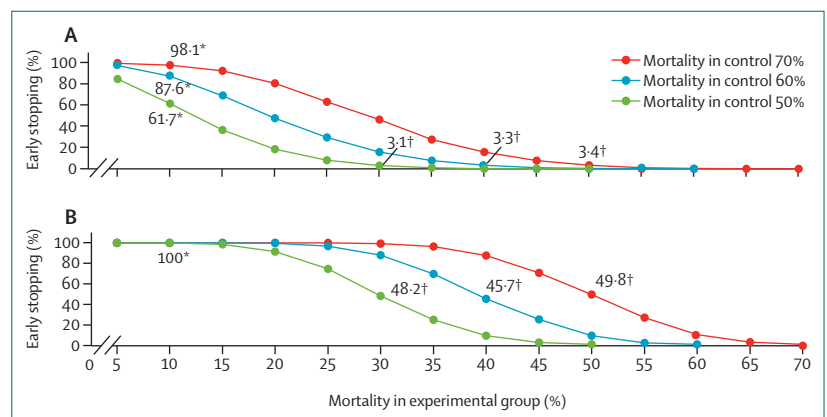

Figure 2: Trial simulation to estimate probability of early stopping
(A) Early stopping estimate at the first interim analysis (overall sample size=70). (B) Early stopping estimate at the second interim analysis (overall sample size=140). *Punctual estimate for early stopping if reported mortality in control group is equal to 10% (ie, extraordinary unexpected efficacy). †Punctual estimate for early stopping if reported mortality is equal to the a priori assumptions.

situations where endpoints can be quickly and reliably assessed. This restricted suitability implies that adaptive RCTs might be unable to assess long-term outcomes. Third, results of interim analyses might influence decisions of the data and safety monitoring boards, researchers, and study participants. Finally, adaptive designs usually include multiple interim analyses, which often leads to an inflated type-I error; as such the adaptive framework should be kept as simple as possible.[35] However, a prudent adaptive design including a small number of clinical centres, a restricted number of interim analyses, and a well understood and validated adaptive framework could easily address all these issues.[37,38]

Conclusions

For life-threatening diseases under the conditions of suboptimum standards of care[40] (such as with the present Ebola outbreak) RCTs that take a very long time to do would not be straightforward or would be unacceptable.[33,39] However, dependence on non-randomised studies to assess the efficacy and harms of interventions might be even worse than RCTs. New RCT designs, such as adaptive designs, can provide the best solution for researchers to obtain robust evidence on the merits of candidate interventions.

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