Elsevier has created a Monkeypox Information Center in response to the declared public health emergency of international concern, with free information in English on the monkeypox virus. The Monkeypox Information Center is hosted on Elsevier Connect, the company's public news and information website.

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Déjà vu all over again? Monkeypox and the urgent need for randomised controlled trials

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5 months into the monkeypox epidemic, there are no proven therapies and no comparative safety and efficacy data in the treatment of affected individuals. The question remains whether we, as a scientific and medical community, will apply the lessons learned from the past decade of outbreaks that well conducted randomised controlled trials can be ethically, safely, and efficiently performed to guide clinical decision making so that the right drug is used for the right patient at the right time. Furthermore, the robust level of evidence from randomised controlled trials is highly relevant to advocating for equitable access to new treatments in low-income and middle-income countries. As with COVID-19, we need to pair optimal supportive care with rigorously designed double-blind randomised controlled trials to elucidate safe and effective therapies for monkeypox. The need remains for the funding and development of predesigned, adaptive trial protocols for diseases with epidemic or pandemic potential that can be timely pulled off the shelf and launched early in an outbreak, leveraging ready clinical trial networks and infrastructure for rapid discovery and implementation of new treatments.

Introduction
As the monkeypox epidemic continues, there are no proven therapies and no comparative safety and efficacy data in the treatment of affected individuals. Tecovirimat, an inhibitor of the orthopoxvirus VP37 envelope wrapping protein, is approved in the USA for the treatment of smallpox. Although animal models suggest it should be evaluated in orthopoxviruses,1 human data on tecovirimat are limited to case reports and case series, neither of which can determine safety or efficacy.2,3

Access to tecovirimat for the treatment of monkeypox is variable across the globe, but it is currently available in some regions through an authorisation for use in extraordinary (Canada)4 or exceptional circumstances (Europe)5 or through an expanded access protocol (USA).6 The Infectious Diseases Society of America and Human Immunodeficiency Virus Medicine Association have advocated for streamlined access to tecovirimat in parallel with National Institutes of Health funding for clinical trials.7 Similarly, WHO has advocated for the rapid implementation of clinical trials to inform patient care and has proposed its CORE protocol for an adaptive, multinational, randomised controlled trial (RCT) for monkeypox antivirals.8

However, in early September, 2022, approximately 4 months into the outbreak, the first two randomised trials for monkeypox antivirals were posted on ClinicalTrials.gov: PLATINUM-CAN (Canada; NCT05534165) and STOMP (USA; NCT05534984). As of Oct 12, 2022, one additional trial planned before the epidemic (PALM 007; NCT05539099) had been launched in the Democratic Republic of the Congo, targeting endemic disease of a different clade, and only PALM 007 and STOMP were actively recruiting.9 Although there could be some utility in the presence of expanded access or compassionate use programmes for particular situations in which observational data might generate hypotheses, there is a tremendous need for the rapid acquisition and dissemination of concurrent comparative data to inform safe and effective clinical decision making and public health messaging.

Currently, data collection on the use of tecovirimat for monkeypox is being conducted through the US Centers for Disease Control and Prevention’s Expanded Access Investigational New Drug protocol, where clinicians are required to provide standard data on patients for whom they use the drug.10 This data collection could provide limited, but unreliable, safety data and might be able to foster comparisons to historical controls in altering the natural history of the disease. However, there are numerous challenges in interpreting and applying this type of data given the absence of a concurrent comparator group and the large heterogeneity of historical controls. Differences in the clade of the virus, temporal and host changes in the affected population, the unique clinical features of the current outbreak, regional differences in the management of monkeypox disease, and improvement in supportive care over time make the use of historical controls problematic, suboptimal, and potentially misleading, because historical controls would not represent today’s affected population. Without a contemporary comparator group, clinicians cannot accurately determine which patients would benefit most from treatment or potentially be harmed (eg, host factors, clinical syndrome, duration of symptoms, and drug side-effects) or learn how to best prognosticate regarding clinical success. Without these reliable controlled data, it is also not possible to adequately counsel patients seeking treatment in whom treatment might or might not be indicated and might or might not be harmful.

The ethical question of whether to administer a potential therapeutic to a suffering patient in the setting of an epidemic disease has been described previously.11 The fact that there remains clinical equipoise regarding the safety and efficacy of tecovirimat in monkeypox requires rigorous evaluation, because clinicians do not know whether the therapy being considered is more...
likely to cause benefit or harm. The difficulty of appropriating potential therapeutics that have a reasonable theoretical basis is not new for emerging and re-emerging infectious diseases, with the most prominent recent examples being Ebola virus disease outbreaks and the ongoing COVID-19 pandemic.

In the 2014 Ebola virus disease epidemic, the National Institutes of Health developed a clinical trial that was launched successfully; however, due to the time it took to design and implement the trial, the epidemic curve of the outbreak waned before determining whether any treatments were effective. Building on the experience of the previous outbreak, a subsequent outbreak starting in 2018 allowed for implementation of a randomised trial and approval of two monoclonal antibodies for the treatment of Ebola virus disease. Without the ready implementation of RCTs in an outbreak setting, there would not be a safe and effective treatment for Zaire Ebola virus.

In the COVID-19 pandemic, there was significant interest in using and evaluating repurposed drugs (eg, hydroxychloroquine) and other treatments that have a potential theoretical basis (eg, convalescent plasma). Emergency use authorisations and expanded-access programmes for such drugs were robust early in the pandemic, and there were initial reports of clinical benefit from observational and non-randomised studies. However, as rigorous randomised trials were undertaken and analysed, these emergency-use therapies have either been deemed ineffective or harmful (ie, hydroxychloroquine) or should only be considered in limited clinical scenarios (ie, convalescent plasma).

The COVID-19 pandemic has shown that rigorously designed and swiftly implemented trials are possible in the setting of emerging infectious disease threats. The Adaptive COVID-19 Treatment Trial (ACTT) was an adaptive study of potential COVID-19 therapeutics that conducted four distinct and iterative trials involving more than 4000 participants globally in just over 1 year, after the first reported case in the USA. The contributions of ACTT have provided clinicians with granular, comparative data that facilitate informed decisions on three effective therapeutics with direct benefits to patient care (ie, remdesivir, baricitinib, and dexamethasone) and one therapeutic with extensive supportive data from in vitro, in vivo, animal, and human studies that showed no benefit for the treatment of patients hospitalised with COVID-19 when tested in the setting of a rigorous RCT (ie, interferon beta-1a).

For the monkeypox epidemic, the question remains whether we, the scientific and medical community, will apply the lessons learned from recent outbreaks that well conducted RCTs can be ethically, safely, and efficiently performed to guide clinical decision making so that the right drug is used for the right patient at the right time. Furthermore, the robust level of evidence from RCTs is highly relevant to advocating for equitable access to new treatments in low-income and middle-income countries. As with COVID-19, we need to pair optimal supportive care with rigorously designed double-blind RCTs to elucidate safe and effective therapies for monkeypox. The need remains for the funding and development of predesigned, adaptive trial protocols for diseases with epidemic or pandemic potential that can be timely pulled off the shelf and launched early in an outbreak, leveraging ready clinical trial networks and infrastructure for rapid discovery and implementation of new treatments.

References
1 Sherwat A, Brooks JT, Birnkrant D, Kim P. Tecovirimat and the treatment of monkeypox–past, present, and future considerations. N Engl J Med 2022; 387: 579–81.
2 Desai AN, Thompson GR, Jrd, Neumanne GM, Arutyunova AM, Trigg K, Cohen SH. Compassionate use of tecovirimat for the treatment of monkeypox infection. JAMA 2022; 328: 1348–50.
3 O’Laughlin K, Tobolowsky FA, Elmor R, et al. Clinical use of tecovirimat (TpoQx) for treatment of monkeypox under an investigational new drug protocol—United States, May–August 2022. MMWR Morb Mortal Wkly Rep 2022; 71: 1190–95.
4 SIGA Technologies. SIGA announces Health Canada regulatory approval of oral TPOXX®. Dec 1, 2021. https://investor.siga.com/news-releases/news-release-details/siga-announces-health-canada-regulatory-approval-oral-tpoxx (accessed Oct 12, 2022).
5 European Medicines Agency. Tecovirimat SIGA. Jan 28, 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/tecovirimat-siga#:~:text=Tecovirimat%20SIGA%20is%20a%20 medicine%20that%20is%20used%20to%20 treat%20monkeys%20for%20smallpox%20infection%20and%20 smallpox%20in%20humans%20and%20other%20monkey%20species%20including%20marmosets%20and%20tamarins%20(accessed%20Oct%2012, 2022).
6 Centers for Disease Control and Prevention. Guidance for tecovirimat use: expanded access investigational new drug protocol during 2022 US monkeypox outbreak. Sept 15, 2022. https://www.cdc.gov/poxvirus/monkeypox/clinicians/tecovirimat.html#:~:text=CDC%20holds%20an%20investigational%20 new%20drug%20protocol%20for%20tecovirimat,to%20 monkeypox%20infections%20in%20the%20US%20 (accessed Oct 12, 2022).
7 McQuillen DP, Haddad M. IDSA/HIVMA support rapid CDC response to monkeypox treatment access issues. Infectious Diseases Society of America. July 21, 2022. https://www.idsociety.org/news-publications-new/articles/2022/idshaivma-support-rapid-cdc-response-to-monkeypox-treatment-access-issues/ (accessed Oct 12, 2022).
8 World Health Organization. Towards the development of a global CORE protocol for evaluation of treatments for MPX leveraging the Congolese experience. 10–11 Jul 2022. https://www.who.int/news-room/events/detail/2022/07/10/default-calendar/towards-the-development-of-a-global-core-protocol-for-evaluation-of-treatments-for-mpx-leveraging-the-congolese-experience (accessed Oct 12, 2022).
9 National Institutes of Health. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/results?cond=monkeypox&term=&cnt ry=&state=&city=&dist= (accessed Oct 12, 2022).

Contributors
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Declaration of interests
DAL and ACK were investigators for the National Institutes of Health Adaptive COVID-19 Treatment Trial.

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Kalil AC. Treating COVID-19-off-label drug use, compassionate use, and randomized clinical trials during pandemics. JAMA 2020; 323: 1897–98.

Mulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med 2019; 381: 2293–303.

COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/ (accessed Oct 12, 2022).

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19–final report. N Engl J Med 2020; 383: 1813–26.

Kalil AC, Mehta AK, Patterson TF, et al. Baricitinib plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-blind, randomised, placebo-controlled trial. Lancet Respir Med 2021; 9: 1165–76.

Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. N Engl J Med 2021; 384: 795–807.

Wolfe CR, Tomashek KM, Patterson TF, et al. Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial. Lancet Respir Med 2022; 10: 888–99.

Kalil AC, Mehta AK, Patterson TF, et al. Efficacy of interferon beta-la plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Respir Med 2021; 9: 1165–76.

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