Although there was no difference in delayed graft function, $HMPO_2$ resulted in significantly lower rates of acute rejection. A possible explanation offered by the authors, which deserves further evaluation, is the selective activation of resilience-associated pathways in donor transplants following circulatory death. Ischaemia–reperfusion injury is linked to upregulation of the innate and adaptive immune system; however, the causal mechanisms between delivery of supraphysiological oxygen and a reduction in acute rejection remain elusive. In-depth collection and analysis of immunological laboratory and clinical data in future studies might reveal links between $HMPO_2$ and dampened allograft immunogenicity.

Machine perfusion represents one of the most important advances in transplantation medicine in the past two decades. The capacity to effectively target ischaemia–reperfusion injury, a crucial determinant in organ viability, is unique. This study adds substantially to the weight of clinical experience with HMP. Using this technique as a platform to deliver oxygen (and possibly other enrichments) to improve donor kidney function and subsequent transplant outcomes is a great step forward. A favourable health economic evaluation would provide added incentive for programmes to adopt this technology. Clinical impetus for the use of HMP still remains and fundamental mechanistic research questions, to determine how machine perfusion can effectively optimise the quality of donor organs and improve transplant recipient outcomes, also need to be answered.

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*Natasha Rogers, *Kate Wyburn*
kate.wyburn@sydney.edu.au

Centre for Transplant and Renal Research, Westmead Institute for Medical Research, Westmead, NSW 2145, Australia (NR); Westmead Clinical School, University of Sydney, Sydney, NSW, Australia (NR); Charles Perkins Centre, The University of Sydney, Camperdown, NSW, Australia (KW); and Department of Renal Medicine, Royal Prince Alfred Hospital, Sydney, NSW, Australia (KW)

1 Lim WH, McDonald SP, Russ GR, et al. Association between delayed graft function and graft loss in donation after cardiac death kidney transplants—a paired kidney registry analysis. *Transplantation* 2017; **101:** 1139–43.
2 Metzger RA, Delmonico FL, Feng S, Port FK, Wynn JJ, Merion RM. Expanded criteria donors for kidney transplantation. *Am J Transplant* 2003; **3** (suppl 4)**:** 114–25.
3 Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. *J Clin Invest* 2011; **121:** 4210–21.
4 Lim WH, Johnson DW, Teixeira-Pinto A, Wong G. Association between duration of delayed graft function, acute rejection, and allograft outcome after deceased donor kidney transplantation. *Transplantation* 2019; **103:** 412–19.
5 Darius T, Vergauwen M, Smith T, et al. Brief O_2 uploading during continuous hypothermic machine perfusion is simple yet effective oxygenation method to improve initial kidney function in a porcine autotransplant model. *Am J Transplant* 2020; **20:** 2030–43.
6 Tingle SJ, Figueiredo RS, Moir JAG, Goodfellow M, Talbot D, Wilson CH. Machine perfusion preservation versus static cold storage for deceased donor kidney transplantation. *Cochrane Database Syst Rev* 2019; **2019:** CD011671.
7 Jochmans I, Brat A, Davies L, et al. Oxygenated versus standard cold perfusion preservation in kidney transplantation (COMPARE): a randomised, double-blind, paired, phase 3 trial. *Lancet* 2020; **396:** 1653–62.

Maintaining confidentiality of emerging results in COVID-19 vaccine trials is essential

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No one disputes the urgent need for safe and effective COVID-19 vaccines. But confidentiality within the processes of vaccine development is also essential. Ensuring rapid availability of COVID-19 vaccines will depend on rigorous evidence of their safety and efficacy.[1] That rigour is threatened if emerging data from trials of candidate COVID-19 vaccines are disclosed in ways that allow them to influence the design or conduct of trials and potentially bias the results. It is widely recognised that emerging data by intervention group from clinical trials must be kept confidential—ie, accessible only to the trial Data Monitoring Committee (DMC).[2] However, less well recognised are the risks to trial integrity from the release of data pooled across vaccine and placebo groups.

Public comments by some sponsors of COVID-19 vaccine trials about the precise timing of efficacy analyses[3,4] or expected trial results[3] suggest that data pooled across vaccine and placebo groups may be routinely shared with vaccine sponsors. Knowledge of the pooled event rate alone, if lower or higher than expected on the basis of the trial design, could lead sponsors and others to predict that a vaccine is better or worse than hoped. If such a prediction led to changes in the trial design—eg, reduction in sample size or change in the primary endpoint if pooled data on a secondary endpoint seemed more promising—this

would seriously damage the interpretability of the final results and violate the fundamental assumption that the same data are not used both to generate and to confirm hypotheses. Similarly, access to information on the timing of events—ie, the event rate by time after randomisation—in the pooled data could be informative about vaccine effects, since such a rate in the placebo group would be expected to be fairly constant over time. Thus, such information should not be used to alter criteria for defining primary events or for changing the time after the last vaccine or placebo dose when events would be included in the primary analysis. Although procedures implemented for data sharing, unfortunately, may allow sponsors ongoing access to information pooled across vaccine and placebo groups in COVID-19 vaccine trials, such sponsor access should not be used to implement protocol changes that bias the likelihood of a trial meeting its success criteria.

As per community standards and best practices for the conduct of clinical trials, key elements of the trial design, especially the primary and secondary efficacy endpoints and success criteria, need to be prospectively defined. Protocol revisions to these crucial elements of a trial design should be prohibited after availability of trial data that may be informative—even indirectly—about vaccine efficacy, unless these potential adaptations were prespecified in the protocol.[5] This issue is important since such revisions to a trial design, if potentially influenced by emerging trial data, would compromise the reliability of a trial originally intended to be confirmatory rather than hypothesis-generating, and since it would be difficult to conclusively show that emerging trial data had no role in decisions about these changes to the trial.[2,5] Design changes during the conduct of a trial—eg, a vaccine regimen is altered or the demographic composition of a trial is changed to include more participants in subgroups in which early results suggest greater efficacy—can compromise the interpretability of the results and the generalisability of the trial findings.

Maintaining confidentiality of emerging data protects trial integrity and credibility in many ways (panel).[2,5–10] Confidentiality of these data reduces the risk of prejudgment and facilitates timely enrolment, targeted levels of adherence to study treatment, and retention of participants in the trial, which are integral to achieving timely and reliable results. Furthermore, this confidentiality reduces the risk of releasing misleading results and the risk that emerging data could, deliberately or inadvertently, inappropriately influence the design or conduct of a trial.

To maintain these benefits of confidentiality, access to emerging data on safety and efficacy is typically allowed only to a trial's DMC and reporting statistician.[2,4] Access to trial data should be on a need-to-know basis to effectively safeguard the best interests of study participants. When the DMC recommends changes to the conduct of a trial, a few individuals from the trial leadership should receive only the information needed to make decisions about those recommendations. There should be a clear firewall between those with access to such data and all others involved in trial design and conduct.[11]

For some COVID-19 vaccine trials, trial sponsor companies have disseminated information about the emerging pooled event rate for the primary endpoint—eg, by disclosing the trial's monitoring boundaries and predictions of the timing of the interim analysis. Whether or not preliminary results of these interim analyses are publicised, dissemination of such information means it will be apparent when interim criteria are not met, which could lead to prejudgments about the ultimate findings of a trial.[12] This situation can lead to potential biases and induce investigators or trial participants to alter their behaviour on the basis of an assumption that vaccine efficacy is lower than originally expected. This concern can be reduced, although not eliminated, by use of conservative monitoring boundaries, such as the O'Brien-Fleming boundaries that require the statistical strength of evidence to be highly persuasive in order to declare success or failure at an interim analysis.[11] Such an assumption about the level of vaccine efficacy could

***Panel:* Reasons to maintain confidentiality of emerging data from ongoing clinical trials**

- Reduce the risk of prejudgment of final trial results
- Increase the ability to achieve: timely enrolment, targeted levels of adherence and retention, and timely trial completion with reliable results
- Reduce the risk of early release of misleading results
- Reduce the risk that emerging data could be used to inappropriately influence trial design or conduct

influence implementation of trial case definitions by trial investigators, with some investigators potentially motivated to obtain data that would please the trial sponsors. Influence of such motivation has been shown in comparisons of open-label investigator versus blinded central evaluations of disease progression in oncology trials.[13] Early clues about preliminary trial results have the potential to influence trial enrolment and health-seeking behaviour, risk behaviours, or reporting behaviours of trial participants, which could alter the likelihood that cases are reported or that cases meet the actual case definition for the primary endpoint or for secondary severe disease endpoints. Careful scrutiny by regulators is needed to ensure these potential biases do not alter COVID-19 vaccine trial outcomes.

Public interest in emerging results from COVID-19 vaccine trials is understandably high. However, public statements by trial sponsors derived from pooled data such as the likely timing of interim or final analyses, announcement that interim analyses do not establish benefit of the vaccine, or public predictions of the outcome of these analyses indicate that influential information is being made available outside of the DMC. Even if the sponsor alone has access to pooled event rates and timing of events after randomisation, this access would be problematic if it could potentially be used to bias trial design or conduct. Given the crucial importance of public confidence in COVID-19 vaccines when they ultimately become available,[1] there should be no room for messaging or behaviours by those conducting the trials that could undermine public confidence in the results of these trials.

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*Philip R Krause, Thomas R Fleming, Susan S Ellenberg, *Ana Maria Henao-Restrepo, on behalf of the †WHO Ad Hoc Clinical Trial Expert Group*
henaorestrepoa@who.int

†The members of the WHO Ad Hoc Clinical Trial Expert Group are: Philip R Krause (US Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Vaccines Research and Review, Silver Spring, Chair of the WHO R&D Blueprint COVID-19 Vaccines Working Group), Thomas R Fleming (University of Washington, Fred Hutchinson Cancer Centre Seattle, WA, USA), Susan S Ellenberg (Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA), Marissa M Alejandria (Professor, University of the Philippines College of Medicine Department of Clinical Epidemiology, Head, Research Implementation and Development Office, University of the Philippines College of Medicine, Director, Institute of Clinical Epidemiology, National Institutes of Health University of the Philippines, Manila, Philippines), Balram Bhargava (Director-General at the Indian Council of Medical Research, New Delhi, India), Patricia J Garcia (Professor, Universidad Peruana Cayetano Heredia and Adjunct Professor, Global Health Department, University of Washington, Seattle, WA, USA), Elizabeth Halloran (Professor, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, WA, USA), Ira Longini (Department of Biostatistics, University of Florida, Gainesville, FL, USA), María Consuelo Miranda Montoya (Investigador Asociado CIDEIM, Sub-Directora Científica de la Red AEDES, Universidad Industrial de Santander, Colombia), Mirta Roses (Academia Nacional de Ciencias de Buenos Aires, Buenos Aires, Argentina), Halvor Sommerfelt (Centre for Intervention Science in Maternal and Child Health, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway, and Norwegian Institute of Public Health, Oslo, Norway), and Ana Maria Henao-Restrepo (Office of the Executive Director [WHE], WHO Health Emergencies Programme, World Health Organization, Geneva, Switzerland).

Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA (PRK); University of Washington, Fred Hutchinson Cancer Centre, Seattle, WA, USA (TRF); Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA (SSE); and Health Emergencies Programme, World Health Organization, CH-1211 Geneva 27, Switzerland (AMH-R)

1 Krause P, Fleming TR, Longini I, Henao-Restrepo AM, Peto R, on behalf of the World Health Organization Solidarity Vaccines Trial Expert Group. COVID vaccine trials should seek worthwhile efficacy. *Lancet* 2020; **396:** 741–43.
2 Ellenberg SS, Fleming TR, DeMets DL. Data monitoring committees in clinical trials: a practical perspective, second edn. New York: John Wiley and Sons, 2019.
3 Business Wire. Pfizer and BioNTech propose expansion of pivotal COVID-19 vaccine trial. *Business Wire*, Sept 12,2020. https://www.businesswire.com/news/home/20200912005013/en/ (accessed Oct 22, 2020).
4 Loftus P. Moderna CEO eyes December for COVID vaccine. *MarketWatch*, Oct 19, 2020. https://www.marketwatch.com/story/moderna-ceo-eyes-december-for-covid-vaccine-2020-10-19 (accessed Oct 22, 2020).
5 Fleming TR, DeMets DL, Roe M, et al. Data Monitoring Committees: promoting best practices to address emerging challenges. *Clin Trials* 2017; **14:** 115–23.
6 Grant AM, Altman DG, Babiker AB, et al. Damocles Study Group. Issues in data monitoring and interim analyses of trials. *Health Technol Assess* 2005; **9:** 23–24.
7 US Food and Drug Administration. Guidance for clinical trial sponsors: on the establishment and operation of clinical trial data monitoring committees. 2006. http://www.fda.gov/OHRMS/ DOCKETS/98fr/o1d-0489-gdl0003.pdf (accessed Oct 22, 2020).
8 WHO. Operational guidelines for the establishment and functioning of Data and Safety Monitoring Boards. 2007. http://apps.who.int/iris/bitstream/10665/69171/1/TDR_GEN_Guidelines_05.1_eng.pdf (accessed Oct 22, 2020).
9 European Medicines Agency. Committee for Medicinal Products for Human Use. Guideline on Data Monitoring Committees. 2007. http://www.emea.eu.int/pdfs/human/ewp/ 587203en.pdf (accessed Oct 22, 2020).
10 National Institutes of Health. Policy for data and safety monitoring. 1998. http://grants.nih.gov/grants/guide/noticefiles/not98-084.html (accessed Oct 22, 2020).
11 Fleming TR. Protecting the confidentiality of interim data: addressing current challenges. *Clin Trials* 2015; **12:** 5–11.
12 Fleming TR, Ellenberg SS, DeMets DL. Data monitoring committees: current issues. *Clin Trials* 2018; **15:** 321–28.
13 Fleming TR, Rothmann MD, Lu HL. Issues in using "progression-free survival" when evaluating oncology products. *J Clin Oncol* 2009; **27:** 2874–80.