Doctopic: Analysis and Interpretation
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The approach to informed consent in acute care research

Authors' reply

Rafael Dal-Ré and Arthur L Caplan state that obtaining consent "was clearly not an issue in RECOVERY [the Randomised Evaluation of COVID-19 Therapy trial]" and use this statement to support their supposition that there is "no need" to reconsider regulations for written informed consent obtained prospectively from acutely ill patients. However, in the RECOVERY trial,[1] if no family member was available, patients who lacked capacity to consent could be enrolled without providing informed consent through the involvement of a doctor (independent of the study team) who could act as the legally designated representative.[2] Additionally, clinicians, rather than research personnel with training in research regulations, were permitted to establish eligibility and to obtain informed consent from patients under their care (table).[1,2] Each of these approaches to informed consent would require an alteration or waiver of informed consent in the USA. We suggest that the contrasting approaches to screening and informed consent processes between the UK and the USA help explain why RECOVERY has enrolled more than 45 000 patients, 50–100 times more than most explanatory trials examining similar topics.

Many have argued that such alterations or waivers of the process for written informed consent are justifiable for studies comparing therapies to which patients would be exposed outside of research.[3] The requirements for trial design and conduct, including the consent process, not only affect trial participants, but also determine which patients have access to trial enrolment and what decisions clinicians are confronted with as part of clinical care when those decisions are not made through trial enrolment. We argue that the approach to patient protection through research in the UK, in trials like RECOVERY, is superior to systems exposing far greater numbers of patients to ineffective or harmful therapies, as observed in usual care in the USA among patients who did not have access to clinical trials.

Author declarations remain the same as in the original Personal View.

	RECOVERY trial	Explanatory trials (eg, ORCHID trial)
If a patient was unable to provide consent and family members were not immediately available, could the patient be enrolled in the trial?*	Yes: a doctor independent of the study team could serve as the legal representative	No
If a family member wanted to enrol a patient in a trial but was unavailable to give written consent, could the patient be enrolled in the trial?*	Yes: a doctor independent of the study team could serve as the legal representative	No
Could clinicians assess patients' eligibility?†	Yes	No: an independent research team was required
Could clinicians obtain informed consent from patients under their care?	Yes	No: an independent research team was required
What were the requirements for general (not trial-specific) training in research regulations and ethics for personnel obtaining consent?	No requirements	Approximately 9 h in total of training in Human Subjects Research and Good Clinical Practice
What duration of trial-specific training for personnel obtaining consent was required to enrol patients?	Approximately 20 min of training in the process of obtaining consent	Approximately 4 h in total of protocol training, database training, and training in consent procedures before trial participation

ORCHID=Outcomes Related to COVID-19 Treated with Hydroxychloroquine Among Inpatients with Symptomatic Disease. RECOVERY=Randomised Evaluation of COVID-19 Therapy. *In the RECOVERY trial, for patients for whom a doctor not involved in the trial acted as the legal representative to provide consent at the time of enrolment, early trial protocols required ongoing attempts to obtain written consent after initiation of trial procedures, whereas later trial protocols recommended notification of enrolment and patient's rights but stated that "it is not necessary to obtain their written consent."[2] Enrolment and initiation of trial procedures without written informed consent from the patient or a legally authorised representative would require an alteration, waiver, or exception from informed consent in the USA. †Dedicated research teams (as used in explanatory trials in the USA) are available in only some hospitals, have limited enrolment capacity, and are usually available for only some days of the week and hours of the day. Embedding enrolment procedures into routine care (as occurs in pragmatic trials like RECOVERY) substantially increases the settings, diversity, and total number of patients potentially able to access clinical trials.

Table: **Approach to consent and enrolment in the RECOVERY trial in the UK and in explanatory trials in the USA**

**Jonathan D Casey, Laura M Beskow, Wesley H Self, Alexandre Mebazaa, Sean P Collins*
jonathan.d.casey@vumc.org

Division of Allergy, Pulmonary, and Critical Care Medicine (JDC), Vanderbilt Center for Biomedical Ethics and Society (LMB), Department of Emergency Medicine (WHS, SPC), and Vanderbilt Institute for Clinical and Translational Research (WHS), Vanderbilt University Medical Center, Nashville, TN 37232, USA; Department of Anesthesia, Burn and Critical Care, University Hospitals Saint-Louis-Lariboisière, AP-HP, Paris, France (AM); INSERM UMR-S 942, MASCOT, Université Paris Cité, Paris, France (AM); Geriatric Research, Education, and Clinical Center, Tennessee Valley Healthcare System, Nashville, TN, USA (SPC)

1 University of Oxford. RECOVERY: Randomised Evaluation of COVID-19 Therapy. RECOVERY trial FAQs for sites. https://www.recoverytrial.net/for-site-staff/site-set-up-1/recovery-trial-faqs-for-study-sites (accessed Aug 31, 2022).
2 University of Oxford. RECOVERY: Randomised Evaluation of COVID-19 Therapy. Study protocol & statistical analysis plan archive. https://www.recoverytrial.net/results/study-protocol-archive (accessed Sept 2, 2022).
3 Beskow LM, Lindsell CJ, Rice TW. Consent for acute care research and the regulatory "gray zone". *Am J Bioeth* 2020; **20**: 26–28.