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The evidence base for emergency use authorizations for COVID-19 treatments: A rapid review

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Abstract

Background and Aims: During the COVID-19 pandemic, US Food and Drug Administration (FDA) permitted emergency use authorizations (EUAs) for vaccines/treatments with promising data. Eight treatments were issued EUAs by May 31, 2021; one of these was approved (Remdesivir for certain populations) and two were revoked (chloroquine phosphate/hydroxychloroquine and bamlanivimab) by September 30, 2021. The aim of this study is to find out what evidence the EUAs were based on and how many studies were published while they remained active (up to September 30, 2021).

Methods: A review of published clinical studies for the 6 months before each EUA was issued, and the time after (until September 30, 2021, or until revoked). PubMed and the identified systematic reviews were the sources for identifying published literature.

Results: The number of clinical studies published pre-EUA varied from a single case study (for chloroquine phosphate/hydroxychloroquine) to numerous studies of multiple types (for convalescent plasma). Four treatments had a single randomized controlled trial (RCT) as evidence (bamlanivimab monotherapy, REGN-COV, bamlanivimab + etesevimab, sotrovimab) and two also had other study types (remdesivir and baricitinib). The number of clinical studies published post-EUA (for those active on September 30, 2021) was widely varied. Eighteen RCTs were published for Convalescent plasma, while Remdesivir had eight. Baricitinib, REGN-COV, and bamlanivimab + etesevimab all had one, but none were published for sotrovimab.

Conclusion: The number of trials for treatments with EUAs was limited in all cases before the EUA was issued, and in most cases for those with EUAs ongoing at the end of September 2021. The presence of EUAs may discourage participation in relevant clinical trials, which delays the widespread implementation of evidenced-based therapies. Large, robust RCTs should be completed, such as the RECOVERY

trial in the United Kingdom, to quickly find the answers desperately required during a pandemic.

KEYWORDS
clinical research, COVID-19, emergency use authorization

1 | INTRODUCTION

The COronaVIrus Disease 2019 (COVID-19) pandemic caused an international emergency throughout 2020 and 2021. This deadly disease is caused by the virus SARS-CoV-2, which newly emerged in 2019, and therefore, there was an urgent need to identify vaccines and therapies for the prevention and treatment of COVID-19. Given the amount of time needed to do so and the lack of available alternatives, the US Food and Drug Administration (FDA) permitted applications for emergency use authorizations (EUAs) for vaccines/treatments which had promising data.[1]

EUAs are issued by the FDA to permit use of unapproved medical products during an emergency situation, such as the COVID-19 pandemic. EUAs were first introduced in 2004 for an anthrax vaccine to protect those at risk of anthrax mail attacks. Since then EUAs have been issued for the treatment of H1N1 swine flu, Middle East Respiratory Syndrome (MERS), Ebola virus, Zika virus, and organophosphorus nerve agents.[1,2] EUAs were also issued for Enterovirus D68 and H7N9 influenza but only for diagnostic tests, and these EUAs remain active.[1] It is not unusual for EUAs to remain active for a long time, for example, the EUA for Atropine Auto-injector for the treatment of organophosphorus nerve agents has been active since 2017 and remains active in 2022.[1] EUAs for COVID-19 differ to the other situations in the relatively large number for treatments and vaccines, possibly due to the higher incidence of COVID-19 infection globally so more nations were invested in finding treatments and preventatives.

The requirements for EUA are less stringent than for full approval. For example, clinical trial data for a vaccine must include follow up of participants for a minimum of 6 months for full approval, whereas for EUA this is only 2 months and only half of participants need to have reached this point.[3] Using Remdesivir as an example, the EUA was issued based on preliminary data from Phase 3 trials; however, it was not until the full data was available that the full approval was issued.[4] The studies used for the decision were randomized controlled trials (RCTs), which are the most robust design of clinical trial.[3,5] In addition to a longer follow-up period, full approval may require additional data and inspections of how the product is made. As such, the review process for full approval takes around a year, compared to only a month for a EUA.[3] The process of collecting data takes more time, however, this can be minimized by having well designed clinical trials. Having results from just one or two RCTs can be sufficient evidence that a treatment is effective and relatively safe if the trials are large and well conducted, otherwise, the strongest source of evidence is a meta-analysis from a number of studies.[6]

The first EUA to be issued for a drug or biological therapeutic product for the treatment of COVID-19 was issued in March 2020 for chloroquine phosphate and hydroxychloroquine (HCQ). It was revoked within 3 months due to lack of efficacy and serious side effects.[2] In the following 17 months (up to May 2021), the FDA issued a further seven EUAs.[1] The EUA for bamlanivimab was revoked, as this proved ineffective against the emerging SARS-CoV-2 viral variants in vitro.[2,7,8] However, bamlanivimab remains in use as a combination therapy with another monoclonal antibody.[1] Details of the drugs/therapeutic products with ongoing EUAs (as of December 2021) are detailed in Table 1.

Although EUAs for two of the drugs or biological therapeutic products for the treatment of COVID-19 were revoked by September 2021, only one of the treatments that were given COVID-19 EUA has proceeded to gain FDA approval.[2] Remdesivir was approved on October 22, 2020, specifically for patients hospitalized with COVID-19 who are 12 years of age or older and weighing 40 kg or more. A EUA remains active for Remdesivir until further data is collected on its efficacy in pediatric patients under 12 years old (Table 1). Given that more treatments have been revoked than approved, this raises the concern of whether the evidence base used in the decision to issue the EUAs was sufficient, and whether the research published since the EUA was issued remains sufficient to justify their continuance. To investigate these concerns, this review aims to determine what evidence base was available when the EUAs were issued and what evidence was available at the time the literature was reviewed (up to end of September 2021) for those that still had active EUAs.

2 | METHODS

2.1 | Search strategy

The literature search was conducted by C. K. and repeated by A. B./J. W./C. W. to check for any discrepancies. Any disagreements were resolved between these researchers. PubMed was the primary source of the search, however, the systematic reviews and meta-analyses identified in this search were also reviewed to identify randomized clinical trials potentially missed by searching a single database. Additionally, where a Centre for Drug Evaluation and Research (CDER) Review was available from the FDA, this was used to determine the studies used in the decision to issue the EUA.

The search terms were the drug name(s), publication period and "coronavirus OR COVID-19 OR SARS-CoV-2." See Supporting Information: Table 1 for the drug names and publication dates searched for each drug.

TABLE 1 Details of drugs/therapeutic products given EUA for the treatment of COVID-19

Drug/therapeutic product	Authorized use: patients	Authorized use: condition	Method of administration	Dose and frequency	Duration
Chloroquine phosphate/ hydroxychloroquine (HCQ) Revoked	Adult and adolescent patients who weigh 50 kg or more, for whom a clinical trial is not available, or participation is not feasible	Hospitalized COVID-19 patients	Oral	Chloroquine phosphate: 1 g on Day 1, followed by 500 mg daily for 4–7 days HCQ: 800 mg on Day 1, followed by 400 mg daily for 4–7 days	5–8 days
Bamlanivimab Revoked	Adults and pediatric patients (12 years of age and older weighing at least 40 kg)	COVID-19 positive and at high risk for progressing to severe COVID-19 and/or hospitalization	Intravenous infusion	Single dose of 700 mg	16–60 min infusion
Remdesivir (Veklury)	(A) pediatric patients weighing 3.5–40 kg and (B) patients under 12 years of age weighing at least 3.5 kg	Hospitalized COVID-19 patients	Intravenous infusion	Patients weighing 3.5–40 kg: 5 mg/kg on Day 1, then 2.5 mg/kg on subsequent days Patients weighing 40 kg or more: 200 mg on Day 1, then 100 mg on subsequent days	30–120 min infusion each day for 5–10 days
COVID-19 convalescent plasma	All patients although risk assessment should be taken for pediatric, geriatric, pregnant, and breast-feeding patients	Hospitalized COVID-19 patients	Intravenous infusion	May first consider starting with one high-titer COVID-19 convalescent plasma unit (about 200 ml), with the administration of additional convalescent plasma units based on the medical judgment and clinical response	Not specified
Baricitinib (Olumiant)	Hospitalized adults and pediatric patients 2 years of age or older	Suspected or laboratory-confirmed COVID-19 requiring supplemental oxygen, IMV, or ECMO	Oral tablets	9 years and older: 4 mg once a day 2–9 years: 2 mg once a day	14 days or until hospital discharge, whichever comes first
REGEN-COV	12 years of age and older weighing at least 40 kg	Mild-to-moderate COVID-19 at high risk for progressing to severe COVID-19	Intravenous infusion or subcutaneous injection	600 mg of casirivimab and 600 mg of imdevimab administered together as a single dose	Minimum infusion time 20–50 min
Bamlanivimab and etesevimab	12 years of age and older weighing at least 40 kg	Mild-to-moderate COVID-19 at high risk for progressing to severe COVID-19	Intravenous infusion	700 mg bamlanivimab and 1400 mg of etesevimab administered together as a single dose	21-70 min infusion
Sotrovimab	12 years of age and older weighing at least 40 kg	Mild-to-moderate COVID-19 at high risk for progressing to severe COVID-19	Intravenous infusion	500 mg as a single dose	30 min infusion

Note: Information correct as of December 12, 2021. Obtained from the FDA "fact sheet for health care providers" for each treatment.

Abbreviations: COVID-19, COronaVIrus Disease 2019; ECMO: Extracorporeal membrane oxygenation; FDA, US Food and Drug Administration; IMV, invasive mechanical ventilation.

2.2 | Inclusion criteria

Research studies that evaluated the effectiveness of the searched treatments/treatment combinations in patients with COVID-19 were included in this review. Given the limited number of studies published ahead of the EUA date of issue, observational and nonrandomized trials were included as well as RCTs and meta-analyses for pre-EUA publications. Inclusion criteria for studies published after the EUA was issued were limited to RCTs and meta-analyses only as these present the highest quality evidence (although for meta-analyses, this is dependent on which studies are included).[9]

2.3 | Exclusion criteria

Duplicate publications, reviews that were not systematic, case series, and case reports were excluded from the meta-analysis. Given that we would expect higher-quality evidence to be published after the EUA was issued, observational studies and non-RCTs were excluded from the post-EUA analyses.

2.4 | Data extraction

Data were extracted by C. K. and checked by A. B./J. W./C. W. Any disagreements were resolved between these researchers. The data extraction sheet was designed and piloted by C. K. The final version used throughout this research is in Supporting Information: Table 2.

The data extracted included:

1. Study title, author, and date of publication
2. Study type, setting, and number of sites
3. Number and type of patients
4. Drug dose, frequency, and duration
5. Primary outcome and results of primary outcome and other relevant outcomes
6. Limitations of the study (either as stated in the publication or as identified by C. K./A. B./J. W./C. W.).

2.5 | Risk of bias evaluation

RCTs included in the analyses were assessed for risk of bias using the Cochrane Risk of Bias tool RoB2[10] and presented on the Robvis bias visualization tool for systematic reviews.[11] The tool was completed for each study by C. K. and checked for agreement by A. B./J. W./C. W.

3 | RESULTS

3.1 | What evidence were the EUAs based on?

The number of studies identified for the 6 months before the EUA was issued and in subsequent months, up to the point they were revoked (for bamlanivimab alone and Chloroquine phosphate and HCQ) are detailed in Table 2. For those that were not revoked by

TABLE 2 Number and types of studies published for each treatment with a revoked EUA in the 6 months before the EUA was revoked (pre-EUA) and up to the date of withdrawal (post-EUA).

	Chloroquine phosphate/HCQ EUA: 28/03/2020		Bamlivimab EUA: 09/11/2020	
	Pre-EUA	Post-EUA	Pre-EUA	Post-EUA
Meta-analysis	0	1	0	0
RCT	0	5[a]	1	1
Non-RCT	0	0	0	0
Observational	0	17	0	2
Cohort	0	1	0	0
Case series	0	5	0	0
Case study	1	15	0	0
Systematic review	0	8	0	0

Note: Study designs that were eligible for data extraction are highlighted in green.

Abbreviations: EUA, emergency use authorization; HCQ, hydroxychloroquine; RCT, randomized controlled trial.

[a]One study was published after the EUA was revoked, but is included as it supported the decision to revoke.

TABLE 3 Number and types of studies published for each treatment with an active EUA as of the end of September 2021 in the 6 months before the EUA was issued and up to the end of September 2021

	Remdesivir EUA: 01/05/2020		**Convalescent plasma EUA: 23/08/2020**		**Baricitinib EUA: 19/11/2020**		**REGN-COV EUA: 21/11/2020**		**Bamlanivimab + etesevimab EUA: 09/02/2021**		**Sotrovimab EUA: 26/05/2021**	
	Pre-EUA	Post-EUA	Pre-EUA	Post-EUA	Pre-EUA	Post-EUA	Pre-EUA	Post-EUA	Pre-EUA	Post-EUA	Pre-EUA	Post-EUA
Meta-analysis	0	15	2	17 (2 are combined with RCT)	0	0	0	0	0	0	0	0
RCT	1	8	2	18	1[a]	1	1[a]	1	1	1	1[a]	0
Non-RCT	1	0	3	17	0	2	0	0	0	0	0	0
Observational	0	5	2	31	0	6	0	6	0	1	0	0
Cohort	0	5	0	11	0	5	0	0	0	0	0	0
Case series	0	5	14	24	0	0	0	0	0	0	0	0
Case study	4	22	13	34	2	4	0	4	0	0	0	0
Systematic review	1	7	4	11	0	0	0	0	0	0	0	0

Abbreviations: EUA, emergency use authorization; FDA, US Food and Drug Administration; RCT, randomized controlled trial.
[a]Published after the EUA but the FDA had access to this data beforehand.

September 2021, studies published up to this time are detailed in Table 3. The extracted data for the pre-EUA meta-analyses, RCTs, non-RCTs, cohort studies, and observational studies and the post-EUA meta-analyses and RCTs are summarized in Supporting Information: Table 3. The results of the Risk of Bias assessment are given in Figure 1.

3.1.1 | Chloroquine phosphate and HCQ

This review identified no clinical studies published before the EUA was issued for chloroquine phosphate and HCQ (Table 2). The letter of authorization dated March 28, 2020, states that the EUA was issued "Based upon limited in-vitro and anecdotal clinical data in case series, chloroquine phosphate and HCQ sulfate are currently recommended for treatment of hospitalized COVID-19 patients."[12]

3.1.2 | Bamlanivimab

The CDER review states that the evidence included one completed RCT and six ongoing RCTs.[2] This is in line with the single published RCT result identified in this study (Table 2). This RCT has low risk of bias (Figure 1) and observed a statistically significant benefit in the primary outcome, viral load, for one of the three doses evaluated, with a difference from placebo in the decrease from baseline of −0.53, 95% confidence interval [CI], −0.98 to −0.08, $p = 0.02$ (Supporting Information: Table 3).

3.1.3 | Remdesivir

For remdesivir, there was one non-RCT in addition to an RCT published before the EUA was issued (Table 3). Although the systematic review for Remdesivir stated there were two RCTs, there was no reference for the other and the outcome (as stated in the systematic review) was just safety, not efficacy.[13] No CDER review is available to confirm what evidence the EUA was based upon.

The RCT identified in this review for remdesivir showed no statistically significant difference in the primary outcome, time to clinical improvement (hazard ratio [HR] 1.52, 95% CI, 0.95–2.43, no p value given). Furthermore, this had "some concerns" for risk of bias (Figure 1) as they did not recruit the preplanned number of participants.[14] The non-RCT that was also published pre-EUA did not have a control group so no comparison to the control treatment could be made (Supporting Information: Table 3).

3.1.4 | Convalescent plasma

Although no CDER review is available to confirm what evidence the EUA for Convalescent Plasma was based on, the results of two published RCTs were available at the time of issue (Table 3). One of the RCTs had low risk of bias and one had some concerns (Figure 1), although neither of these showed a statistically significant treatment effect. One of the three nonrandomized trials and one of the two observational studies had a control group for comparison. The nonrandomized trial observed a reduction in length of hospitalization stay in the plasma group compared to control group (9.54 days compared to 12.88 days, $p = 0.002$) but did not observe a statistically significant effect of convalescent plasma on patient survival (14.8% mortality in the plasma group compared to 24.3% in the control, p value reported as NS). The observational study did observe a statistically significant reduction in mortality with convalescent plasma of 19.7%–62.1% (95% CI; $p = 0.02$). There were also two meta-analyses available, unlike for the other treatments. These both found a potential benefit of convalescent plasma on mortality (odds

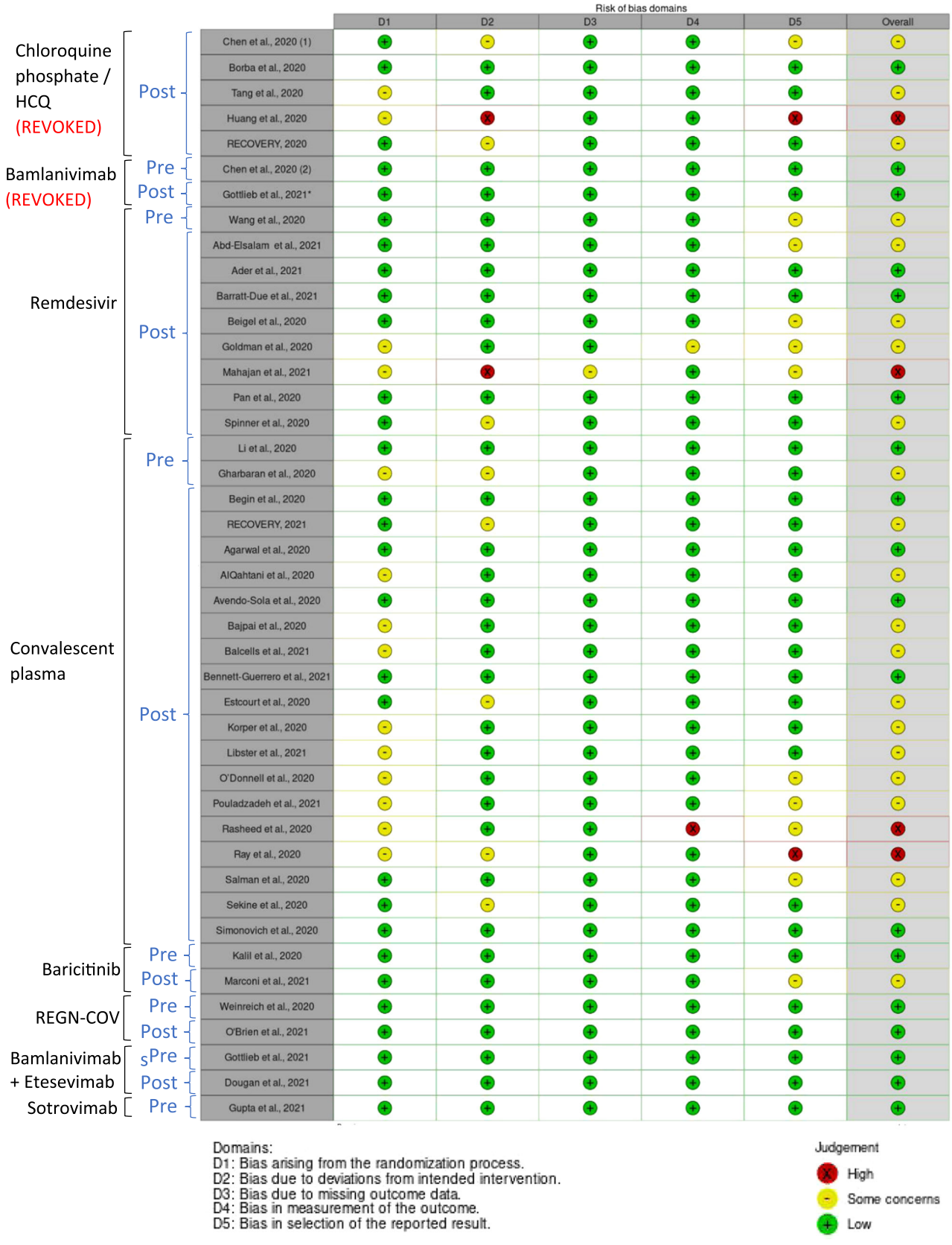

FIGURE 1 Risk of bias for the RCTs published for each treatment with EUA in the 6 months before it was issued (pre) and up to the point it was revoked (if applicable) or up to the end of September 2021 if still active at this time (post). EUA, emergency use authorization; RCT, randomized controlled trial.

ratio [OR] = 0.44, 95% CI, 0.25–0.77, $p = 0.004$ in one and OR = 0.32, 95% CI, 0.19–0.52, $p < 0.001$ in the other) but concluded that the evidence was low quality with a high risk of bias (Supporting Information: Table 3).

3.1.5 | Baricitinib

This review only identified two case studies published before the EUA for baricitinib, however, the FDA had access to the data for one RCT ahead of publication[2] (Table 3). This was the sole RCT supporting the EUA request.[1] The RCT had low risk of bias (Figure 1) and reported a significantly shorter time to recovery compared to the control arm (rate ratio for recovery, 1.16; 95% CI, 1.01–1.32; $p = 0.03$; Supporting Information: Table 3).

3.1.6 | REGN-COV

The published clinical evidence available before the EUA for baricitinib was limited to one RCT (Table 3). This showed reduced viral load compared to control from Day 1 to 7 [−0.56 log10 copies per milliliter (95% CI, −1.02 to −0.11) among patients who were serum antibody–negative at baseline and −0.41 log10 copies per milliliter (95% CI, −0.71 to −0.10) in the overall trial population], but it is not stated whether this is statistically significant,[15] probably because the results are from an interim analysis. Otherwise, the study has low risk of bias (Figure 1). The CDER review confirms that this interim analysis was the main data supporting the EUA, alongside another four RCTs that were ongoing.[1]

3.1.7 | Bamlanivimab + etesevimab

No clinical studies for bamlanivimab + etesevimab as a combination treatment were published before the EUA, but the FDA had early access to the data from two RCTs.[1] The one that was identified in this review had low risk of bias (Figure 1) and showed a statistically significant difference in the primary outcome (change in viral load) for the combination treatment of bamlanivimab + etesevimab compared to placebo at Day 11 (between-group difference, −0.57 [95% CI, −1.00 to −0.14], $p = 0.01$; Supporting Information: Table 3). The other RCT was not published at the time of this review.

3.1.8 | Sotrovimab

No clinical studies for sotrovimab treatment were published before the EUA, but the FDA had early access to the data interim analysis from one RCT,[1] which otherwise had low risk of bias (Figure 1) and reported significantly reduced clinical progression by 85% (97.24% CI, 44%–96%; $p = 0.002$; Supporting Information: Table 3). The CDER reports using data from four other RCTs, all of which were still ongoing at the time.[1]

3.2 | How many studies were published before the EUAs were revoked?

After the EUA for chloroquine phosphate/HCQ was issued, and before it was revoked, four RCTs were published, plus numerous nonrandomized studies (Table 2). The EUA was revoked as these studies showed no significant effect of chloroquine phosphate/HCQ on viral clearance, caused serious cardiac adverse events, and the large RECOVERY trial (for which the FDA had early access to the data) did not observe a benefit on mortality (rate ratio 1.09, 95% CI, 0.97–1.23, $p = 0.15$; Supporting Information: Table 3).[2,16]

Forbamlanivimab, only one other RCT and two observational studies were published before it was revoked (Table 2). However, these did not influence the decision to revoke the EUA. It was revoked due to emerging variants not being susceptible to this monoclonal therapy in vitro.[2,7,8]

3.3 | What evidence is there for the continuation of the EUAs?

As of September 2021, the EUAs were still active for Remdesivir, convalescent plasma, baricitinib, REGN-COV, bamlanivimab + etesevimab combination therapy, and sotrovimab. The number of studies published after a EUA was issued until September 2021 varied by treatment, as shown in Table 3. The results of the Risk of Bias assessment for the RCTs are shown in Figure 1.

3.3.1 | Remdesivir

A number of studies were published for Remdesivir post-EUA, including eight RCTs (however, the RCT article by Abd-Elsalam et al. has since been retracted), three of which had low risk of bias (Figure 1), and nearly twice as many meta-analyses (Table 3). There were also a large number of case studies and several observational/cohort studies and case series published (Table 3). Nine of the 15 meta-analyses identified a statistically significant benefit in terms of clinical improvement for patients treated with Remdesivir (Supporting Information: Table 3). However, an improvement in mortality rates was not observed to a significant degree by any of the eight RCTs (Supporting Information: Table 3).

3.3.2 | Convalescent plasma

For convalescent plasma, there were a large number of studies of all types, including 18 RCTs and almost as many meta-analyses (Table 3). Only five of the RCTs had low risk of bias (Figure 1).

The meta-analyses had varied findings, with nine of the 17 showing a statistically significant improvement to mortality (refer to Supporting Information: Table 3 for ORs, CIs, and *p* values as reported for each study). However, the seven meta-analyses, which included eight or more RCTs to evaluate the effect on mortality concluded that convalescent plasma does not significantly affect mortality.[17–23] In two of these studies, only when other study types were included, was there a significant improvement detected for outcome measures (refer to Supporting Information: Table 3 for ORs, CIs, and *p* values as reported for each study).

3.3.3 | Baricitinib

Between the date that the baricitinib EUA was issued and the end of September 2021, one RCT plus several other study types were published but no meta-analyses (Table 3). The RCT had low risk of bias (Figure 1) and showed no significant effect of this treatment on the primary outcome, disease progression (OR 0.85, 95% CI, 0.67–1·08, $p = 0.18$), but did find a significant benefit in terms of mortality (HR 0.57, 95% CI, 0.41–0.78, nominal $p = 0.002$ at 28 days, HR 0.62, 95% CI, 0.47–0.83, $p = 0.005$ at 60 days; Supporting Information: Table 3).

3.3.4 | REGN-COV

Between the date that the REGN-COV EUA was issued and the end of September 2021, one RCT plus several other study types were published but no meta-analyses (Table 3). The RCT for REGN-COV as a COVID-19 prophylactic had low risk of bias (Figure 1) and observed that REGN-COV reduced the risk of infection by 81.4% ($p < 0.001$). This study also found that in those participants who did develop COVID-19, the symptom duration was shorter by 2 weeks (no *p* value given; Supporting Information: Table 3).

3.3.5 | Bamlanivimab + etesevimab

Between the date that the bamlanivimab + etesevimab EUA was issued and the end of September 2021, one RCT plus one observational study were published but no meta-analyses (Table 3). The RCT had low risk of bias (Figure 1) and reported significant improvements in Covid-19-related hospitalization and mortality with this combination compared to placebo (absolute risk difference, −4.8 percentage points; 95% CI, −7.4 to −2.3; relative risk difference, 70%; $p < 0.001$); Supporting Information: Table 3).

3.3.6 | Sotrovimab

No further RCTs were published for sotrovimab after the EUA was issued up to September 2021 (Table 3).

4 | DISCUSSION

This review identified that, in general, the FDA had very little evidence to base their EUA decision on. The first EUA issued, for Chloroquine phosphate and HCQ, was based on no RCTs. For subsequent treatments, the results of only a single RCT were available in most cases. The number of RCTs and meta-analyses published post-EUA, for treatments with active EUAs up to the end of September 2021, was very high for convalescent plasma, moderate for Remdesivir, nonexistent for sotrovimab, and limited to a single RCT for the other three treatments.

Sparse evidence ahead of the EUA decision is to be expected, as the EUAs were issued to allow patients to receive experimental treatments before trial results were available. While understandable, this policy is problematic as it prevented the treated patients from being enrolled into a trial evaluating the experimental treatment and thereby delaying the production of robust evidence. In the United Kingdom, for example, off-license use of potential treatments was discouraged by the National Health Service (NHS) and participation in trials was encouraged, especially in one of three large adaptive trials (including RECOVERY) so that evidence could be generated before approving use outside of a trial.[24] The strengths of the RECOVERY trial were the adaptive design that allowed for quick addition of new treatment arms and the speed with which it set up a large number of sites and recruited a large number of patients. The only weakness is how long it has taken the RECOVERY trial to be adopted by sites in other countries. The global research community can learn from this by strengthening processes for international trials and implementing similar designs should there be another emergency in the future.

The lack of studies overall meant that conclusive decisions have yet to be made for most of the treatments. Having just one or two RCT results is only sufficient evidence that a treatment is effective and relatively safe if it is large and well-conducted, otherwise the strongest source of evidence is a meta-analysis.[6] Given that neither were available for most of the treatments with active EUAs, this is likely to be why the FDA has chosen not to issue full approval, but instead to keep the EUA in place until further evidence is published.

Only the EUA for chloroquine phosphate and HCQ included the condition that it should only be used if a clinical trial is not available/appropriate. This is likely due to the lack of evidence for this treatment, being the only EUA issued without any clinical trial data. One could speculate that the FDA was under pressure from politicians and the media to issue this EUA ahead of sufficient evidence, given unfounded beliefs in its effectiveness.[25] This could be because people wanted to believe that this inexpensive and widely available drug worked, rather than accept there was no treatment available with strong evidence for an effect. We would argue that all of the EUAs should have been issued with the condition to only use if no trial is available as this would have sped up recruitment to trials and the time to making definitive conclusions about their efficacy.[26] Or better yet, avoid EUAs altogether so that all hospitals which want to use the treatments are encouraged to take part in clinical trials.

In this review, there were fewer published studies identified for the four treatments with the most recently issued EUAs. This could be because the FDA issued approval for Remdesivir on October 22, 2020,[27] which would have made it the primary treatment option. It appears though that the bulk of research following this focussed on convalescent plasma rather than the other four treatments. This is likely because it was effective for other viral infections,[28] and there was some hope that despite unpromising results using plasma with higher titer antibodies,[18] earlier transfusion[18] and more selection of recipients could be the answer to its success.[29] However, even when meta-analysis was limited to RCTs using "high titer" convalescent plasma there was no overall difference to mortality.[22] Accordingly, the World Health Organization (WHO) concluded in December 2021 that convalescent plasma should not be used to treat COVID-19.[30]

Of the treatments with active EUAs in September 2021, all except Remdesivir remain in place 6 months later (June 17, 2022).[1] We suspect it is not a coincidence that this is the treatment with the most RCTs published (except Convalescent plasma). Although Remdesivir was approved just 5 months after the EUA was issued, baricitinib has yet to be approved by the FDA despite WHO guidance recommending it for severe or critical COVID-19 in March 2022,[31] 16 months after the EUA was issued. In addition to the two RCTs for baricitinib identified in this review, the recommendation was given by the WHO based on the results of a further RCT published in October 2021.[32,33]

This study has a number of limitations. The search for publications was limited to one database, Pubmed, plus the studies included in the identified systematic reviews. This was due to time limitations and means that there could be articles missed. Furthermore, as the search was limited to only publications in English, there may have been some missed that were published in another language. There may also have been completed studies that were not published, perhaps because they showed a lack of effectiveness of the treatment, or because they were in the often lengthy publication process and, therefore, did not make the cut offs for inclusion.

In conclusion, research should have been the main focus for novel COVID-19 treatments; to speed up the time to find out if these treatments were effective and use this evidence to reduce morbidity from COVID-19 and save lives. A focus on high-quality research in the form of RCTs with minimal bias would reduce the number of patients who receive ineffective treatments and suffer their side effects. The RECOVERY trial (NCT04381936) is an excellent example of a trial that recruited a large number of patients, from a large number of hospitals in the United Kingdom, to provide conclusive results on a number of treatments. If more trials like this had been done, and if those patients who received treatment under EUA had been given the opportunity to take part in a clinical trial instead, hypothetically we could have had conclusive results much quicker.

AUTHOR CONTRIBUTIONS

Catherine Knowlson: data curation; methodology; project administration; visualization; writing – original draft; writing – review and editing. **Ailish Byrne**: validation; writing – review and editing. **Jacqueline Wilkinson**: validation; writing – review and editing. **Claire Whitmore**: validation; writing – review and editing. **David Torgerson**: conceptualization; methodology; supervision; writing – review and editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its Supporting Information.

TRANSPARENCY STATEMENT

The lead author Ailish Byrne affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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