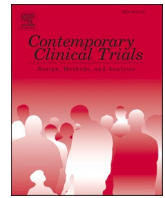




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Research Article

Implementation of platform trials in the COVID-19 pandemic: A rapid review

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ABSTRACT

Motivation: Platform designs - master protocols that allow for new treatment arms to be added over time - have gained considerable attention in recent years. Between 2001 and 2019, 16 platform trials were initiated globally. The COVID-19 pandemic seems to have provided a new motivation for these designs. We conducted a rapid review to quantify and describe platform trials used in COVID-19.

Methods: We cross-referenced PubMed, ClinicalTrials.gov, and the Cytel COVID-19 Clinical Trials Tracker to identify platform trials, defined by their stated ability to add future arms.

Results: We identified 58 COVID-19 platform trials globally registered between January 2020 and May 2021. According to trial registries, 16 trials have added new therapies (median 3, IQR 4) and 11 have dropped arms (median 3, IQR 2.5). About 50% of trials publicly share their protocol, and 31 trials (53%) intend to share trial data. Forty-nine trials (84%) explicitly report adaptive features, and 21 trials (36%) state Bayesian methods.

Conclusions: During the pandemic, there has been a surge in the number of platform trials compared to historical use. While transparency in statistical methods and clarity of data sharing policies needs improvement, platform trials appear particularly well-suited for rapid evidence generation. Trials secured funding quickly and many succeeded in adding new therapies in a short time period, thus demonstrating the potential for these trial designs to be implemented beyond the pandemic. The evidence gathered here may provide ample insight to further inform operational, statistical, and regulatory aspects of future platform trial conduct.

1. Introduction

The urgency posed by the COVID-19 pandemic was met with a large number of clinical trials worldwide. Within two months of the World Health Organization declaring a global pandemic, over 1000 interventional clinical trials had been registered, and this number has risen above 6000 as of June 2021 [1,2]. The number of these trials has highlighted many of the known efficiencies of clinical development, while also providing an opportunity to implement novel designs.

Platform clinical trials have gathered significant attention in recent years. They are considered a type of master protocol, which provides an overarching protocol designed to answer multiple questions; platform protocols adaptively allow for experimental therapies to enter or leave the trial over the course of the trial [3].

The simultaneous assessment of multiple experimental therapies under a single protocol offers many attractive and efficient features compared to traditional two-arm trials, including fewer required patients, shorter time to treatment evaluation, and greater power to

identify effective therapies [4]. These advantages are similarly found in other adaptive designs, whereby trial features are amended during the trial based on prespecified criteria [5]. However, platform designs also introduce additional complexities in the design, analysis, and logistics of conduct [4,6,7].

In a recent study, Park et al. (2019) identified 16 platform trials initiated between 2001 and 2019, with numbers increasing over time [8]. While the majority of platform trials have been conducted in cancer, their use for viral illnesses and disease outbreaks is not a new concept. REMAP-CAP, a large-scale international platform trial, was initiated in 2016 for community-acquired pneumonia [9]. Berry et al. (2016) designed an adaptive platform trial to assess therapies for the 2014 West Africa Ebola outbreak, although the epidemic was contained before the trial started [10].

More recently, the COVID-19 pandemic has provided a new motivation for using these designs. Perhaps most well-known in the UK is the RECOVERY trial, which launched in March 2020 and has received considerable attention from the research community and public alike.

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Not only was RECOVERY extremely effective in its initiation, recruiting its first patients 9 days after protocol submission, but it was also able to release conclusive results in a timely manner. By April 2020, at least 97 registered clinical trials were testing the efficacy of hydroxychloroquine [11]. On June 3, 2020, RECOVERY trial investigators declared the treatment ineffective, and by June 17, 2020 the UK Medicines and Healthcare products Regulatory Agency (MHRA) instructed trials to discontinue recruitment to hydroxychloroquine arms [12–15].

In addition to the RECOVERY trial, REMAP-CAP has not only been running since 2016, but was able to quickly expand from community-acquired pneumonia to also COVID-19 [80,81]. The Solidarity master protocol by the World Health Organization has also initiated multiple substudies on a global scale. The efficiency of such large trials makes it clear why platform trials have become a central point of discussion. However, the extent of their use in the broader COVID-19 clinical trial landscape has not yet been quantified. Details of their implementation, including design and conduct, may provide crucial information for our understanding of these innovative designs. We conducted a rapid review with an emphasis on trial operations (e.g. adding/dropping treatment arms), data sharing policies, transparency in methods and trial operations, and trial design (e.g. use of adaptive features).

2. Methods

We performed database searches at two time-points in October 2020 and June 2021. On October 21, 2020 (search 1) and June 22, 2021 (search 2), we searched [ClinicalTrials.gov](https://www.clinicaltrials.gov) and PubMed for master protocols in any indication. The full Cytel COVID-19 Clinical Trials Tracker [16] dataset was retrieved on November 4th for COVID-19 trials of any design. Additional trials were identified through reference by trials retrieved from searches. Details on the search strategy are provided in Table S1 in the Supplementary material.

Platform definitions vary across the literature with regard to drug class, randomization, and other features, and the lack of consensus in these areas has been previously documented [17–21]. The most pervasive defining characteristic is the flexibility to add/drop arms from the platform. In looking at characteristics of published platform trials, it is unclear whether a trial must allow for both adding and dropping to be considered platform. For example, the plasmaMATCH trial in breast cancer consists of multiple non-comparative single-arm substudies, where it allows for the addition of experimental arms but each arm does not necessarily have early stopping criteria, therefore it is not clear whether an arm can be dropped. It is however referred to as a “phase 2a, platform trial” [22]. Therefore, in this study, we have labeled a trial as platform if it is stated on the trial registration webpage, in a publication, or in the full study protocol that the trial allows for the addition of future arms [3]. A trial was labeled as “potential” platform if the listed sources contained language that suggested but could not confirm the flexibility to add arms, or the trial self-identifies as platform but has no further information; for example, trial NCT04426695 defines itself as a master protocol without further detail, but the [ClinicalTrials.gov](https://www.clinicaltrials.gov) history of registration changes shows that an arm was added in the two months following the trial start date in June 2020 [23].

Search results were split and screened by two independent reviewers (AMV and ZY); a sample of 28 trials was reviewed to verify consistency (Cohen's kappa 0.89, 95% CI: (0.77, 1.0)). Platform trial information was retrieved through manual search for the identified trials between December 1–3, 2020 for search 1 and June 30 – July 13, 2021 for search 2. Information was collected from trial registration pages, trial websites, study documents, and publications. Data was extracted by AMV and confirmed by ZY and CY. Disagreements were resolved through discussion and consensus.

In the results below, we descriptively examine trial operations and conduct, transparency and data sharing, and design features.

3. Results

We identified a total of 58 registered platform trials (45 in search 1, 9 in search 2, and 4 by backward citation searching through the 9 trials from search 2) in COVID-19 treatments and prophylaxis (including 10 potential) registered between January 2020 and May 2021 (Figs. 1, S1, S2) [9,13,24–79]. Of these, 19 (33%) are trials within a larger master protocol or research initiative, including Solidarity (CATCO [74], Dis-CoVeRy [75], and EU SolidAct [55]), ACTT (ACTT-1 [34], ACTT-2 [40], ACTT-3 [35], ACTT-4 [36]), TACTIC (TACTIC-R [70] and TACTIC-E [62]), and ACTIV (ACTIV-1 IM [28], ACTIV-2 [29], ACTIV-3 [25], ACTIV-4 [30–32], ACTIV-5 BET-A and ACTIV-5 BET-B [24], and ACTIV-6 [33]), and TOGETHER (TOGETHER 1, 2 [52], and 3 [73]). We found no details about TOGETHER 1, other than referencing in the TOGETHER 2 protocol [52].

Thirty-eight trials (65%) identify themselves as “platform”. Of these, 30 trials also give a statement about the flexibility to add arms, while the remaining 8 trials have insufficient further information on trial design. Overall, 48 trials (83%) reference an ability to add future interventions.

3.1. Operations and conduct

The earliest registered trial ACTT-1 began recruiting patients on February 21st in the US [34]. REMAP-CAP enrolled its first COVID-19 patient on March 9th in its sub-platform REMAP-COVID [80,81]. Nearly all trials are entirely publicly funded (48, 83%), and all but a few trials are ongoing and actively recruiting patients (Fig. 2). Four trials (CROWN CORONA [48], ENFORCE [63], COVERALL [60], and NCT04889209 [50]) assess potential vaccines. As of July 12, 2021, 46 trials (79%) are ongoing, 4 (7%) are completed, 5 (9%) are not yet recruiting, 1 (PROTECT) is withdrawn [66], and the status of 2 (ACCORD 2 [27] and TOGETHER 1 [52]) are unknown, according to the latest information on trial registry websites.

Using [ClinicalTrials.gov](https://www.clinicaltrials.gov)'s History of Changes, we found that several trials have added and/or closed arms over the course of conduct. Due to the variability in updates to registration pages, we may underestimate exact numbers, particularly for dropped or suspended arms. In total, 16 trials have recorded the addition of experimental therapies

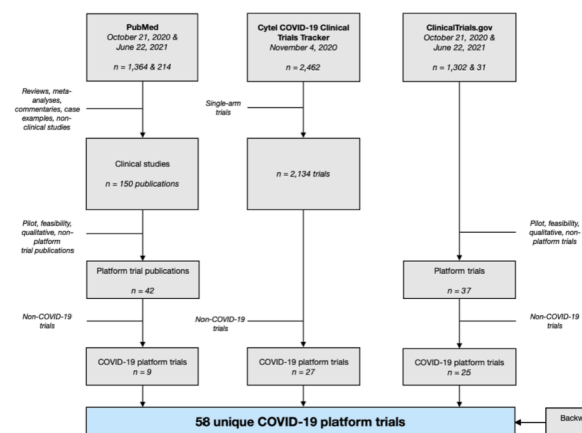


Fig. 1. PRISMA flowchart for combined search and selection at two time points. We searched [ClinicalTrials.gov](https://www.clinicaltrials.gov) for master protocols in any indication (October 21, 2020) and COVID-19 (June 22, 2021). We searched PubMed for master protocols in any indication (October 21, 2020 and June 22, 2020). The full Cytel COVID-19 Clinical Trials Tracker dataset was retrieved on November 4th for COVID-19-specific trials of any design. A trial was labeled as platform if it is stated on the trial registration webpage, in a publication, or in the full study protocol that the trial allows for the addition of future arms [3]. A trial was labeled as “potential” platform if the listed sources contained language that suggested but could not confirm the flexibility to add arms, or the trial self-identifies as platform but has no further information.

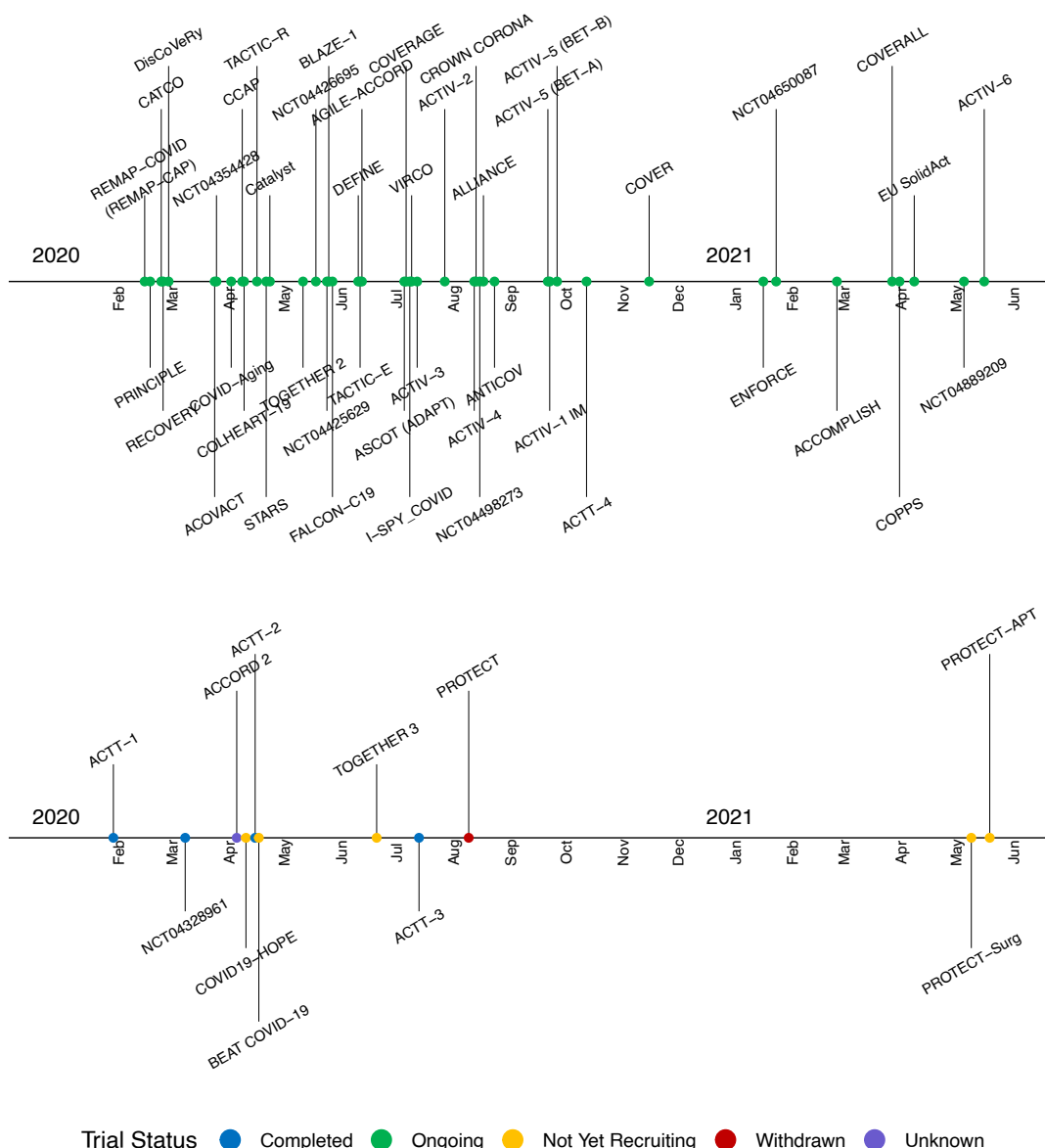


Fig. 2. COVID-19 platform trial initiation from January 2020 through May 2021. Trial status is shown as classified in [ClinicalTrials.gov](https://clinicaltrials.gov). A completed trial is one where the final data collection for the primary endpoint has been done for all enrolled participants. None of the four completed trials (ACTT-1, ACTT-2, ACTT-3, and NCT04328961) showed evidence of having added any treatment arms.

[9,25,26,32,37,48,57,59,68,72,74,75,77,79,82,78] and 12 have recorded arm discontinuations [25,30,48,53,59,68,72,74,75,77,78,82] (Table 1). For trials with available information, there have been a median of 3 added arms (IQR 4) and 3 dropped arms (IQR 2.5). Four trials stand out. As of May 5, 2021, RECOVERY has added 10 arms and closed 8. REMAP-COVID was initiated with 5 interventions and has since added 9 new therapies as of October 8, 2020, although the number of dropped arms was unavailable [83]. ACTIV-2 has added 9 arms and dropped 3 [82]. And, I-SPY COVID has added 6 arms and dropped 4 [59]. None of the four completed trials (ACTT-1 [34], ACTT-2 [84], ACTT-3 [35], and NCT04328961 [85]) showed evidence of having added any treatment arms.

3.2. Transparency and intention to share data

Transparency in research encompasses easy and free access to trial documents, clear description of design and statistical methods, and timely dissemination of results. At the fast rate of COVID-19 platform trial implementation, protocol release is likely the most direct means of

accessing design and analysis information. We found that 29/58 (50%) platform trials made their full protocol publicly accessible. In December 2020, we found 23/45 trials (51%) had publicly accessible protocols; since then, 12/45 (27%) trials have released new or updated versions (Table S2). The proportion of industry-funded and non-industry-funded trials that share protocols are similar; 55% (5/9) and 50% (24/48), respectively. Of the 14 trials that fall under a larger master protocol, only CATCO does not have publicly accessible documents [74].

Accessing IPD is important for replicating final analyses, generating new hypotheses, and applying new statistical methods to real data [86,87]. We located trial data sharing statements through [ClinicalTrials.gov](https://clinicaltrials.gov), publications, and the official trial protocol where available.

Thirty-one trials (53%) have stated an intention to share IPD; 20 by private request, 7 on a public data sharing platform, and 4 are unclear about how data will be shared. Two trials have conflicting data sharing statements across sources. NCT04425629 and BLAZE-1 committed on [ClinicalTrials.gov](https://clinicaltrials.gov) to provide IPD on the Vivli platform [88], but both later published statements in the *New England Journal of Medicine* saying that they would not be sharing IPD [26,69,89,90].

Table 1

Selected features of COVID-19 platform trials, as explicitly stated in registry pages, study documents, or trial websites as of July 13, 2020. If information was not available across these sources, it is designated as NA (“—”).*

	Trial registration ID	Trial phase	Platform designation	Adaptive features	Pre-specified decision rules	Bayesian methods	Available protocol	Available statistical analysis plan	Data sharing policy	Arms added	Arms dropped
ACTT-1	NCT04280705	III	Yes	Sample size reassessment, graduation to control, futility stopping, efficacy stopping.	No	–	Yes	Yes	Public	–	–
REMAP-COVID (REMAP-CAP)*	NCT02735707	IV	Yes	Response-adaptive randomization, futility stopping, efficacy stopping, safety stopping, change in endpoint	Yes	Yes	Yes	Yes	By request	9	–
PRINCIPLE	–	III	Yes	Sample size reassessment, adaptive randomization, futility stopping, efficacy stopping, graduation to control	Yes	Yes	Yes	Yes	By request	–	–
CATCO	NCT04330690	II	Yes	Change in primary endpoint, sample size reassessment	No	–	–	–	unclear	3	2
RECOVERY	NCT04381936	II/III	Yes	Yes, unclear.	No	Yes, for pediatrics	Yes	Yes	By request	10	8
DisCoVeRy	NCT04315948	III	Yes	Efficacy stopping, futility stopping, graduation to control	Yes	–	Yes	–	By request	2	3
NCT04328961	NCT04328961	II/III	Yes	Sample size reassessment	No	–	Yes	–	By request	–	–
ACOVACT	NCT04351724	II/III	Potential	–	No	–	–	–	By request	5	2
NCT04354428	NCT04354428	II/III	Yes	Sample size reassessment, futility stopping, safety stopping, adaptive randomization	Yes	Yes	Yes	–	By request	5	2
COVID-Aging	NCT04359953	III	Yes	–	No	–	–	–	–	–	–
CCAP	NCT04345289	III	Yes	Futility stopping, graduation to control	No	–	–	–	–	–	3
COLHEART-19	NCT04355143	II	Potential	–	No	–	–	–	–	–	–
COVID19-HOPE	NCT04374903	–	Yes	Yes, unclear	No	–	–	–	–	–	–
ACTT-2	NCT04401579	III	Yes	Futility stopping, efficacy stopping, safety stopping, sample size reassessment, graduation to control	No	–	Yes	–	Public	–	–
TACTIC-R	NCT04390464	IV	Yes	–	Yes	Yes	Yes	–	–	–	–

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Table 1 (continued)

	Trial registration ID	Trial phase	Platform designation	Adaptive features	Pre-specified decision rules	Bayesian methods	Available protocol	Available statistical analysis plan	Data sharing policy	Arms added	Arms dropped
BEAT COVID-19	-	III	Yes	Response adaptive randomization, futility stopping, efficacy stopping	No	Yes	-	-	-	-	-
STARS	NCT04357730	II	Yes	Response adaptive randomization Efficacy stopping, safety stopping, futility stopping, adaptive enrichment, sample size reassessment	Yes	-	-	-	By request	-	-
Catalyst	-	II	Yes	Futility stopping, efficacy stopping	Yes	-	-	-	-	-	-
NCT04426695	NCT04426695	I/II/III	Potential	-	-	-	-	-	Public	1	-
NCT04425629	NCT04425629	I/II/III	Yes	Futility stopping, efficacy stopping, population enrichment, sample size estimation, endpoint selection for III	No	Yes	Yes	-	Public/none	-	-
BLAZE-1	NCT04427501	II	Yes	Adaptive randomization, sample size reassessment, futility stopping	No	Yes	Yes	Yes	Public/none	1	-
FALCON-C19	NCT04408170	observational	Potential	Yes, unclear	No	-	-	-	-	-	-
DEFINE	NCT04473053	II/III	Yes	Safety stopping	No	-	Yes	-	-	-	-
TACTIC-E	NCT04393246	II/III	Yes	Futility stopping, safety stopping, efficacy stopping	Yes	Yes	Yes	-	-	-	-
TOGETHER 3	-	-	Potential	Yes, unclear	No	-	-	-	Unclear	-	-
ASCOT (ADAPT)	NCT04483960	III	Yes	Efficacy stopping, safety stopping, adaptive randomization	Yes	Planned as frequentist, has now moved to Bayesian	Yes	Yes	By request	4	2
COVERAGE	NCT04356495	III	Yes	Futility stopping, efficacy stopping, safety stopping, graduation to control	Yes	-	Yes	-	By request	2	-
I-SPY_COVID	NCT04488081	II	Potential	Futility stopping, efficacy stopping, graduation to control	No	Yes	-	-	By request	6	4
VIRCO	NCT04445467	II	Yes	Yes, unclear	No	-	Yes	-	By request	-	-
ACTIV-3	NCT04501978	III	Yes	Efficacy stopping, futility stopping, safety stopping, graduation to	Yes	-	Yes	-	By request	3	1

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Table 1 (continued)

	Trial registration ID	Trial phase	Platform designation	Adaptive features	Pre-specified decision rules	Bayesian methods	Available protocol	Available statistical analysis plan	Data sharing policy	Arms added	Arms dropped
ACTIV-2	NCT04518410	II/III	Yes	control, sample size reassessment Efficacy stopping, safety stopping	Yes	Yes	Yes	–	–	9	3
ACTIV-4	NCT04505774	IV	Yes	Efficacy stopping, futility stopping, safety stopping, graduation to control	Yes	Yes	Yes	–	Unclear	2	1
CROWN CORONA	NCT04333732	III	Yes	Response adaptive randomization, futility stopping	No	Yes	–	–	By request	1	3
NCT04498273	NCT04498273	III	Potential	Yes, unclear	No	–	–	–	–	–	–
ALLIANCE	NCT04395768	II	Yes	Sample size reassessment, efficacy stopping, futility stopping, safety stopping	No	–	–	–	–	–	–
ANTICOV	–	III	Yes	Futility stopping, efficacy stopping, response adaptive randomization	Yes	Yes	Yes	–	Unclear	–	–
ACTIV-5 (BET-A)	NCT04583956	II	Yes	Futility stopping, efficacy stopping	Yes	–	Yes	–	By request	–	–
ACTIV-1 IM	NCT04593940	III	Yes	Futility stopping, efficacy stopping, safety stopping, sample size reassessment, graduation to control	Yes	–	Yes	–	–	–	–
ACTIV-5 (BET-B)	NCT04583969	II	Yes	Futility stopping, efficacy stopping	Yes	–	Yes	–	By request	–	–
PROTECT-Surg	NCT04386070	III	Yes	Futility stopping, efficacy stopping	No	Yes	–	–	–	–	–
AGILE-ACCORD	NCT04746183	I/II	Yes	Futility stopping, efficacy stopping, sample size reassessment, change in primary endpoint	Yes	Yes	Yes	–	By request	4	–
ACCORD 2	–	II	Yes	Futility stopping, sample size reassessment	No	–	Yes	–	Public	–	–
COVER	NCT04561063	II	Yes	Yes, unclear	No	–	–	–	–	–	–
PROTECT	NCT04389359	II/III	Yes	Sample size reassessment	No	Yes	–	–	–	–	–
COPPS	NCT04662086	II	Potential	Yes, unclear.	–	–	–	–	–	–	–
EU SolidAct	NCT04891133	II/III	Yes	Graduation to control	No	–	Yes	–	Public	–	–
PROTECT-APT	NCT04844541	Observational	Yes	–	No	–	–	–	–	–	–

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Table 1 (continued)

	Trial registration ID	Trial phase	Platform designation	Adaptive features	Pre-specified decision rules	Bayesian methods	Available protocol	Available statistical analysis plan	Data sharing policy	Arms added	Arms dropped
NCT04650087	NCT04650087	III	Potential	–	No	–	–	–	–	–	–
ENFORCE COVERALL	NCT04760132	IV	Yes	–	No	–	–	–	–	–	–
NCT04889209	NCT04889209	I/II	Yes	–	No	–	–	–	–	–	–
ACCOMPLISH	NCT04829188	Not Applicable	Potential	Yes, unclear	No	–	–	–	–	–	–
OPTIMISE-C19	NCT04790786	III	Yes	Adaptive randomization	–	Yes	Yes	–	By request	–	–
ACTT-3	NCT04492475	III	Yes	Sample size reassessment	No	–	–	–	–	–	–
				stopping, futility							
				stopping, safety							
				stopping, graduation to control, sample size reassessment							
ACTIV-6	NCT04885530	III	Yes	Sample size reassessment, futility	Yes	Yes	Yes	–	By request	–	–
				stopping, efficacy							
				stopping							
TOGETHER 2	NCT04403100	III	Yes	Adaptive randomization, efficacy	No	Yes	Yes	–	By request	–	–
				stopping, sample size reassessment							
TOGETHER 1	–	Unknown	Yes	–	–	–	–	–	–	–	–
ACTT-4	NCT04640168	III	Yes	Efficacy	No	–	–	–	–	–	–
				stopping, futility							
				stopping, safety							
				stopping, graduation to control, sample size reassessment							

* REMAP-CAP consists of many treatment domains.

3.3. Design features and statistical methods

Design and analysis methods for platform trials are less established and potentially more complex than in standard trial designs, generating a need for clear presentation of methods. A trial design is adaptive when it has pre-planned and pre-specified opportunities to modify design aspects based on accumulating trial data while preserving the trial's validity and integrity [5,91]. We found that 49 trials (84%) clearly present adaptive features in addition to adding arms. These include futility stopping (29, 50%), early efficacy stopping (25, 44%), sample size reassessment (20, 34%), and adaptive randomization (11, 19%). Twelve trials (21%) included the ability for the control arm to be replaced by an experimental arm that has demonstrated sufficiently superior efficacy ("graduation" to control). Thirteen trials (23%) use a seamless design (2 phase I/II, 9 phase II/III and 2 phase I/II/III). Nine trials (16%) state themselves to be adaptive, but further details were unavailable (Table 1). Detailed statistical methods for these features are not listed on trial registry websites, but of the 29 trials with publicly available trial documents, 16 provide specific decision algorithms for at least one of their adaptive components. Six (10%) trials have made their full statistical analysis plans (SAPs) public – up from 3 (7%) in December 2020 – and others have given plans to release their SAPs before final analysis (Table S2).

Finally, 21 trials (36%) clearly state use of Bayesian methods. ASCOT stated in its protocol dated May 18, 2020 [72] that it may change the analysis from a frequentist to Bayesian framework; in a subsequent

protocol dated October 30, 2020, it is now using Bayesian methods [92].

4. Discussion

We conducted a database search on October 21, 2020 and identified 45 COVID-19 platform trials. A follow-up search seven months later returned 13 more platform trials initiated in that span. We collected information on operations (e.g. adding arms), data sharing and transparency, and trial design and methods (e.g. statistics and adaptive features).

4.1. Definition of platform trial and relationship with adaptive feature reporting

Amidst the excitement surrounding platform trials, some facets of their design and conduct remain ambiguous. Many authors have cited inconsistencies in platform definitions found in the literature. For example, in a systematic review by Siden et al. (2019), they identified 25 unique definitions of "platform trial" [18]. Additionally, the most recent FDA draft guidance on master protocols (2018) lacks a concrete definition of "platform trial" [96].

In this review, we opted for an inclusive definition of "platform", requiring self-identification and/or evidence suggesting that arms may be added. We relax other characteristic requirements sometimes included in the literature, such as dropping arms and randomization [18,93]. As explained previously, this was motivated by the design of

ongoing trials [22]. While the flexibility to drop arms is likely implied or intended in the trials we identified, nearly half (26 trials, 44%) lack any documentation of this design feature. Thus, this broad definition allowed us to capture the magnitude of trials that may be considered platform, which may additionally facilitate future consensus on definition. It also highlights the lack of consensus regarding platform trial classification, as we saw 20 trials (35%) do not self-identify as platform.

Additionally, we restricted our data collection only to publicly available information. Trial methods and results are notoriously underreported, but readily and timely availability in a pandemic is arguably necessary. While non-publicly available trial documents may be obtained directly from trial investigators, this extra barrier can slow evidence generation in a setting where treatments have been urgently needed.

4.2. Design features and statistical methods

The flexibility to add arms throughout the trial is a central feature of platform design that offers substantial efficiencies over standard design – in theory. A review from 2015 showed that new treatment arms were not commonly added in practice [94]. This may be due to many factors, including statistical considerations, logistics, and short-term costs [94]. However, we found that at least 16 COVID-19 platform trials have successfully added arms in a short period of time, characterized by rapid amendments, uninterrupted accrual, quick release of information, and speedy results.

The CONSORT extension guidelines for adaptive trials can be applied to the reporting of platform trials, since the addition and dropping of treatment arms is itself adaptive [5]. The Adaptive Platform Trials Coalition (2017) also requires that a platform trial pre-specify decision algorithms [93]. As the addition of arms is dependent on future emerging science, this feature may be exempt. Still, not all included trials satisfy these reporting requirements for other design features. However, there may be valid reasons for this, including the urgency these trials faced and the accelerated timelines from conception to recruitment. We encourage retrospective release of statistical analysis plans for greater insight into trial design.

The use of Bayesian methods distinguishes itself from the standard approaches to trial design [95]. However, it is difficult to compare Bayesian and Frequentist design reporting. The nature of these frameworks is different, and as Bayesian methods become increasingly implemented, investigators should be careful to adhere to appropriate reporting requirements [96]. Still, once more outcome data is available, it would be interesting to compare trials that use Bayesian vs. Frequentist methods with regard to number of enrolled patients, complexity of implementation, reporting quality, and replicability.

4.3. Statements on data sharing

About half of platform trials have given a statement with an intention to share IPD. Dillman et al. (2020) found that 77% of randomized controlled trials in COVID-19 (completed as of June 2020) planned to share IPD [97]. One possible explanation for the slightly lower rates in our dataset is that 79% of COVID-19 platform trials are ongoing and their data sharing plans might be updated during conduct, whereas Dillman et al. examined only completed trials [72,96,95,97]. In fact, AGILE-ACCORD did update their policy; their protocol dated May 7, 2020 stated that access to IPD may be approved upon request, and in a publication submitted on May 27, 2020 and published on June 19, 2020, it stated that IPD will be uploaded to sharing platform Clinical Study Data Request [27,37].

Still, there are outstanding issues. [ClinicalTrials.gov](https://www.clinicaltrials.gov) includes a field where it may be specified whether a trial intends to share IPD (“Yes”) or not (“No”), or if they’re undecided (“Undecided”). For trials that say “Yes”, there are multiple degrees of sharing ranging from uploading the IPD to a data sharing platform to releasing IPD to investigators by

approval and only for specific purposes [98]. “Data sharing” itself can mean many things, and details are not always provided.

An increasing number of journals are requiring data sharing policy statements as a condition of publication [99–101]. Still, the specificity of these statements varies greatly, and may not be sufficient to measure commitment to share data; even studies that have committed to sharing IPD on an open platform often don’t comply [102]. When they do, the path to access is lengthy and tedious [103].

Data sharing rates in the non-COVID-19 trial sphere are dismal – one review found that 68% of published studies included a statement of intent to share data, but only 0.6% made them publicly available, and 19% made them available through data repositories [102]. Comparable rates of data sharing statements between the COVID-19 and non-COVID-19 domains is slightly discouraging. Research was rapidly initiated at the start of the pandemic, but there has not been an equally rapid and widespread global sharing of discoveries about the nature of the virus, symptoms, treatments, and risk factors – ideally through IPD [97,104]. This may be crucial for this and future outbreaks; however, structural changes are required and may be more efficiently enacted if enforced by funders.

Platform trials may face additional unique challenges, however; for example, relating to securing agreements with different partners or ongoing statistical comparisons with a shared control arm. The seemingly living nature of these data sharing policies may allow researchers to gain further insight into such operations. Future work may be done to explore this topic.

4.4. Platform trials for pandemics

Our findings show quick initiation of new platform trials in the first 10 months after declaring COVID-19 a global pandemic, which was followed by slower initiation since December 2020 (Fig. 2). This trend reflects the general COVID-19 trials landscape, according to [ClinicalTrials.gov](https://www.clinicaltrials.gov) as of July 19, 2021 [2]. But given the success of many trials in adding new arms, this may have replaced the need for new trials, given already well-established platforms. It would be interesting to quantify the extent to which the conduct of these platform trials reduced the need for new RCTs, if possible and if at all.

It may be that COVID-19 has provided a unique research environment for which the speed to find effective treatments amongst many candidate therapies is vital, and platform designs are particularly well-suited to answer that call. Unprecedented levels of coordinated collaborative efforts (including from the government, regulators, funders, industry partners) and additional resources to help to overcome many challenges that have deterred their implementation in the past, have enabled many platform trials to be set up and recruit in record time.

Funding has historically been a challenge to secure and is a major hurdle to both starting new platform trials and adding arms to existing platforms [94]. In COVID-19 research, funding applications were fast-tracked which facilitated rapid trial initiations [105]. And we saw in our review that new arms were added in many trials. The pandemic has shown that perpetual trial conduct is not only possible, but effective. The use of platform design beyond the pandemic and the agility of the system to facilitate this uptake will depend on regulatory willingness and efforts. Moving forward, governments and funding bodies can learn from the success of these processes and establish infrastructure to better facilitate and secure funding for platform trials in the wider clinical trial landscape [106].

The public release of trial information during the pandemic reached record levels, both in volume and quickness. Press releases to communicate findings can facilitate adjustments in ongoing global research as was seen with RECOVERY [12,107]. However, press releases lack information needed to assess methods and translate findings into practice [107,108]. Science journalism can also lead to misinterpretation, and it is suggested that early release of vaccine trial data has contributed to vaccine hesitancy [109].

5. Conclusions

The scientific research community acted quickly in the implementation of clinical trials worldwide. We found that the number of platform trials far exceeds past numbers, and may offer ample insight into the design and conduct of platform trials, including barriers and shortcomings. Synthesizing such information can potentially accelerate our understanding of these designs, and may even transform evidence generation in drug development.

Limitations

We are limited by the amount and quality of data available, as registration pages are often sparse and lack detail. Thus, various aspects we report here, especially protocol amendments, adding and dropping treatment arms, and design features may be underestimated.

Declarations

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Potential conflicts of interest: CY serves as a consultant/independent contractor with Faron Pharmaceuticals, and as an honorarium recipient with Celgene. JMB reports grants and non-financial support from AstraZeneca, Merck Sharp & Dohme, Puma Biotechnology, Clovis Oncology, Pfizer, Janssen-Cilag, Novartis, Roche, and Eli Lilly.

Declaration of Competing Interest

CY serves as a consultant/independent contractor with Faron Pharmaceuticals, and as an honorarium recipient with Celgene. JMB reports grants and non-financial support from AstraZeneca, Merck Sharp & Dohme, Puma Biotechnology, Clovis Oncology, Pfizer, Janssen-Cilag, Novartis, Roche, and Eli Lilly.

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Appendix A. Supplementary data

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