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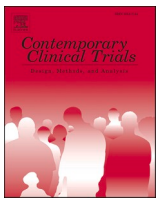

Bringing platform trials closer to reality by enabling with digital research environment (DRE) connectivity

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ABSTRACT

Platform trials are generally regarded as an innovative approach to address clinical valuation of early stage candidates, regardless of modality as the evidence evolves. As a type of randomized clinical trial (RCT) design construct in which multiple interventions are evaluated concurrently against a common control group allowing new interventions to be added and the control group to be updated throughout the trial, they provide a dynamic and efficient mechanism to compare and potentially discriminate new treatment candidates. Their recent use in the evaluation of new therapies for COVID-19 has spurred new interest in the approach. The paucity of platform trials is less influenced by the novelty and operational requirements as opposed to concerns regarding the sharing of intellectual property (IP) and the lack of infrastructure to operationalize the conduct in the context of IP and data sharing. We provide a mechanism how this can be accomplished through the use of a digital research environment (DRE) providing a safe and secure platform for clinical researchers, quantitative and physician scientists to analyze and develop tools (e.g., models) on sensitive data with the confidence that the data and models developed are protected. A DRE, in this context, expands on the concept of a trusted research environment (TRE) by providing remote access to data alongside tools for analysis in a securely controlled workspace, while allowing data and tools to be findable, accessible, interoperable, and reusable (FAIR), version-controlled, and dynamically grow in size or quality as a result of each treatment evaluated in the trial.

1. Introduction

A platform trial is a type of prospective, disease-focused, adaptive, RCT comparing multiple, simultaneous, and possibly differently-timed interventions against a single, constant control group [1]. Platform trials attempt to address the selection of which therapy will best treat a particular disease. Platform trials are unique in their utilization of a common control group and their opportunity to alter therapies investigated during the active enrollment phase. Platform trials commonly take advantage of Bayesian statistics but may incorporate elements of classical frequentist statistics and/or machine learning. Likewise, the implementation of these advanced statistical methodologies is not easily accomplished in a traditional, often compartmentalized, drug development setting; especially when multiple stakeholders are involved. Beyond their use for comparative treatment assessment, platform trials benefit operational efficiency and can reduce cost. In a conventional two-arm trial the infrastructure for recruitment, intervention delivery and outcome assessment is usually set up for every trial and dismantled at its end. Although this is effective to determine whether an intervention works and is safe, the process is inefficient when multiple treatment options are to be evaluated. Likewise, platform trials use a shared infrastructure, in which several interventions are deployed under the same 'master protocol' and tested against a shared control condition and provide less regulatory overhead as well.

Platform trials provide an informative design when multiple therapies are under investigation at the same time competing for the same patient population and even under sponsorship by different organizations. At the onset of the COVID-19 pandemic, it was clear that there would be multiple different therapies that would require investigation, but that these therapies would be discovered at different times in the pandemic timeline, making a platform trial a useful design [1,2]. Platform trials have found use in other patient populations including

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oncology, pediatrics, Alzheimer's disease, and pneumonia research [3–6]. The deployment of adaptive trials including platform trials in a rolling manner have been proposed for the evaluation of new tuberculosis (TB) regimens, especially in the context of various combinations as opposed to monotherapy are warranted [7]. Platform trials can be a superior design compared to a basic 2-arm clinical design when multiple therapies need investigation as it requires only a single control group. This results in the fact that platform trials can be conducted with fewer enrolled patients than a set of potentially redundant control groups in a series of separate 2-arm trials. This in turn allows for results to be published sooner for time-sensitive diseases, and for fewer patients to be exposed to the risks of a clinical trial [5]. Platform trials may be appropriate for phase II-IV trials [1,2].

Platform trials, like any clinical trial, have elements that must be established before starting enrollment and often articulated in the study protocol. While platform trials have the ability to alter or modify the investigated therapies of interest, there are still many elements of these trials that remain constant and regulated. Common, stable elements of platform trials are typically described in the master protocol and include: qualified clinical operations staff members, trial sites, recruitment criteria, enrollment procedures, pre-set criteria for adding/discontinuing new therapies, communication plans, and statistical analysis plans. The master protocol is submitted to the Institutional Review Board (IRB) and once approved, only arm-specific appendices need to be submitted for IRB approval in the event of changes to the trial arms. Establishing a stable master protocol with adaptive therapy arms allows for faster, more efficient trial execution. One of the defining aspects of a platform trial is the shared control group that all interventional arms are compared to as part of the design and the analysis plan. While a conventional RCT would generally have half of all enrolled patients in the control group, platform trials have a higher total number of patients in various interventional groups, allowing for fewer patients to be enrolled, saving money, and accelerating completion time [8].

Platform trials are often large, multi-site investigations and as a result, master protocols frequently try to identify common human and physical infrastructure to maximize resource availability and efficiency. Examples of this include identifying/creating a single IRB to review the trial for all sites, creating a single database for collecting data, and creating a single randomization mechanism for all enrolled patients. The recent successful platform trials completed in support of treatment options to combat the pandemic [2,3] all accomplish these tasks via coordination of personnel as shown in Table 1 and not via an environment which facilitates coordination and manages data and decision logic. The recent platform trial examples with platform and performance assessment shown in Table 1 also highlight missed opportunities for data sharing.

2. Necessity of IP and data sharing

Open science refers broadly to the principle that all research methodologies, tools, documentation, data, and other material should be readily accessible to other researchers [9]. Full and complete sharing of research materials may be beneficial in a number of ways, such as by increasing confidence in research findings, facilitating collaborations among researchers, and advancing scientific innovation. The U.S. National Institutes of Health (NIH) has implemented policies that require the sharing of data from any NIH-funded clinical trial, and both the NIH and the National Library of Medicine released strategic plans that emphasize FAIR (findable, accessible, interoperable, and reusable) data-sharing standards for all funded studies [10].

Despite the potential for greater discovery and transparency and the added ethical benefits of sharing clinical trial data, barriers to sharing and accessing clinical trial data persist. One such barrier is the wide variability in information provision across clinical trial data-sharing platforms, complicating the ability of users to choose a technology platform that suits their data-sharing or access needs. Other challenges include technical barriers to entry such as lack of technical skills and digitization of traditional data and record-keeping [11]. This often leads to debating costs and benefits of a make or buy decision, and the long-term implications of operational and maintenance requirements on sustainability and adoption [12]. Part of the challenge is identifying appropriate technologies that can scale and adapt to growing demand and future trends, while still balancing the necessary protection of IP with collaboration and data access.

If these challenges can be overcome, the opportunity of real-time data availability and reduced resourcing (both time and personnel) would be a boon to platform trials [11,13]. It also holds the potential for unlocking institutional knowledge sharing at scale and preventing the erosion of legacy knowledge (i.e., data, descriptive metadata, and supplementary information about past trials) over time which could lead to new insights and domain-specific breakthroughs [14]. Leveraging cloud technology in conjunction with FAIR principles can offer scalable solutions to capturing and retaining such institutional data and metadata and help prevent the accumulation of siloed, inaccessible knowledge and data. This can be enhanced further by embracing FAIR data sharing and leveraging tools to enrich data with metadata and ontologies could also lead to discovering novel connections between data and patient outcomes previously thought to be unrelated [15]. None of the platform trials shown in Table 1 benefitted from data sharing technology during the in-process stage of the trial – a missed opportunity particularly from the point of view of permitting regulators and other subject matter experts (SMEs) from a real-time assessment of study progress and clinical interpretations.

3. DRE capabilities for data sharing, trial management and simulation

Platform trials can borrow some of the well-established processes involved in large scale, distributed software development. Different teams borrow (branch) from the main software line (control group) and have freedom to work independently on their new task (hypothesis). If successful, the branch is connected back to the main software line and future experimental branches iteratively build from this.

The architecture of the DRE enables this distributed experimentation approach to work with data, models, code, and results. Using platform trial simulation tools on the DRE, for example, allows for adaptive trial design and iterative learning where simulation models can be used a priori to test the trial design and performance throughout the trial, and can be reviewed by different teams as trial data develop. The DRE provides platform arms where individual sponsor's teams can maintain control of their own trial protocol if they choose to or be hopefully managed by a joint team acting on behalf of the entire study – flexibility being the key. Crucially in any case, the DRE captures all events such as interactions with data, code changes, experimentation, and results associated with the platform arm with full audit and reporting capabilities.

Additionally, the DRE allows for necessary adaptive experimentation and tailoring throughout platform trials. For example, interactive tooling can be used to building custom patient cohorts to identify and allocate subgroups for study according to the statistical analysis plan. The DRE's Cohort Builder facilitates adaptive trial design central to the flexibility and adaptability of successful platform trials. This enables real-time enrollment adaptivity throughout the trial to dynamically build and evaluate patient cohorts for statistical relevance, heterogeneity, and other markers while simultaneously investigating multiple treatments. Operationally, the DRE service is purchased from a vendor that creates and maintains the data and workspace services at the behest of the sponsor (potentially more than one sponsor in the case of a platform trial) utilizing a cloud provider (AWS, Azure, Google Cloud, etc.) while maintaining security and access controls in accordance with the instruction provided by the sponsor(s).

While the platform trial runs, new platform arms can join or leave the

Table 1
Recent platform trial examples with platform and performance assessment.

Trial (reference)	Therapeutic area (treatment arms)	Data sharing platform?	Performance / outcomes
Randomized Evaluation of COVID-19 Therapy (RECOVERY) [3]	Infectious disease – COVID-19 (dexamethasone, hydroxychloroquine, lopinavir–ritonavir, or azithromycin)	No centralized platform for data or analysis; hospital principal investigator (PI) coordinated effort	• Provided impactful evaluation of potential treatments post infection • Decisions made on removing or adding therapies were difficult • Prespecification of rules for making decisions could have been better
Plasma Based Molecular Profiling of Advanced Breast Cancer to Inform Therapeutic Choices (plasmaMATCH) [20]	Breast Cancer (4 treatment arms: ESR1 mutations receiving 500 mg fulvestrant; HER2 mutations receiving 240 mg neratinib; AKT1 mutations and oestrogen receptor-positive breast cancer receiving 400 mg capivasertib p.o. BID for 4 days followed by 3 days off continuously with fulvestrant 500 mg i.m, standard dosing; AKT pathway activating mutation (mutations in AKT1 with oestrogen receptor-negative breast cancer, or PTEN inactivating mutations receiving 480 mg capivasertib p.o. BID for 4 days on, followed by 3 days off, continuously)	No centralized platform for data or analysis	• Clinically relevant activity of targeted therapies against rare HER2 and AKT1 mutations, confirming these mutations could be targetable for breast cancer treatment.
STAMPEDE [17]	Prostate Cancer (control and 5 treatment arms: Hormone therapy alone – control; Hormone therapy + zoledronic acid; Hormone therapy + docetaxel; Hormone therapy + celecoxib; Hormone therapy + zoledronic acid + docetaxel; Hormone therapy + zoledronic acid + celecoxib)	No centralized platform for data or analysis; hospital PI coordinated effort with some support from industry	• Safety and activity data presented to the IDMC but timing was less efficient due to manual processes • Analyses performed and reviewed in a sequential process outside any data staging; trial recruitment continued during interim analyses.
I-SPY2 [18,19]	Breast Cancer weekly paclitaxel at a dose of 80 mg per square meter of body-surface area intravenously for 12 doses, alone (control) versus treatment (Veliparib–Carboplatin combination)	No centralized platform for data or analysis	The combination of veliparib plus carboplatin achieved the prespecified efficacy threshold with regard to the biomarker signature of triple-negative breast cancer, with an estimated probability of pathological complete response of 51%, versus an estimated rate of 26% in the control group.
Platform Randomized trial of Interventions against COVID-19 in older people (PRINCIPLE) [4]	Infectious Disease – COVID-19 (hydroxychloroquine, azithromycin and doxycycline)	No. COVID-19 'hot hubs' and directly through the trial website for data management only.	• Community care focus, positioning it to test interventions for COVID-19 at earlier and milder stages. Symptoms, medication side effects and Serious Adverse Events (SAEs) collected from participant daily diaries, calls to participants/study partners, medical records, notes reviews and extracts form routinely collected medical records. SAE information analyzed as part of interim and whole trial analysis reviewed at each DMSC meeting.
Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU) platform trial [23]	Alzheimer's Disease (200 participants enrolled, randomized to receive Eli Lilly's solanezumab, Roche's gantenerumab or placebo. A third drug arm testing a betasecretase inhibitor was launched but terminated early because of safety concerns.)	Public-private partnership created to facilitate the development of AD therapeutics and advance scientific understanding of the optimal ways to prevent and treat AD. Trials network managed the trials; no master protocol.	• Failure to detect a significant cognitive difference between groups: 1) although the dose was increased part way through the trial, most participants had received lower doses; by the time they were switched to the high dose, many symptomatic participants had already declined substantially, thus limiting the ability to evaluate the effect of the high dose; 2) some asymptomatic trial participants failed to decline and in some cases improved; thus it was not possible to detect a drug effect in those participants.
REthinking Clinical Trials (REaCT) platform and National Surgical Quality Improvement Program (NSQIP) [24]	Elective Surgery (no preparation versus preoperative oral antibiotics alone for surgical site infection rates in elective colon surgery)	National Surgical Quality Improvement Program (NSQIP) has automated data collection for surgical patients.	• Using the 'integrated consent model', and randomization on a mobile device completed by the surgeon in a single clinical encounter. • Data collection for the primary end point is automatic through NSQIP. Efficiency gains realized.
Antivirals for influenza-Like Illness? An RCT of Clinical and Cost-effectiveness in primary CarE (ALIC^{4}E) [25]	Influenza (platform, response-adaptive, open trial designs implemented in primary care; oseltamivir groups assessing age, duration of symptoms before initiation of treatment, comorbidity and illness severity)	No centralized platform for data or analysis	• ALIC^{4}E goes beyond determining the average treatment effect in a population to determining effects in patients with combinations of pre-specified characteristics (e.g. age, symptom duration, illness severity and comorbidities). • The platform design allows the study to remain relevant to evolving circumstances, with the ability to add and drop treatments arms.

DRE and can do this independently of the other arms. Platform arms have the flexibility to publish results, models, and data at any point and at any level of detail necessary as pre-specified by the protocol to inform others of progress. This offers dynamic technical capabilities that support adaptive trial design and create opportunities for collaboration, pooling of data, code, or other resources. Certain other clinical operational aspects of a trial can be facilitated with the DRE as well such as the maintenance and compliance of study blinding and the communication with the drug and safety monitoring board (DSMB). In both situations, secure and private communication with protocol-predefined roles can be managed with data and workspace services. Sponsors control the access and sharing of data based on an "airlocking mechanism" which is part of the workspace functionality. Specifically, a workspace with protocol-specified unblinded data and individuals can be maintained with study monitors and other clinical roles dealing only with accession numbers. Likewise, a secure workspace can be created with only the DSMB where data, results and listings can be accessed per protocol and only for finite observation times (i.e., DSMB members are "invited" to access the workspace at certain times without access to other study-related data).

4. How it could work

Fig. 1 above shows an architectural and workflow overview of how a platform trial on the DRE would work in practice. Trial arms would upload their trial dataset into FAIR (e.g., programmatic upload via Application Programming Interface (API), comma-separated values (CSV) file upload, or via read-only connection to external data sources). The trial arm sponsor would be the data controller for this dataset meaning that they (and they alone) never lose control or authority on the use and access to this dataset. FAIR allows the data controller to publish as much, or as little, metadata about the dataset as they deem appropriate.

The trial arm sponsor can authorize transfer of the trial arm dataset to a Workspace for interim analysis or assessment in accordance with the specified trial design. The Workspace is also under the control of the trial arm sponsor, meaning they have authority on who to invite to be part of their scientific team. The team now works in a safe, secure sandbox with freedom to follow their trial protocols and adjust as necessary based on results. A full audit trail of transactions and changes is automatically part of their Workspace. Results can be airlocked (barriers implemented so that the environment can track requests and transactions from both sides to ensure that everything is approved, secure and safe) from the Workspace 'back to' FAIR and metadata published describing to the wider community progress made or reasons for closing down the trial arm. Either way, new knowledge is created and available to the community.

As stated a key objective in running a platform trial is to facilitate collaboration to a greater degree than currently exists. The DRE is designed specifically for this purpose. Trial sponsors can collaborate at a level of detail that they determine appropriate, starting small and building as confidence and trust grow. Workspaces can be constructed into a hierarchical network where two or more trial arm sponsors each airlock content from their private Workspace into a newly created shared Workspace for collaboration under joint administration in a secure cloud environment. This promotes a new trial arm with a modified set of protocols constructed from the real-world experience of the older trial arms and the process repeats itself. Future workspace functionality will include the ability to generate synthetic data as a service with the possibility of using such a feature to generate a synthetic data generated control arm that could be utilized for clinical trial simulations, further de-risking the design and approach and evaluation the probability of technical success.

One of the biggest trial performance gains expected with the DRE-engagement in a platform (or any clinical trial frankly) is the speed with which data can be made operational to various stakeholders (clinical operations, biostatistics, the DSMB, any external SMEs, senior management and potentially regulatory authorities). These gains are made from both the combination of FAIR data and workspace services. Specifically, while many sponsors have invested in various electronic data capture and management systems there is still the need to coordinate across sites, occasionally adjudicate suspect data and investigate potential protocol violations at each site causing delays in the availability of in-process data of any status (e.g., non-quality assured (QA), QA or other status delaying data joins and analysis). As the data and workspace integration maintains a full audit trail, data can be joined at risk with caveats around the status in certain data once joined with analyses being rerun automatically when the status changed. In this way, various stakeholders can be informed in a quasi-real-time manner about the progress of the study with an understanding of the risks which change over time as the study progresses.

Fig. 2 provides an overview of the interplay between data and workspace services enabled with the DRE to manage a platform trial with multiple sponsors. Some of the specific study deliverables (e.g.,

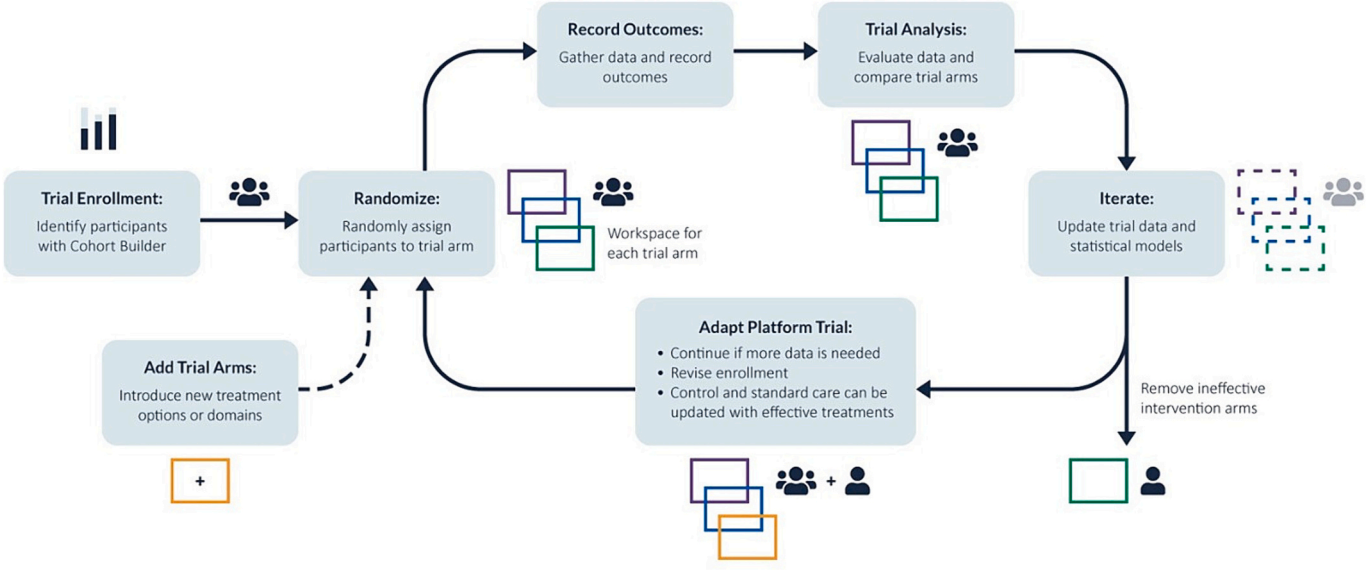

Fig. 1. Schematic illustrating platform trial architecture and workflow within a digital research environment (DRE).

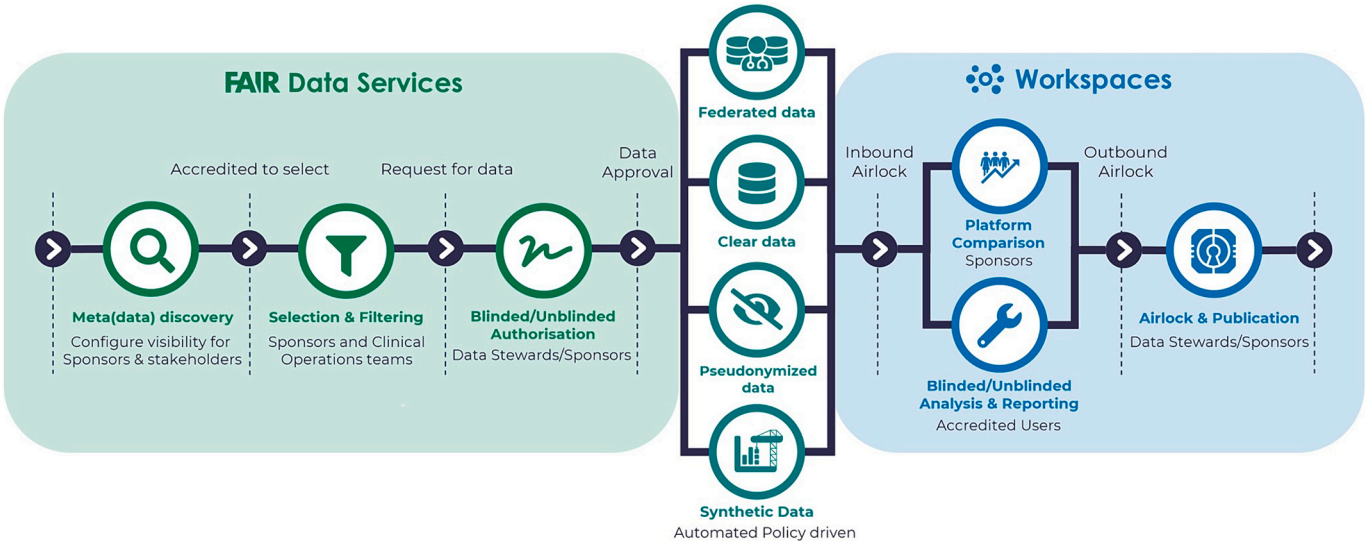

Fig. 2. DRE-enabled data and workspace flow to support a prospectively designed platform trial with multiple sponsors.

comparison of treatments and blinding/unblinding analyses) may be completed by different individuals or scripted and run in an automated manner once data is available in a workspace. Hence, agreed upon study conduct actions can be executed in the manner and timing desired with execution tracking via the audit trail. The financial savings conducting a platform trial versus conventional trial(s) should be well appreciated [16]. Recent findings exploring cost comparison [16] found that despite having larger initial setup requirements, consolidating clinical evaluation of multiple interventions into a single platform trial drastically reduced cost and efforts. These findings were concluded in the absence of a DRE where additional savings would be expected both from the standpoint of data management as well as reporting and other operational costs. Traditional business models for clinical trials (single or platform) have flawed economic incentives whereby a contract research organization (CRO) or a Research site is typically paid (directly or indirectly) on patients enrolled or screened and/or time spent. Data is captured manually or through bespoke electronic data capture forms and goes through a number of integrations before being consolidated with other site and other trial data. The DRE makes use of product based integration technology that allows direct connection between lab systems, electronic health records, in essence making secondary use of previously collated data. The DRE is typically run by a Managed Service Provider who acts as the data processor for all data flows across the trial. The Service Provider is paid to run the platform and the service relying on automation and integration through the 'supply chain' of data. Performance is more measurable (real-time), quality of cohort selection and associated data is derived from primary sources of data and data modelling and reporting is templated through trusted and validated clinical analytics modules that are generally open source with full visibility of code, methods and results.

5. Great idea, why isn't it happening more?

Most of platform trials conducted to this date have taken place for oncology [17–20] and infectious disease [21,22] studies, but there are ongoing platform trials in other therapeutic areas such as elective surgery [21], influenza [22], Alzheimer's disease [23], pediatric immunotherapy [6] and pneumonia [22] highlighting that other disease franchises are beginning to explore these methods. The reasons for the slow adoption and limited application are well appreciated [24,25] but perceived complexity and delays in clinical conduct are often initial barriers in addition to perceived uncertainty around IP disclosure that dissuade sponsors. As platform trials become more common, it will be important that guidance on their fundamental principles become available for clinical investigators and also that the field benefits from improved coordination and efficiency through modern technology.

DRE implementation would surely be able to improve upon current efficiency metrics and also addresses IP, security and other collaborative considerations. The benefits of the DRE to optimize the design, conduct and analysis of clinical trials of novel design features including backet trials, umbrella trials and adaptive designs in general should be obvious for all the aforementioned reasons. One would hope that a greater adoption by industry sponsors is in the future and that expansion of platform trials beyond a few therapeutic areas with more diverse public-private partnerships is on the horizon.

Obstacles to platform trial implementation include the heterogeneity of the drugs being studied, specifically those attributes that make the clinical operations component of trial execution difficult to manage or blind. Different routes and modes of administration further complicate platform trials. Participants' acceptance of a treatment may vary by route of administration (e.g., oral more likely to be preferred over an intrathecal treatment). Combining placebos when there are different modes of administration may also not be feasible. Other challenges such as potential adverse events across trial arms and whether parents would preferentially enroll in one over another may arise, however, these can apply to other trial methods, not just platform trials.

Future efforts including precision dosing-based designs will rely on both highly coordinated clinical operations and real-time access to various RWD sources including electronic medical records (EMR data). Recent efforts in pediatric oncology [6] are likely to be the starting points for additional and more collaborative platform trials. Coordination of such approaches though networks such as the Children's Oncology Group (COG) and the European Reference Network for Pediatric Oncology (ERN) or contract research organizations supporting the interests of various pharmaceutical sponsors would likely add value to these efforts.

Platform studies may also be challenging from a sponsor perspective since they are expensive, complex, and may compete for resources with individual molecule programs. Collaboration of different company sponsors has the potential to share costs and risks but presents other challenges including protection of intellectual property and data. Industry representatives worry that as data accumulates on a platform and the ability to use that data grows, care must be taken to ensure the data is appropriately used. Typically, such concerns can be mitigated by a well-designed data collaboration agreement (DCA). It is also well appreciated that the importance of ensuring that the community of

funders and sponsors understand the benefits and challenges associated with platform trials and that both public and private support are essential for this complex endeavor to proceed efficiently and transparently. Again, examples like those shown in Table 1 contain a great deal of operational agreement both during and post-trial execution that support and maintain good relationships.

Beyond the clinical operations efficiency gains, platform trials further enabled via the DRE would have the advantage to supporting and maintaining regulatory compliance via hosting and tracking the necessary qualifications (site qualifications, audits, etc.), systems qualifications and audit tracking documentation in a secure environment (e.g., QA/Audit workspace) where timelines and readiness can be tracked. In process trial data can similarly be flagged for status that evolves over time with select data made available for certain roles (e.g., safety liaison, statistician, principal investigator (PI), etc.) in separate, secure workspaces.

Traditionally challenging areas to study, such as rare diseases, are likely to remain such, not only for the finite and difficult to define / identify populations but also for logistical and planning complexities. Platform trials may offer notable benefits to limited patient communities previously unaddressed by clinical trials such as rare disease trials where multiple therapies may be developed concurrently with only a limited number of patients available for control and treatment arms [26]. This would be ideal to define a control group that could be utilized across multiple trials. In addition, novel design constructs such as enrichment trials could be enhanced by DRE management to accumulate essential biomarker data, provide it to select study roles in a secure workspace and process actions (e.g., randomization) via tooling available in the workspace and then publish the intermediate results and actions to yet another workspace in which clinical operations staff can act on and manage across sites. Comparison of study results to historical control arms (e.g., natural history data), can be difficult to come by and may not be accepted by regulatory agencies but is also easily accommodated in the DRE. Advancing planning, simulation, and adoption of integrated platforms such as the DRE over time will hopefully help to address gaps [25,26] in implementation of future platform and similar trials.

Principal investigator's statement

The authors confirm that Jeffrey S. Barrett, PhD, FCP is the PI responsible for this research and analysis.

Ethics approval and consent to participate

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Consent for publication

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Authors' contributions

Concept (JB, DS, SM), design (JB, KL, DS), data acquisition (SR, KL, D), data analysis (SM, TM, KL, SR), drafting (JB, KL, DS), approval (all authors).

Declaration of competing interest

The authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data generated herein are based on literature and web-review but is available from the Principal Investigator (PI) upon request.

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