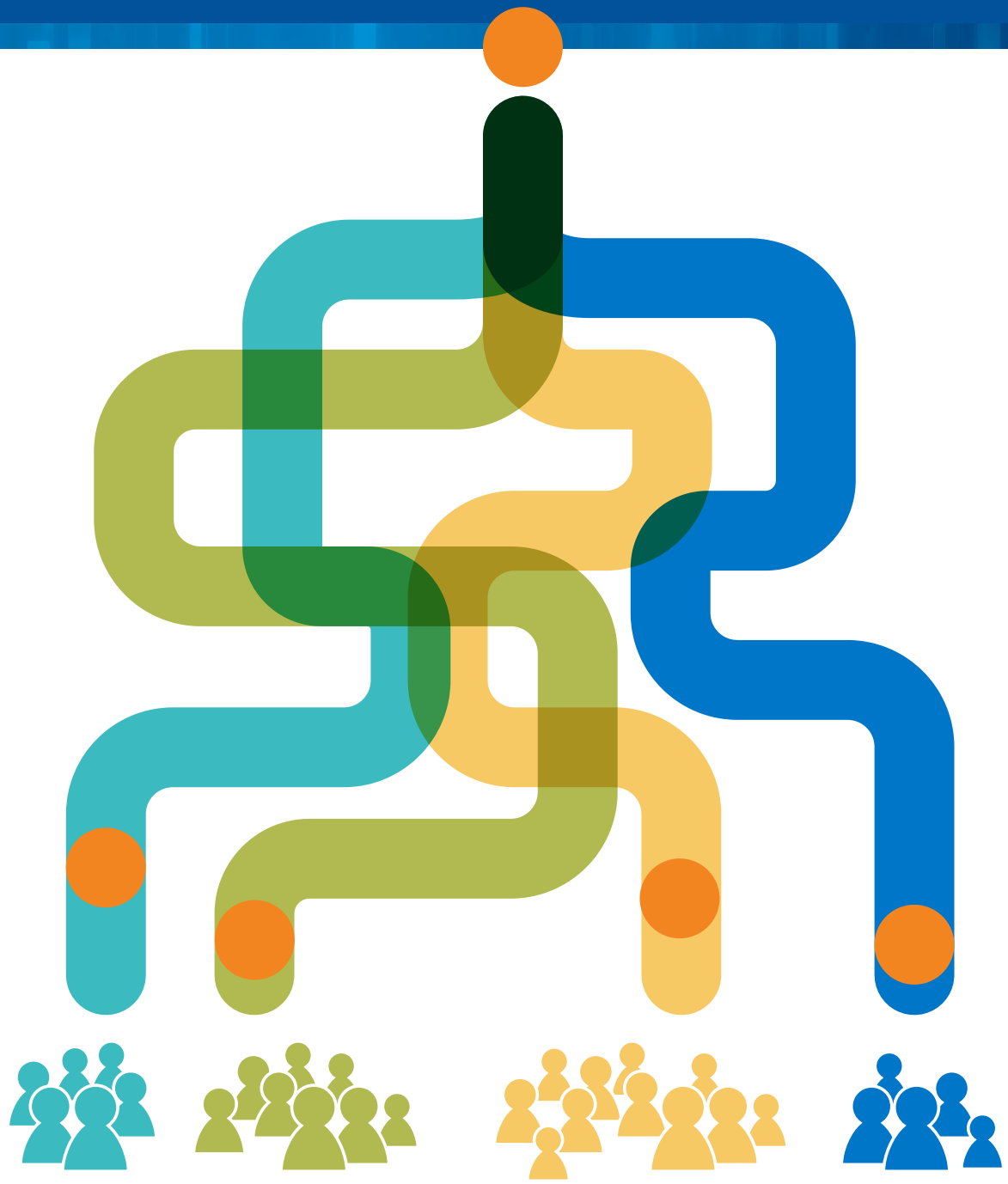
June 15, 2023

Drug Repurposing for Pandemic Innovation: Establishing an Effective and Efficient Ecosystem



Duke | MARGOLIS CENTER *for* Health Policy

Authors: **Beth Boyer**
Ethan Chupp
Tanisha Carino

INTRODUCTION

Effective treatments for both existing and emerging diseases may already be available on pharmacy shelves. Many approved drugs have more than one use or benefit but are rarely researched beyond the initial indication for which they are approved. Such research to identify new indications for already-approved drugs is known as drug repurposing.

Drug repurposing is viewed by some as a faster, cheaper, and less risky approach to drug development. The development of a *de novo* drug is reported to take an average of 8-10 years and cost as much as $2.8 billion. Since they have been approved by a regulatory body, repurposed compounds have already demonstrated safety in humans. Therefore, earlier stages of drug discovery and clinical trials can be bypassed, and development efforts can focus on demonstrating efficacy for the new indication. Because of these advantages, there has been growing interest in drug repurposing in recent years, particularly in disease areas with poor commercial markets. Drug repurposing of approved drugs gained further attention and played an important role in response to the COVID-19 pandemic, as was underscored by Greenblatt et al.'s recent Health Affairs article.

Despite the advantages and potential of drug repurposing, several challenges and barriers exist. In a recent systematic review, Miller et al. found six common barriers to repurposing drugs: inadequate resources, trial data access and transparency around abandoned compounds, expertise, uncertainty about value, liability risks, and intellectual property challenges. Consistent with these conclusions, Greenblatt et al. also found "weak incentives and organizational barriers," gaps in regulatory supports, a lack of clarity on the risk-benefit trade-off of drug repurposing trials, and poor coordination in the context of repurposing for COVID-19.

Addressing these identifiable challenges and barriers is essential for pandemic preparedness efforts. On Day 1 of an emerging pandemic or health threat, drug repurposing represents a critical path to quickly identify potential treatments along with *de novo* drug development and repositioning of compounds in development which have not received regulatory approval. In the case of COVID-19, most United States' (US) clinical trials in the first two quarters of 2020 included at least one repurposed Food and Drug Administration (FDA) approved drug. Although, as time passed the majority of trials were focused on new drugs. This exemplifies that drug repurposing stands as the first line of defense against a new threat and serves as an essential complement to *de novo* drug development efforts.

A central and elusive question among experts is how to define success in drug repurposing efforts. On one hand, using traditional metrics of an individual company's internal rate of return (IRR), repurposing efforts have been viewed as largely unsuccessful relative to financial investment and number of regulatory approvals. However, an alternative view is that this metric is too narrow, and measures of success need to include the number of lives saved, patients who avoid hospitalization, and speed of adoption compared to *de novo* research and development. In their Health Affairs article, Greenblatt et al. argued that the inclusion of repurposed drugs in treatment guidelines (National Institutes of Health (NIH) and Infectious Disease Society of America) for COVID-19 demonstrates that drug repurposing "lived up to its promise of quickly leading to the development of effective COVID-19 therapeutics." By this standard, drug repurposing for COVID-19 was a success.

Although definitions of what represents success in drug repurposing efforts vary, the White House has demonstrated an understanding of the value of expediting drug development in response to public health threats. In October 2022, it released its "Strategy to Strengthen Health Security and Prepare for Biothreats." The strategy includes ambitious targets for therapeutic development in response to an emerging pandemic, including the identification, testing, authorization, manufacture, and deployment of repurposed therapeutics within 90 days of determination of a potential nationally or internationally

significant biological incident. Along with investments to ensure that we have strong clinical trial infrastructure and a ready base for manufacturing, maintaining an efficient and effective system for drug repurposing is a critical strategy to achieve these goals.

To that end, the Duke-Margolis Center for Health Policy convened a private roundtable meeting on drug repurposing for pandemic innovations on January 23, 2023. The meeting sought to understand lessons learned on drug repurposing for recent public health threats and determine the key research questions to establish an effective and efficient ecosystem for repurposing in response to future emerging pandemics and health threats. The purpose of this white paper is to provide a comprehensive look at drug repurposing for pandemics, lessons learned, and outstanding research questions. Building on initial recommendations and ideas shared at this meeting, we aim to provide insight into the value of drug repurposing, highlight best practices, and identify important areas where more work is needed to clarify priorities and align incentives among stakeholders.

Components of a Successful Drug Repurposing Ecosystem for Public Health Emergencies

Taking learnings from the COVID-19 experience, experts in our roundtable discussion identified the following foundations of success in drug repurposing: clear governance to set priorities and guide investments; speed and efficiency in developing clinically useful insights to guide prescribing; and close coordination with and the ability to leverage capital and talent of both the public and private sectors.

Given this foundation, we have identified the following three core components to establish such an effective and efficient ecosystem for drug repurposing:

- **Governance;**
- **Ready infrastructure and capacity; and**
- **Administrative structures and supports.**

In the sections that follow, we explore each of these components more deeply and identify both best practices and areas of further research.

Governance

Central governance is a critical component for drug repurposing efforts. This component is centered around the unique role that the government has in virtually every aspect – from setting priorities to allocating resources and establishing incentives to coordination among all stakeholders. Recent experience with repurposing drugs for COVID-19 demonstrated the complexity of the efforts that existed among governments, non-governmental organizations (NGOs), research institutions, pharmaceutical companies, regulators, and healthcare providers, and the need for central coordination.

Based on our research and engagement with experts, therapeutic development including drug repurposing efforts did not receive the same level of centralized coordination, funding, and prioritization as vaccines, which were the primary focus of efforts like Operation Warp Speed. The success of Operation Warp Speed demonstrates the importance of centralized governance led by the federal government to drive successful research and development. Unfortunately, as noted by experts in our meeting, much of the drug repurposing efforts were disjointed and underfunded. There were efforts led by government agencies, such as the Accelerating Coronavirus Disease 2019 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership, and private sector efforts, such as the COVID Research and Development Alliance. However, it is broadly recognized that these efforts would have benefited from a more formal central coordinating body to support speed and efficiency.

We have identified the following best practices in governance:

- *Establish a centralized governance and coordination entity.* A centralized approach to governance and coordination is necessary to ensure the proper allocation of resources, prevent duplication of efforts, and streamline the process of drug repurposing research and trials. A shared view in our expert roundtable discussion is that this role is best suited for a government entity that: 1) can access information from an early warning system, 2) is positioned to directly collaborate with other governments and international NGOs, 3) has authority to align policies and resources, and 4) can effectively engage and coordinate with the private sector. However, there is an outstanding question of where in the U.S. government this centralized effort should perpetually reside – and there are multiple candidates. For example, in 2022 Congress created a permanent Office of Pandemic Preparedness and Response Policy in the White House to coordinate pandemic response activities across the federal government for all public health threats. This body along with the National Security Council and the Office of Science and Technology Policy were all raised as possible homes for this effort given their proximity to the authority of the President and their ability to engage across the whole of government, not just the health-related departments. However, to date, the Office of Pandemic Preparedness and Response Policy lacks an appointed lead and the sufficient number of staff needed to execute its mandate.

  A centralized approach to governance is also important to ensure that regulatory frameworks are aligned with research goals. For example, the coordinating body should ensure that the standards and criteria for issuing emergency use authorizations (EUAs) are consistent, and that the laws around data privacy, data reuse, and data security are designed in such ways that they facilitate – not hamper – the large-scale collaboration involved for drug repurposing trials.

- ***Conduct ongoing threat identification and set research priorities.*** In preparation for pandemics, experts agreed that a primary role of the centralized body should be to lay the groundwork needed for drug repurposing trials before a threat emerges. This begins with the identification of potential threats, including viral families from which pandemic strains are likely to emerge. In addition, drug repurposing begins with a thorough screening and matching process to identify potential candidates that can target the pathogen or the conditions the pathogen causes (e.g., immunomodulators to suppress immune response). Systematic identification and selection for clinical trials can be a time-consuming process that cannot be afforded in a public health emergency. Efficiencies can be created by taking steps in non-emergency times for preparedness and establishing processes and networks that can be quickly deployed when a public health crisis occurs.

  From there, the government entity can set a research agenda that can be shared with researchers and industry, including the testing of existing antiviral drugs on identified viral families, and recommend how funding and incentives for the private sector can lead to focused efforts. Once a public health emergency begins, it is important that the coordinating agency's primary responsibilities include setting research priorities and coordinating response efforts across various stakeholders. This will serve to expedite clinical trials, mobilize funding as quickly as possible, and improve communication among all stakeholders.

- ***Communicate and coordinate with the private sector.*** Another critical role of the centralized governance body is clear communication with the private sector and the role of being a "single front door" to the government. By streamlining and centralizing communications for future emergencies, private sector stakeholders will be easier to engage and quickly coordinate. Key areas for communication include: 1) formal agreements to allow for the confidential exchange of information between the government and the private sector; 2) continuous communication of research priorities; and 3) the exchange and sharing of scientific discoveries.

- ***Ensure flexibility of funding.*** Government agencies are better suited than private stakeholders to fund projects that may generate a fiscal loss. This is important in the context of a public health emergency when an "all-of-the-above" approach – researching as many repurposed drugs as possible – is most societally beneficial. Despite the increasing interest in drug repurposing research, it is still unclear which government agency should take the lead on the coordination of funding. Many agencies with the ability to fund research projects operate independently from each other and are spread across multiple departments. There is some

enthusiasm that the recently launched Advanced Research Projects Agency for Health (ARPA-H) could be a potential funder for these drug repurposing efforts, although questions remain about how to ensure long-term sustainability of any ARPA-H funded projects. Additionally, there is uncertainty regarding the extent of flexibility required by different government agencies to fund drug repurposing trials. Federal funding is often earmarked for specific purposes which limits the ability to quickly mobilize funds for a response. It is crucial to clarify these funding requirements and to communicate all relevant information to stakeholders before an emergency arises.

Ready Infrastructure and Capacity

Establishing at-the-ready infrastructure is another critical component of a drug repurposing ecosystem that can effectively respond to emerging public health threats. This infrastructure includes processes for candidate selection, clinical trial networks and protocols, and manufacturing capacity. In a public health emergency, it is important to move quickly and nimbly, as there is little time to find, build, or develop the needed networks and processes. Preparing these essential components before a threat emerges enables greater speed and efficient use of resources.

We identified the following best practices for establishing the prepared infrastructure needed for drug repurposing efforts:

- ***Create open-source databases and tools to support candidate selection.*** Open access to critical data on a pathogen and the drug mechanisms of action tested against it can support and expedite early decision-making processes. During the COVID-19 pandemic, the nonprofit group Every Cure created an open-access database called the CORONA Project, which aided in the selection of candidates for large trials such as ACTIV. Every Cure creates such databases to support other repurposing projects and represents a best practice for this important step. Additional databases for viral families that pose potential threats can be started and built upon should a public health threat emerge.

  Access to such databases is also critical for leveraging computational tools, such as knowledge graphs and artificial intelligence (AI) approaches that can streamline the matching and selection process. For example, Benevolent AI leveraged knowledge graphs and AI tools for target identification and identified baricitinib as a potential candidate for COVID-19 as early as February 2020. Linking initiatives that curate databases, develop knowledge graphs, and use AI matching approaches can drive more targeted candidate selection and enhance speed-to-trial.

- ***Improve real-world data to capture off-label drug use.*** At the start of a public health emergency, another tool for identifying potential candidates for further research is off-label prescribing practices in clinical settings. As patients fall ill, physicians will often use existing products to manage the condition and symptoms. Using real-world data on these prescribing practices in clinical settings could inform which drugs or drug classes show promise and should be studied in a randomized controlled trial. In a paper published by the ACTIV Therapeutics Clinical Working Group, they note that "if available, real-world evidence that suggests available agents already in use clinically with potential for treating a new disease could be considered earlier in the prioritization process." Improvements in the collection of and access to such data can further support candidate selection.

- ***Establish standing research groups and protocols.*** The identification process will result in a list of potential candidates, yet not all can or should be studied at once. A prioritization protocol is needed to determine which candidates should be advanced into clinical trials first. Part of this process may include selecting a certain number of candidates per drug class to get an idea of which class may be most promising. The ACTIV Therapeutics Clinical Working Group developed a framework to guide the prioritization of candidates for trials. However, amid a rapidly unfolding pandemic, developing the framework and evaluation groups was challenging and took up valuable time. ACTIV's lessons learned paper underscores the importance of proactively

forming "a standing evaluation group that tracks important agents in development for these types of diseases." Additionally, the prioritization frameworks used for COVID-19 can be adapted to inform and expedite prioritization by the evaluation groups for future public health emergencies.

- ***Develop target product profiles.*** The prioritization of clinical trial candidates can be further guided by the development of target product profiles. A target product profile outlines desired characteristics of a product in development for a specific disease or set of diseases, such as target population, temperature stability, route of administration, dosing frequency, cost, and clinical efficacy. The World Health Organization, for example, uses target product profiles to set priorities for drug development that addresses unmet global health needs. A centrally coordinated drug repurposing effort would benefit from the development of target product profiles to guide research priorities and candidate selection (e.g., products for children or those that can be administered in the home rather than a hospital setting). These profiles can be developed by the central governance entity described above.

- ***Implement adaptive platform clinical trial designs.*** The probability of any particular drug succeeding is low, and the best preparation may be to study multiple drugs and have a range of options available. Adaptive platform trials, which allow for the testing of multiple drugs in a single, large study population, offers a more efficient trial design. These trials offer flexibility to remove and add new drugs as indicated by study data. This trial design also improves cost-effectiveness – trials for individual drugs can be costly but adaptive trial designs manage costs by using the same participants, control group, and study protocol to assess multiple drugs at once. In an emergency context where there is an urgent need for therapies, this type of trial offers the advantage of quickly studying a range of candidates simultaneously. Several platform trials were established in response to the COVID-19 emergency, including RECOVERY (United Kingdom [UK]), ACTIV (US), ACT (Canada), TOGETHER (international consortium), and ANTICOV (Drugs for Neglected Diseases Initiative). Specific best practices learned from these trials can be found in the points that follow.

- ***Establish a "warm base" research network and clinical trial infrastructure.*** Warm base clinical trial capacity can allow for quick movement of identified repurposed drugs into clinical trials. Creating an extensive network of clinical trial sites with central coordination can support the large-scale recruitment of diverse populations. These networks can benefit from considering decentralized or point-of-care approaches to streamline the necessary tasks and make it easier for more sites and providers to participate in evidence generation. The RECOVERY Trial in the UK exemplified the advantage of having an established clinical trial network that can be quickly deployed across a large and geographically diverse study population in an emergency **(see Box 1).** It was able to begin enrolling patients as early as March 2020, and its network included over 190 active sites globally. In the US, the ACTIV Trial was established in April 2020, in the midst of the pandemic, but took months to bring partners together, form working groups, establish master protocols, identify trial sites, and enroll patients. The first trial did not start until October 2020. Valuable time was lost in creating a clinical trial network from the ground up during a public health emergency. However, building the necessary clinical trial infrastructure and related agreements during "peacetime" could better position the US in the future to rapidly begin clinical trials that test repurposed drugs against a new threat. In fact, the Health Security and Biothreats strategy released in October 2022 sets a target of having ready clinical trial infrastructure that can begin administering a countermeasure within 14 days of identifying a viable candidate. We are already seeing some interest in maintaining activity through the ACTIV network with the creation of ACTIV STRIVE (Strategies and Treatments for Respiratory Infections and Viral Emergencies), and in pursuing an international clinical trial network that can help achieve the 14 day target.

- ***Establish "warm" and scalable manufacturing capacity.*** Readily available manufacturing capacity that can be tapped to scale-up production of repurposed drugs for testing – and if successful, for widespread use – can also support the establishment of studies in an emergency response. Since repurposed drugs are already used to treat other conditions, reallocating a portion of the supply for clinical trials or even off-label use carries a risk of creating shortages. The concerns grow

larger if the drug demonstrates benefit and is included in clinical guidelines because demand for the drug will grow and may outpace manufacturing capacity. Increasing the production of an existing drug is not a straightforward process. There is finite manufacturing capacity for drugs, meaning there are tradeoffs when increasing production of one drug – capacity may be diverted from other products resulting in shortages of other drugs.

The establishment of "warm capacity" that can be activated in a public health emergency is one way to address these concerns. Warm capacity refers to manufacturing capacity that is readily available to address a surge in demand due to a public health emergency or to address shortages while ensuring other patients do not suffer. Idle or warm base manufacturing capacity and workforce that is not being fully deployed to produce profit-generating products, however, causes increased costs for manufacturers. Due to the uncertain nature of when capacity for a public health threat is needed, there is a need for incentives to keep capacity warm.

- ***Utilize innovative manufacturing approaches and technology.*** Another solution to address manufacturing capacity concerns for repurposed drugs is the use of continuous manufacturing technology. In continuous manufacturing, materials are moved nonstop through an integrated equipment train, eliminating hold times between processing steps, minimizing active pharmaceutical ingredient usage, and increasing control over manufacturing parameters. While a promising solution for many pharmaceutical types such as small molecules, this process is more difficult to implement for some complex products such as biologics for which real-time testing needs further development. Other new manufacturing technologies could be explored as well. For example, small-scale, flexible manufacturing processes can allow for quick deployment and efficient production of low-volume products, which could be useful for initial clinical trials while other manufacturing capacity solutions are explored. Manufacturers need adequate incentives to adopt such technologies that can improve their ability to scale up capacity in an emergency response. The *Duke-Margolis Drug Supply Chain Resilience Consortium* is looking further into this particular challenge and has developed initial recommendations for policymakers.

BOX 1 Lessons from a Successful Model: The RECOVERY Trial

The UK's RECOVERY Trial for COVID-19 treatments is an example of many of the success factors described in this paper, particularly around ready infrastructure. Founded in March 2020 by the UK Research and Innovation (UKRI)'s Medical Research Council (MRC) and the National Institute of Health Research (NIHR), and run by Oxford University, the RECOVERY Trial represents a centrally coordinated, government-funded effort. Although the trial was not solely focused on repurposed drugs, initial studies conducted by RECOVERY were on repurposed drugs including dexamethasone, hydroxychloroquine, and lopinavir – exemplifying repurposed drugs as the first line of defense.

The trial investigators utilized an adaptive platform trial design which allowed for several drugs to be tested at once. It also employed a decentralized approach, with more than 190 trial sites throughout the UK and around the globe. Leveraging the UK's National Health Service (NHS) as an established network, the RECOVERY Trial was able to begin studying repurposed drugs very quickly – it began enrolling patients in March 2020. Thanks to the adaptive platform design, investigators were able to add new potential treatments as they were identified or as others were removed because they failed to demonstrate efficacy (e.g., hydroxychloroquine). One of the first successes of the RECOVERY Trial was dexamethasone – early results demonstrated that the low-cost, generic steroid reduced mortality in hospitalized COVID-19 patients. To date, the RECOVERY Trial has studied and generated results on 12 potential treatments for COVID-19 in over 48,000 patients.

Administrative Structures and Supports

There are other structures and processes that can be established to support drug repurposing efforts in response to a public health threat. These include regulatory supports and structures to improve efficiency. We identified the following potential supports to drive efficiency and impact of drug repurposing efforts:

- ***Create structures to drive efficiency in drug repurposing studies.*** Administrative actions and supports can improve efficiency, from identification of candidates to clinical trials. Standard material transfer agreements can support faster agreements among partners. Centralized institutional review boards (IRBs) can address inefficiencies in starting multi-center clinical trials by streamlining the process and removing the need for multiple IRB reviews. Liability insurance can reduce risk for drug sponsors conducting studies on their drugs already being marketed for other diseases in the event that new safety concerns emerge. For drugs that are still patent protected, expedited processes for licensing and conducting technology transfers can support quick movement into studies led by government or academic researchers.
- ***Consider and explore supportive regulatory processes.*** The primary regulatory pathway for a repurposed drug that already has FDA approval is a label extension to add a new indication or usage. To do this, a sponsor must have data to support the addition and then submit a prior approval supplement to the FDA. For a drug that is still protected by patent or does not have competitors on the market, the originator may be incentivized to sponsor this label change and market their product to a larger patient population. But for drugs that are off-patent and have generic competitors, the process is less clear, and drugs are often used off-label without regulatory authorization for that condition, provided that clinical data supports its inclusion in guidelines. This was the case for dexamethasone as a treatment for COVID-19 **(see Box 2).** Dexamethasone demonstrated efficacy in reducing mortality for hospitalized patients. Based on this data, it was included in NIH and Infectious Disease Society of America (IDSA) treatment guidelines for COVID-19, even though dexamethasone has never received an EUA or undergone US FDA regulatory review for use as a COVID-19 treatment. While there may be low concern with this off-label use pathway, a study conducted by Johns Hopkins University suggests the lack of an EUA or other regulatory approval resulted in slower uptake by physicians and hospitals in the US and patients missing out on the benefit of the treatment. The lack of a clear pathway for label expansion of generic drugs necessitates further consideration on the best regulatory process for repurposed drugs that can support use in clinical practice, patient trust, and access.

BOX 2 The Dexamethasone Story

Dexamethasone was initially developed by Merck & Co. and approved by the FDA in 1958 for treatment of rheumatoid arthritis. It was among one of the first repurposed drugs tested by the RECOVERY Trial for treatment of COVID-19, and study results demonstrated reduced mortality in hospitalized patients receiving respiratory support. Since dexamethasone has been on the market for over 60 years, it has readily available generics and is cheap to produce and purchase. This provides an advantage for widescale access in the context of a global pandemic but was a disadvantage in that it offered low incentive for a sponsor to submit for regulatory approval. The originator, Merck, did not have an incentive to sponsor the trial or take the liability risk of studying dexamethasone for a new indication. Therefore, it was studied by researchers in the RECOVERY Trial and demonstrated efficacy in hospitalized COVID-19 patients, but never received regulatory approval as a treatment for COVID-19 (in the UK, EU, or US).

Future Directions

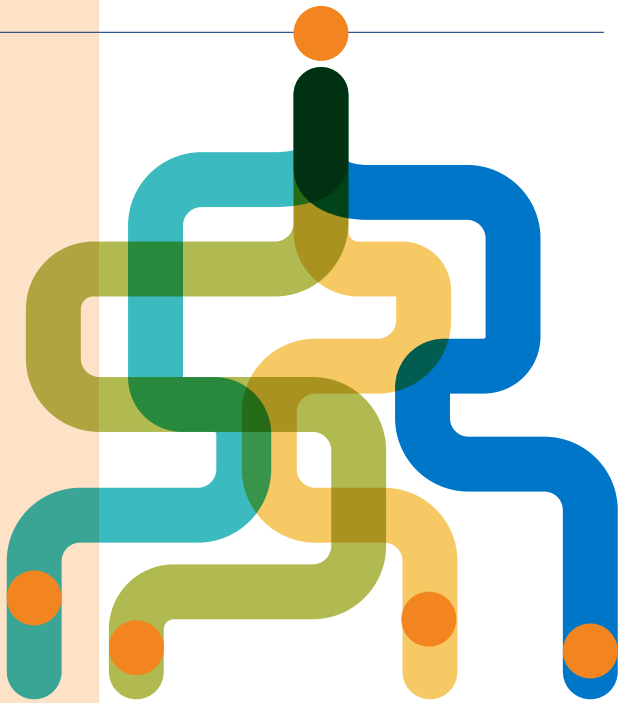
The best practices described here offer a starting point for establishing an efficient and effective drug repurposing ecosystem that can respond to emerging health threats. If established, a drug repurposing ecosystem could not only serve as an essential tool for future pandemics and health threats, but also as a critical pathway for developing drugs for diseases with unmet clinical need. Yet, there are still some outstanding questions about how to operationalize, fund, and implement these best practices to form that ecosystem.

Funding and incentives remain a central question for all components of a drug repurposing ecosystem. The structure of the pharmaceutical market provides little financial incentive for research and development of repurposed drugs and there is little public or nonprofit funding directed to support such efforts. Even for a government-led effort, such as ACTIV, there are not always sufficient incentives for private companies to participate or share data. It is critical to understand the concerns and motivators for companies to engage in drug repurposing efforts, such as large platform trials. This understanding can inform the creation of incentives that support a well-functioning drug repurposing ecosystem and can rapidly respond to an emerging threat. Further research is needed to better understand these concerns and identify incentives to coordinate and collaborate across sectors on drug repurposing efforts to address future threats.

In addition, there is a need for a strong, well-developed case for a government-led and -funded effort and where within the government these responsibilities should reside. There are some existing government efforts across the domains we have identified, such as for clinical trial networks and manufacturing capacity, but there is a need for an entity that can work across the government and partner with other sectors with a focus on enhancing the drug repurposing ecosystem.

Conclusion

We are at a pivotal moment for action on pandemic preparedness. As the COVID-19 emergency comes to an end, the opportunity is ripe to apply the best practices to strengthen systems for response against future threats. Drug repurposing is a critical complement to *de novo* drug development in response to an emerging threat and should be established as a core component of preparedness efforts. The reauthorization of the Pandemics and All-Hazards Preparedness Act (PAHPA) is expected this year, offering a prime pathway for building a centrally coordinated drug repurposing ecosystem as a tool against public health emergencies. Now is the time to conduct a deeper examination of the outstanding questions about a repurposing ecosystem and form critical recommendations for policymakers.



SUMMARY TABLE

	Best Practices	Research Questions
Governance	• Establish a centralized governance and coordination entity • Ongoing threat identification and setting research priorities • Communication and coordination with the private sector • Flexible funding	• Where in government should a central governance body reside? What government entity is best positioned for coordination and flexible funding? • What is the business/financial case for investment in a centrally coordinated drug repurposing ecosystem?
Infrastructure	• Creation of open-source databases and tools to support candidate selection • Improve real-world data to capture off-label drug use in clinical settings • Develop target product profiles • Establish standing research groups and protocols • Implement adaptive platform clinical trial designs • Establish a "warm base" research network and clinical trial infrastructure • Establish warm and scalable manufacturing capacity • Utilize innovative manufacturing approaches and technology	• How can the ACTIV network, particularly ACTIV6 which is focused solely on repurposed drugs, be sustained with warm trial capacity in case of future public health emergencies? • When discussing "warm capacity", how much capacity needs to be reserved in case of a public health emergency for both manufacturing and clinical trials? Can we quantify this and estimate how much it would cost to maintain that warm capacity? • What incentives can support investment in or retaining "warm capacity"?
Administrative Structures and Supports	• Create structures to drive efficiency in drug repurposing studies • Consider and explore supportive regulatory processes	• What are the appropriate regulatory mechanisms for repurposed generic drugs? Is there a need for new pathways that can incentivize potential sponsors and promote access? • What administrative supports would be of most value to stakeholders in repurposed drug development, particularly in driving efficiency? What is needed to establish these supports?

Acknowledgements

Duke-Margolis would like to thank the experts listed below for their participation in our roundtable meeting, Drug Repurposing for Pandemic Innovation, on January 23, 2023 and for their insightful contributions both during and after the discussion, which have informed the development of this paper. Duke-Margolis' independent analysis put forward in this brief does not reflect their views, opinions, or positions. In addition, the authors would like to acknowledge the contributions and guidance of Duke-Margolis researchers Mark McClellan, Marianne Hamilton Lopez, and Trevan Locke during both the meeting and development of this paper. We also wish to acknowledge Patricia Green from the Center for her communications guidance and Laura Hughes for her support in designing this paper.

Stacey Adam, Foundation for the National Institutes of Health

Luciana Borio, Council on Foreign Relations

Alan Carr, BARDA

David Fajgenbaum, University of Pennsylvania; Castleman Disease Collaborative Network

Simone Fishburn, BioCentury

Matthew Hall, National Center for Advancing Translational Sciences

Anne Heatherington, Takeda Pharmaceutical Company

Matt Hepburn, Office of Science and Technology Policy

David Hone, Defense Threat Reduction Agency, Department of Defense

Rob Jordan, Bill & Melinda Gates Foundation

Martin Landray, University of Oxford; RECOVERY Trial

Chris Lindsell, Duke Clinical Research Institute; ACTIV-6 Study

Hilary Marston, U.S. Food and Drug Administration

Jennifer Miller, Yale University

Andrea Noda, Arnold Ventures

Sandeep Patel, BARDA

Revell Phillips, Defense Threat Reduction Agency, Department of Defense

Leonard Sacks, U.S. Food and Drug Administration

Marco Schito, Critical Path Institute

Kristin Schneeman, FasterCures, Milken Institute

Joanna Shields, BenevolentAI

Tania Simoncelli, Chan Zuckerberg Initiative

Grail Sipes, Office of Science and Technology Policy

Heather Stone, U.S. Food and Drug Administration

Alex Tropsha, University of North Carolina