

REVIEW

A public-private collaboration model for clinical innovation

Craig D. Wegner[†] | Bobbie Ann Mount | Christine M. Colvis

National Center for Advancing Translational Sciences (NCATS), Rockville, Maryland, USA

Correspondence

Christine M. Colvis, National Center for Advancing Translational Sciences, NIH, 6701 Democracy Blvd, Rm 996, Bethesda, MD 20817.

Email: christine.colvis@nih.gov

Funding information

No funding was received for this work.

Abstract

Launched in May 2012 as part of the New Therapeutic Uses program, the National Center for Advancing Translational Sciences (NCATS)' National Institutes of Health (NIH)-Industry Partnerships initiative fostered collaboration between pharmaceutical companies and the biomedical research community to advance therapeutic development. Over the 10-year life of the initiative, the industry partners included: AstraZeneca; AbbVie (formerly Abbott); Bristol-Myers Squibb; Eli Lilly and Company; GlaxoSmithKline; Janssen Pharmaceutical Research & Development, L.L.C.; Pfizer; Sanofi; and Mereo (out licensed assets). The initiative provided researchers at academic medical centers with a rare opportunity to propose clinical trials to test ideas for new therapeutic uses for a selection of clinic-ready and often previously proprietary experimental pharmaceutical assets that were provided by industry partners. Here, we describe the process by which collaborations between pharmaceutical companies with viable experimental assets and academic researchers with ideas for new uses of those assets were established; and how NCATS/NIH funding supported not only phase I and II clinical trials as well as any nonclinical studies needed before testing in a new patient population, it also provided an opportunity for testing innovative outcome measures for proof-of-concept trials. Although the program did not demonstrate improved success rates for phase II clinical trials, this collaboration model leverages the strengths of each party and with a focus toward evaluating an innovative outcome measure, could be used to reduce patient burden and trial costs, and improve patient engagement.

INTRODUCTION

Therapeutic development is a costly, complex, and time-consuming process. The average length of time from target discovery to approval of a new drug can be up to 18.7 years. There is failure at every stage of the process, and the cumulative cost per successful drug can be \$2.6 billion

or more.¹ The high therapeutic development failure rate means there are potentially many existing, partially developed therapeutic candidates that were in development for one indication that could be repurposed for use in a new disease indication ("Drug Repurposing"; [Figure 1](#)).

Two large companies with several phase II failures, as well as some successful phase II clinical studies, have

[†]AstraZeneca (retired), National Center for Advancing Translational Sciences special volunteer.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](#) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Clinical and Translational Science* published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics. This article has been contributed to by U.S. Government employees and their work is in the public domain in the USA.

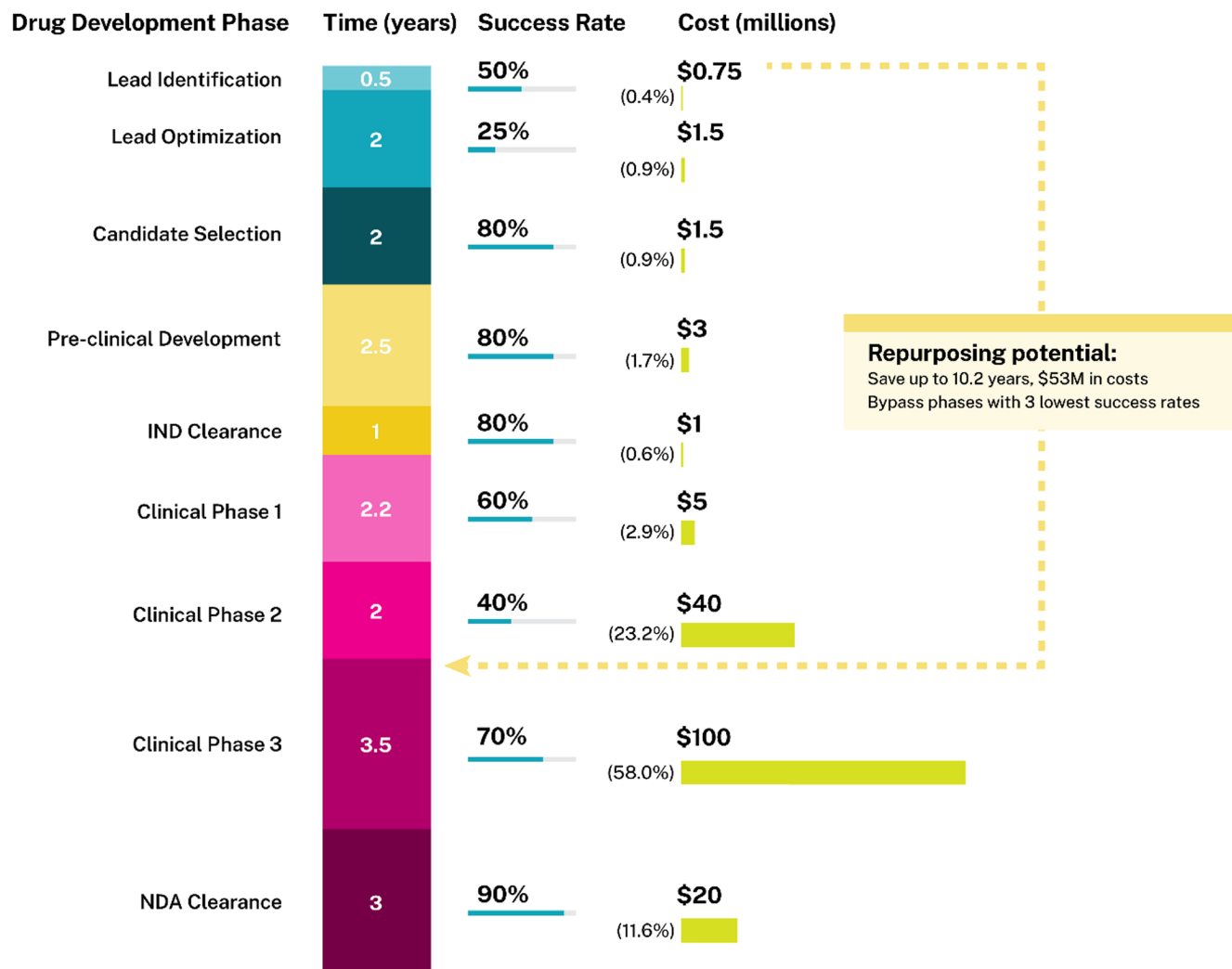


FIGURE 1 Industry-based standard drug development timeline versus drug repurposing. Represented in the graphic are typical timelines and pharmaceutical company costs for drug development at each stage in the drug development process. IND, Investigative New Drug; NDA, new drug application.

performed in-depth analyses to understand and construct prospective strategies to correct the increased and unsustainable attrition in phase II. The first was Pfizer² who in reported their immensely disappointing finding that an unacceptable percentage of their phase II clinical studies lacked confirmational data for sufficient molecular target engagement. Hence, they were unsure if the molecular targets for the diseases addressed in hypotheses had even been tested. So, conclusions could not be reached whether better assets for their molecular targets were prudent to pursue, or if future efforts should focus on other molecular targets. As a consequence of this finding, Pfizer proposed and has implemented the “3 Pharmacokinetic Pillars of Success” to ensure sufficient target engagement by novel assets before advancing to hypothesis testing in phase II clinical testing.² Two years later, AstraZeneca built upon the Pfizer publication, by proposing “5Rs” for success based on an analysis of their phase II failures.³

In addition to evidence of sufficient target engagement, which they termed Right Tissue to emphasize sufficient pharmacokinetics in the desired tissue (e.g., central nervous system [CNS]); Right Target, which Pfizer called “target precedence”; Right safety; Right Patient; and Right Commercialization potential. Four years later, the same AstraZeneca scientist reported that implementing the 5Rs in their portfolio decision making resulted in an almost five-fold increase in phase II to phase III survival (progression) rate.³ In addition to these factors determining phase II survival versus attrition, there is an important largely unavoidable strategy concern that has been and will continue to be practiced by nearly all large pharmaceutical companies and even many smaller biotechnology companies. To ensure adequate commercial value and return on investment, companies focus their research and development (R&D) expertise and portfolio of new assets on “major” diseases with a large population, frequency, and

unmet medical need. Most common diseases have been studied for decades, so the opportunity for a break-through therapy is challenging and unlikely. At the same time, the failure rate means there are potentially many existing, partially developed therapeutic candidates that were in development for one indication that could be repurposed for use in a new disease. By partnering with government and academic researchers, companies can improve the progression rate even further by making the assets available for testing in additional indications that make sense scientifically, but were not a priority for the company. The National Center for Advancing Translational Sciences (NCATS) initiative supported shorter early-stage clinical trials for 2–3 years at a lower cost ranging from \$1.2 to \$11.3 million (depending on the disease area and methods used) for the entire project including university overhead. This is considerably less than the typical cost to companies for phase I and II clinical trials (Figure 1). By providing support for three-way partnerships for phase II clinical trials, three of the phases in drug development with the lowest success rates can be mitigated (Figure 1, yellow arrow). This saves time (up to 10.2 years) and money (up to \$53 million) over starting de novo with a new chemical entity.

Benefits of drug repurposing: Cost, time, and success

Despite pronounced interest in both pharmaceutical R&D spending and evidence-based targets (e.g., genetic, from genome advances) over the past decades, the number of approved therapeutics has steadily decreased. Specifically, there has been a dramatic decrease in pharmaceutical R&D “productivity” or “efficiency”; and there has been a concomitant increase in cost per fully approved and commercialized drug.¹ The first time a novel agent is assessed for efficacy in phase II clinical trials is known as clinical proof-of-concept (POC) and is the stage of development that has the highest failure rate¹ (Figure 1). Multiple analyses of the drug development landscape consistently show that phase II attrition exceeds all other clinical phases. To counterbalance the high attrition at phase II, one strategy is to demonstrate clinical POC in another indication or different patient population using drug repurposing. The R&D cost and time for the new indication is shortened by leveraging the prior investments, while providing another opportunity for the asset to succeed.

The repurposing of an existing asset (compound or biologic) that has advanced to clinical phase II or beyond, beginning with a proposal for testing in a new patient population (either a new indication or a disease subpopulation), can greatly increase the frequency and breadth

of New Drug Approvals. It also creates opportunities to consider more niche indications (i.e., therapies for orphan and neglected diseases, or modest advancements over standard of care). Smaller overall commercial value can be more acceptable when starting from POC. Smaller, shorter (hence, less costly) phase III studies and timelines through approval are also often possible for these indications, especially orphan and neglected diseases. Because there is a large unmet medical need and/or small patient population.

Although pharmaceutical companies often own clinical assets that may be effective for indications other than those for which the assets were originally developed, the company may focus on limited disease domains in their business model. This, in turn, generally leads to a lack of broad disease expertise to identify many of the potential indications for a given asset. The three-way partnership model described below is one way to inspire and advance many drug repurposing ideas.

THREE-WAY PARTNERSHIP MODEL

Templates for success

During the pilot phase of the new therapeutic use initiatives, NCATS tested the utility of newly created template legal agreements. Six to 9 months prior to publicly posting assets, NCATS/National Institutes of Health (NIH) worked with each company to establish template legal agreements.

- 1. Confidential Disclosure Agreements (CDAs):** Spelled out how proprietary information would be handled by all parties involved in the collaboration. The NCATS/NIH entered a CDA with each pharmaceutical company. For those applicants that were put in contact with a pharmaceutical company, a separate CDA was signed between an academic institution and the pharmaceutical company before any information was exchanged by each party.
- 2. Collaborative Research Agreements (CRAs):** A CRA is important to both parties because it describes how intellectual property, patents, and licensing will work during the term of a project. The templates that were established by the NIH were a starting point for negotiations between academic medical centers and a pharmaceutical company if a proposed project was selected for support by the NIH. A letter of assurance that the template legal agreements would be used was required as part of the application submitted to NCATS. This greatly accelerated the establishment of a collaboration between the company and the academic medical

center and kept the focus on the hypothesis to be tested rather than the terms of the collaboration.

Template legal agreements were effective in facilitating negotiations, enabling the research to begin more quickly. The template agreements were successfully demonstrated and have since been used outside the NCAT/NIH programs by a few pharmaceutical companies when establishing academic collaborations outside the New Therapeutic Uses program.

Crowdsourcing

Crowdsourcing occurs when an investigational drug is publicly posted for investigators to propose ideas for new therapeutic uses. Generally, crowdsourcing is an approach used for investigational therapeutics, not therapeutics approved by the US Food and Drug Administration (FDA), because approved drugs already are known to the public. The design of the New Therapeutic Uses initiative required pharmaceutical companies to make limited information about their previously proprietary assets publicly known. This limited, public information would serve as the basis for an academic investigator to submit a hypothesis for a new use of the asset in the form of a brief five-page pre-application. Via this crowdsourcing technique, the researchers, who have access to patient populations and an understanding of diverse disease biology, developed new studies to test these assets in novel disease systems.

Pharmaceutical assets

In this program, NCATS invited prospective pharmaceutical companies to partner with NCATS to create an opportunity for academic researchers to explore new indications for their assets across a broad range of human diseases. Pharmaceutical partners offered a minimum of three drug candidates (assets) for which regulatory documents for an Investigative New Drug (IND) would be made available for meritorious applications. Asset characteristics included the following:

- Mechanism of action was known.
- Pharmacokinetics were suitable to explore the mechanism in a new indication in humans.
- Phase I clinical trial was completed – safety profile was understood.
- Assets currently in clinical development were included.
- Clinical supply (including matched placebo) could be made available at no cost.

- Pharmaceutical companies provided documentation to enable funded investigators to file an IND application with the FDA.

Project team

Each project had a project team that consisted of the NIH, pharmaceutical partners, and applicant institutions (Figure 2).

NCATS/NIH

By publicly posting pharmaceutical companies' assets, NCATS was able to crowdsource ideas for new uses of those assets from the collective intelligence of the scientific community. By coordinating the access that scientists nationwide have to existing clinical assets that have already cleared several key steps in the development process, NCATS was able to stimulate therapeutic innovation and development to hopefully get more treatments to all people more quickly.

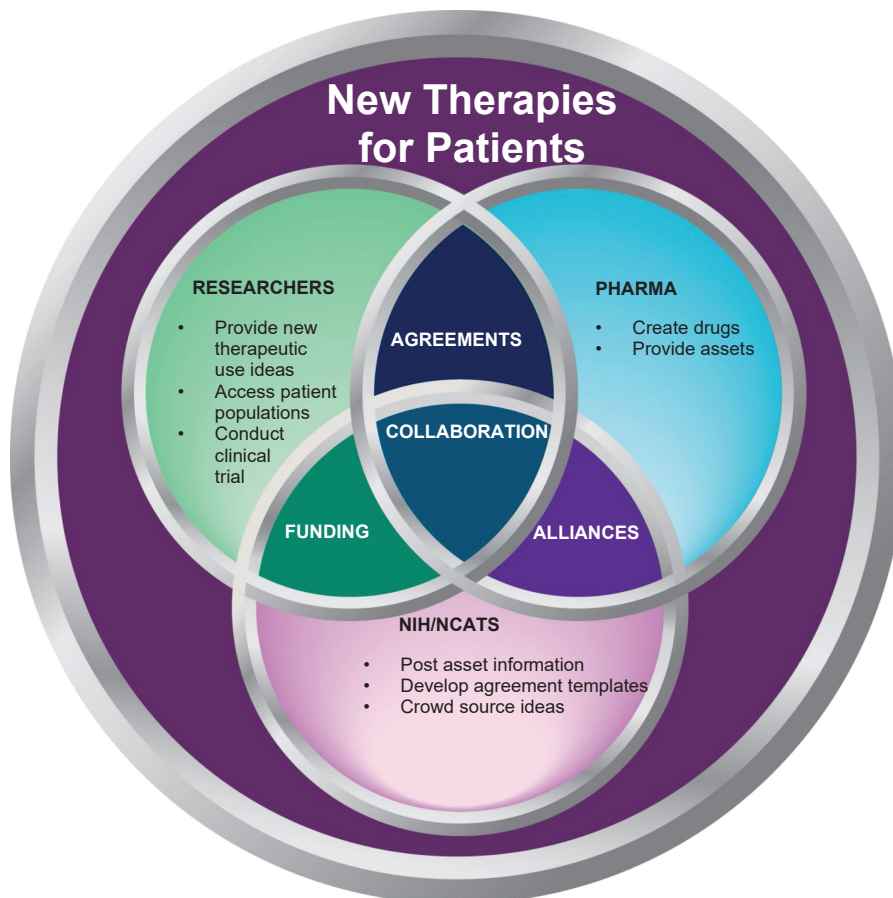
Protracted legal agreements are a translational science barrier that can slow the rate of scientific progress. It can sometimes take a year or more to establish CRAs between an academic institution and the pharmaceutical company that owns an experimental asset. The NCATS/NIH also provided template agreements to the researcher and their pharmaceutical asset provider to accelerate the establishment of a collaboration between the two. Use of template legal agreements shortened the time to establish three-way drug repurposing collaborations between the government, applicant institutions, and pharmaceutical companies to 3–4 months.

Once funding was awarded, NCATS/NIH provided oversight and guidance to the partnership to increase repurposing of assets for new indications.

Pharmaceutical team

The pharmaceutical team included scientists, and lawyers who assisted with establishing the template Collaborative Research Agreement and Confidential Disclosure Agreement negotiations. After pre-applications were received, investigators of the most meritorious applications were put in contact with pharmaceutical partners to exchange information under an NCATS pre-negotiated standard confidential disclosure agreement. While the pharmaceutical partner was providing additional information about the asset, the applicant was providing additional information about their hypothesis. At that point, a joint decision was made to apply for funding or not.

FIGURE 2 Three-way partnership model. This infographic depicts the three-way partnership between academia, government, and pharmaceutical partners and the responsibilities of each party. This partnership brought together specific compound information, formulation, and clinical design expertise from pharmaceutical companies and disease experts in academic medical centers that had access to new patient populations. NCATS, National Center for Advancing Translational Sciences; NIH, National Institutes of Health.



Following NCATS peer review and funding of the application, pharmaceutical partners provided drug products and placebo (if applicable) for projects that were selected for funding. The partner manufactured the drug and placebo and sent it to the clinical trial sites. Documentation needed for regulatory clearance was provided by the pharmaceutical partner with the applicant investigator providing the disease-related update (e.g., background information) and proposed clinical trial design details. Liaisons from the company providing the asset, participated in milestone progress update calls for active projects.

Major responsibilities of the pharmaceutical partner included:

- Provided asset information to be posted on the NCATS website.
- Provided clinical supply for phase I and phase I clinical studies (drug or biologic and placebo).
- Provided regulatory documents (i.e., cross-reference letter or study reports) to enable a funded investigator to file an IND application in time to meet project timeline and milestones.
- Agreed not to remove assets 90 days before a pre-application receipt date for a funding opportunity, unless something unanticipated (e.g., new safety information from the FDA) becomes available.

Researchers at academic medical centers

Beyond the new therapeutic use idea, investigators brought three crucial additional aspects to the potential collaboration: (1) expertise in the disease beyond that existing within the pharmaceutical partner, (2) access to patients at their clinic/institution and/or network, and (3) disease relevant symptom or biomarker progression end point measurements.

Eligible institutions included small businesses or academic medical centers. Although small businesses were eligible, they were generally only interested in out-licensing, which was not an option. As a result, applications from small businesses were rare and all the awarded projects were made to academic medical centers. Applicant institutions that had access to patient populations and an understanding of diverse disease biology submitted ideas for testing assets in novel disease systems. The most meritorious applicants were awarded support for conducting pre-clinical efficacy, safety, and toxicity studies when needed for the new indication. If preclinical milestones were met, then funding was awarded for early-stage clinical trials. In some cases, projects could proceed directly to phase II clinical trials based on the data from the original pharmaceutical company sponsored clinical trials. If necessary, phase I clinical trials were conducted in the novel target

population to evaluate safety, determine a safe dose range, verify target engagement, and identify side effects prior to conducting a phase II clinical trial. If the phase I clinical trial milestones were met, support was provided for the proposed phase II clinical trial. Phase II clinical trials were conducted in a large enough population to provide POC.

The process

The timeline and actions for each step of the partnering process are shown in Figures 3 and 4. Assets were publicly posted on the same day that funding opportunities were published. Applicants submitted a one-page specific aims page and a four-page research strategy that covered a plan to test a new therapeutic use of one publicly posted asset. The preliminary ideas underwent a nontraditional mail-in review. There was no meeting or discussion concerning the pre-applications and no final impact score. Reviewers submitted a short, written critique with a rating of acceptable, acceptable with modifications, or an unacceptable/unaddressable weakness. Suggestions to improve or strengthen the application were encouraged. After the evaluation of pre-applications, the most meritorious applicants were put in contact with a pharmaceutical partner for the asset or mechanism of action that was selected for study in the pre-application. They were expected to execute an appropriate CDA within 30 days of receiving the

pharmaceutical company contact information from the NIH. Under the CDA, the applicant and pharmaceutical company partner exchanged additional information on the assets and studies to test the proposed new therapeutic use of the asset. Subsequently, both parties made a joint decision whether to submit a full application for funding and negotiate a CRA. Applicants were required to submit documentation of access to the asset and associated data as part of their applications. Applications that were received by the NIH underwent peer review, and summary statements were issued. The NIH negotiated milestones for the most meritorious applications, and awards were made following the NCATS council review. The NIH and pharmaceutical partners participated in monthly or quarterly meetings to follow the milestone progress.

USE CASES

A total of 16 projects were selected for support by NCATS⁴. Four projects did not meet preclinical go/no-go decisions for lack of efficacy in an animal model. Eleven projects proceeded to clinical testing. One clinical project was discontinued early for a safety and toxicity issue for a co-administered drug. The co-administered drug safety issue came up in two cancer clinical studies that did not receive support from NCATS. Two projects are still active (as of March 2022). For the eight clinical studies that are

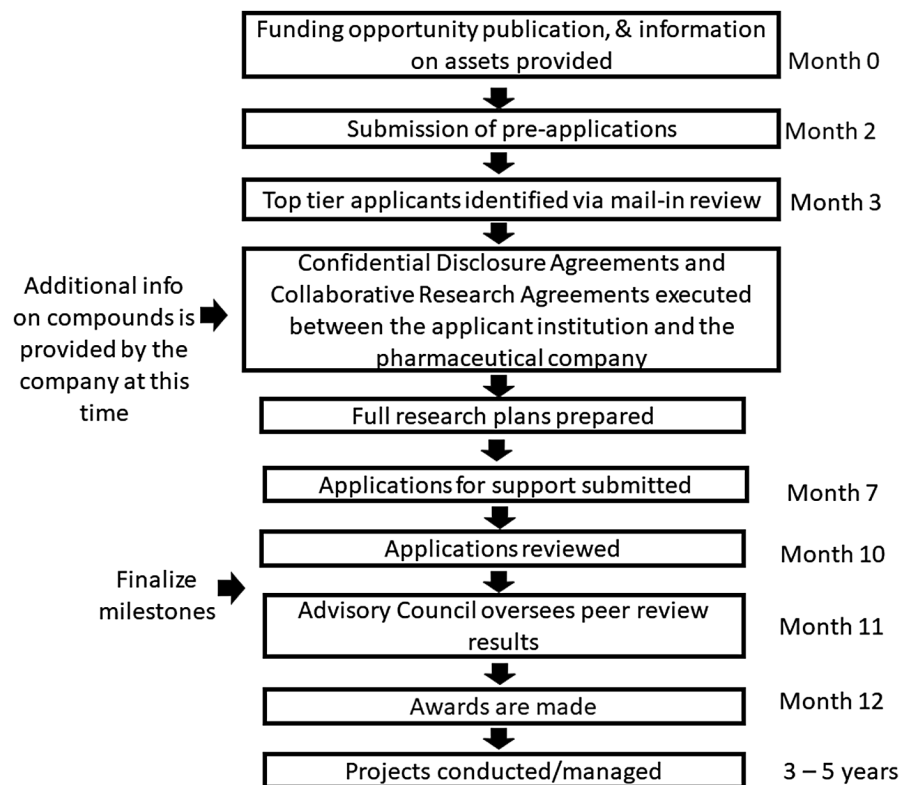


FIGURE 3 This figure depicts the process steps and time needed for three-way partnerships among academic medical centers, the National Institutes of Health (NIH), and pharmaceutical partners.



FIGURE 4 This figure depicts the process for an academic medical center and a pharmaceutical partner to establish a collaboration after top tier pre-applications are identified and put in contact with a pharmaceutical partner. CDA, Confidential Disclosure Agreements; CRA, Collaborative Research Agreements.

complete, some individual successes were achieved and reported as case studies below.

Individual project success stories

1. **Steven Strittmatter, MD, PhD**, was the principal investigator on an award made to Yale University. He discovered in an animal model that Fyn kinase, a member of the Src family kinases, plays a fundamental role in the pathogenesis of Alzheimer's disease. At the same time, he found a clinical compound that was originally developed for cancer posted by AstraZeneca (**AZD0530**: link to ncats.nih.gov/files/AZD0530.pdf) on the NCATS website. Although the project had challenges achieving desired dosing in humans in the CNS, the NCATS investment enabled the collection of long-term administration safety data that enabled many other projects using this asset to be tested clinically for other chronic conditions.⁵⁻¹⁰ Because AstraZeneca had been developing the compound for cancer, the long-term exposure studies would not have been completed without the NCATS support. In addition to measuring efficacy with traditional Alzheimer's memory tests, this trial demonstrated fluorodeoxyglucose (FDG)-positron emission tomography (PET) as a more objective and quantitatively reproducible

POC end point for Alzheimer's trials. This end point decreased the POC study size and duration, thus, increasing the likelihood of more frequent testing of novel agents (previously limited by study expense) for this indication in the future.¹¹

2. **Alan Breier, MD**, was the principal investigator on an award made to Indiana University to test an Eli Lilly drug (**LY500307**: link to ncats.nih.gov/files/LY500307.pdf) in patients with schizophrenia. As anyone who has conducted a trial knows, subject retention can be very challenging for studies that go on for several months. Loss of study subjects can result in failed trials due to a loss of power and ultimately a missed opportunity to evaluate a potential treatment for patients. For this study, the clinical trial team undertook personalized outreach and in person visits, achieving a participant dropout rate of 3%, whereas the typical dropout rate in clinical studies for this population is 20-40%.^{12,13}
3. **Brian Annex, MD**, was the principal investigator on an award made to University of Virginia to test an AstraZeneca drug (**ZD5054** link to: ncats.nih.gov/files/ZD5054.pdf) in patients with peripheral artery disease. The trial used imaging as a noninvasive method to measure calf blood flow at rest and during exercise was used as a more objective and quantitatively reproducible POC end point compared to the traditionally used subjective and effort-dependent 6-min walk test

measuring the distance traveled over a 6-min period.¹⁴ This was also shown to decrease POC study size and duration, thus, improving the likelihood of more frequent testing of novel agents (previously limited by study expense, subjectivity, and outcome variability) for this indication in the future.

4. **John Krystal, MD** (link to: <https://reporter.nih.gov/search/B9Xu1HDwMUKpl1maeyaAPg/project-details/8913287>) was the principal investigator on an award made to Yale University to test a Pfizer drug (PF-03463275; link to ncats.nih.gov/files/PF-03463275.pdf) in patients with schizophrenia. The phase II trial was conducted to inform the design of a clinical trial to evaluate the capacity of the Pfizer GlyT1 inhibitor to enhance cognitive remediation to treat cognitive impairments associated with schizophrenia. They concluded that whereas the Pfizer asset did not show evidence of facilitating NMDA-R function based on a ketamine assay in healthy subjects, it did enhance neuroplasticity in patients with schizophrenia.¹⁵
5. **James McKerrow, MD, PhD** (links to: <https://reporter.nih.gov/search/B9Xu1HDwMUKpl1maeyaAPg/project-details/8996043>) was the principal investigator on an award made to University of California, San Diego, CA, to test a chronic pain drug owned by Sanofi (SAR114137 link to: ncats.nih.gov/files/SAR114137.pdf) against chagas disease. This Cathepsin S inhibitor did not have efficacy against changes in preclinical studies. Through the program, the investigator then obtained access to another Cathepsin S inhibitor offered by Janssen (RWJ-445380). Although the Janssen compound also did not show efficacy, the collaboration with Janssen led Janssen to provide the investigator access to thousands of other assets for high throughput screening.^{16,17} This opportunity was greatly facilitated by the program.
6. **Jordan Miller, PhD** (links to: <https://reporter.nih.gov/search/B9Xu1HDwMUKpl1maeyaAPg/project-details/8913790>) was the principal investigator on an award made to Mayo clinic to test a Sanofi drug (Ataciguat; links to ncats.nih.gov/files/HMR1766.pdf) in patients with calcific aortic valve stenosis. Currently, the only treatment for this condition is surgical valve replacement. Ataciguat would offer an alternative to surgery. The award jumpstarted drug development at Mayo Clinic. It is also the first project awarded under New Therapeutic Uses that is proceeding to phase III clinic testing. Under the terms of the CRA, Sanofi had the first right of refusal for commercializing the therapy. Sanofi helped Mayo Clinic find another partner for phase III clinical testing. Rancho Santa Fe Bio, Inc. has entered a worldwide licensing agreement with Sanofi to test Ataciguat in the United States and select

international countries. Rancho Santa Fe Bio, Inc. also has a worldwide exclusive licensing agreement with Mayo Clinic for the use of Ataciguat in patients with calcific aortic valve stenosis.¹⁸

CHALLENGES AND POSSIBLE SOLUTIONS TO DRUG REPURPOSING OF CLINICAL STAGE COMPOUNDS

As noted above, public-private collaborations can provide huge advantages as well as opportunities for drug repurposing and, hence, important therapeutic innovation to the benefit of patients, and the NCATS-NTU program is a substantial facilitator of this.

However, there remains significant challenges as well as potential solutions to be considered. First, the number of compounds suitable for drug repurposing is not nearly as numerous as one would think. As an example, a dedicated team at one large pharmaceutical company recently filtered through over 450 compounds that had been nominated for clinical development.¹⁹ These compounds had been extensively characterized, including potency, selectivity, preclinical in vitro and in vivo pharmacology, complete pharmacokinetic and safety packages, target engagement, and experience in humans. Only 22 were found suitable for drug repurposing via crowdsourcing through the NCATS-NTU program. Suitability was based on data from the previous/original clinical development program demonstrating acceptable tissue exposure, safety margin, and target engagement. Adding compounds that remain in active phase III development and/or that have launched would dramatically increase the otherwise limited number of clinical stage compounds available for repurposing consideration. Yet, this presents additional challenges. Compounds that have advanced to phase III are the prized jewels of any company and as such the company is unlikely to be willing to see them explored in another indication before FDA approval, fearing the generation of any unexpected data that could delay a future FDA review and approval process. As any new (approved) drug will eventually be exposed to a wide population of patients, proponents for this approach argue that it is better to know any unexpected findings (e.g., adverse effects in another subpopulation of patients) earlier as opposed to later. Already marketed compounds carry the concern of expiring composition of matter patent rights, the strongest exclusivity protection. Yet, subsequent approval in a new indication is granted “data exclusivity” for that new indication by regulatory agencies. Current policies provide such additional

protection for 5 years in the United States, 7 years in the European Union, and 10 years in Japan. Although comparatively short, this exclusivity period can support the reduced cost of development and hence viable return on investment (ROI) for many new indications. In fact, the biotech company Valperion Pharmaceuticals, is solely focused on such opportunities as their business plan. Finally, commercialization protection via a new “Method of Use” patent offers 20–25 years of protection that may be practical for the new indication. The risk for such, however, is that prior to phase II clinical POC, the data that led a physician-scientist to propose and obtain approval to test in the new indication could be used as “prior art.” A patent examiner may reject the patent application or others to challenge its validity, even if granted based on “obviousness to one skilled in the field.” For this reason, intellectual property (IP) attorneys generally consider these patents more vulnerable to legal challenge than the stronger composition of matter patent. Moreover, whereas method of use patents may afford protection against generic entry in the United States, a “method of treatment” for a pharmaceutical therapy is not patentable in Europe or in many other countries. Yet, given the record of poor success (well <50:50) in phase II clinical POC studies (Figure 1), one can argue that success of a molecular target to disease hypothesis in patients is far from obvious even with strong preclinical or other existing data. To our knowledge, such an argument has never been attempted: hence, success is not assured. Additionally, if ROI is insufficient to justify further development by the originating compound owner due to lack of commercial exclusive, licensing to a biotech (e.g., Valperion Pharmaceuticals, who are proficient with such opportunities), or approval via “emergency” or “compassionate” use, can be considered to achieve an adequate ROI. The latter are especially applicable for rare and orphan diseases. Finally, combinations of a new dose or formulation can avoid generic competition. The NCATS Pharmaceutical Collection (NPC) has created a collection of drugs that are already marketed/approved somewhere in the world to facilitate drug repurposing of such advanced compounds. The NPC collection is used in NCATS’ in vitro high-throughput robotics facility for disease-relevant phenotypic screening.

Ultimately, we learned many lessons about steps in the partnering process where having a checklist of the many things that need to be considered and/or discussed can facilitate effective collaborations between researchers at the academic medical centers and pharmaceutical partners. As some of the steps in the drug development process that occur in pharmaceutical companies are not familiar to principal investigators at academic medical centers, who

often may be repurposing a drug for the first time (see Tables 1 and 2). However, even with the best laid plans, there are many factors that influence successful completion of a trial – enrollment, retention of subjects, commitment and experience of the trial team, sufficient time and funding for the trial, etc. Although this program was designed with very aggressive timelines, the confounding factors were the ultimate determinants of successful completion.

SUMMARY

Repurposing of clinical stage compounds can greatly enhance therapeutic testing, innovation, and efficiency to benefit patients and advance medical science. By starting with an existing compound that has already been in phase I clinical trials or beyond, the cost and timeframe for therapeutic development is almost half that of starting de novo with a novel therapeutic. Under these circumstances, niche improvements to existing standards of care as well as orphan disease indications would offer an acceptable ROI. Yet, challenges, such as the number of “clinical stage” compounds available, availability of drug product (including matched placebo), pharmacovigilance concerns, regulatory studies to meet the FDA requirements for IND clearance for the new indication, Investigator’s Brochure updates for compounds under development, liability for any unexpected adverse events in clinical POC testing for the new indication, and concerns regarding patent protection and ROI are potential barriers to further development.

We have described a process by which collaborations between pharmaceutical companies and academic medical centers were established around experimental assets from companies and ideas for therapeutic uses of those assets was proposed by academic researchers. In addition to testing the assets in new indications, which in one case led to third party support for a phase III clinical trial, some projects provided data to support the use of innovative quantitative measures for POC trials, seeded new collaborations between academic researchers and companies beyond the program.

The template agreements that were critical to establishing the collaborations were also adopted by some of the companies involved in their negotiations with academic institutions outside the program.³ Demonstration and dissemination of the agreements was so successful that several other NIH programs adopted the template agreements (<https://ncats.nih.gov/pubs/features/ntu-template>).

In addition to template agreements, advantages for the pharmaceutical partners participating in the program included:

TABLE 1 Checklist for pharmaceutical partners to discuss with academic medical centers

Discuss while preparing a research plan	Timeline considerations	Timeline for application content	To be negotiated with PI at time of award	To be submitted during the study
<input type="checkbox"/> Access to the investigator's brochure <input type="checkbox"/> Access to assay protocols <input type="checkbox"/> Draft clinical protocol <input type="checkbox"/> Plan for IND approval (including IND material to be referenced or IMP materials to be used) <input type="checkbox"/> Plan for IRB approval(s) <input type="checkbox"/> Recruitment sites and site assessment <input type="checkbox"/> Feasibility assessment <input type="checkbox"/> Internal deadlines <input type="checkbox"/> Personnel availability	<input type="checkbox"/> Timing of when a decision will be made to move forward <input type="checkbox"/> CDA should be completed by date <input type="checkbox"/> CRA should be completed by date <input type="checkbox"/> Timing for investigator studies and drug delivery <input type="checkbox"/> Timing of availability of data for IND needs (especially if clinical trials done in the EU) <input type="checkbox"/> Availability of tablet doses <input type="checkbox"/> Product development plan <input type="checkbox"/> Timeline for investigator studies and drug delivery	<input type="checkbox"/> Letter of support <input type="checkbox"/> Commitment, ability, and timing of availability of API <input type="checkbox"/> Timing of availability of tablets <input type="checkbox"/> If no IND on file, date IMP information from EU trials will be available <input type="checkbox"/> What doses will be provided? <input type="checkbox"/> Who will do the packaging? <input type="checkbox"/> Who will collect safety data (AEs)? <input type="checkbox"/> Will a third party be involved with the manufacturing, packaging, or collecting safety data? <input type="checkbox"/> Will a third-party agreement be required?	<input type="checkbox"/> What is the plan if a manufactured batch fails QC and cannot be delivered on time? <input type="checkbox"/> How will the AEs be collected? <input type="checkbox"/> List of dates for update teleconferences <input type="checkbox"/> When will the investigator's brochure be available to the PI? <input type="checkbox"/> Confirm Steering committee quarterly meeting schedule <input type="checkbox"/> Availability for answering FDA questions about IND submission	<input type="checkbox"/> Weekly animal/preclinical results <input type="checkbox"/> Recruitment status <input type="checkbox"/> Study status updates <input type="checkbox"/> Safety reports <input type="checkbox"/> FDA correspondence (IA)

Abbreviations: AEs, adverse events; API, active pharmaceutical ingredient; CDA, Confidential Disclosure Agreements; CRA, Collaborative Research Agreements; EU, European Union; FDA, US Food and Drug Administration; IA, information amendment; IMP, investigational medicinal product; IND, investigational new drug; IRB, institutional review board; PI, principal investigator; QC, quality control.

TABLE 2 Checklist for academic medical centers to discuss with pharmaceutical partners and NIH

Discuss while developing a research plan	To be negotiated with NIH prior to award	To be submitted after negotiations and prior to study initiation	To be submitted during the study
<input type="checkbox"/> Draft clinical protocol <input type="checkbox"/> Plan for IND approval, including IND material to be referenced or IMP materials to be used <input type="checkbox"/> Plan for IRB approval(s) <input type="checkbox"/> Recruitment sites <input type="checkbox"/> Timeline for investigator studies and drug delivery <input type="checkbox"/> Feasibility assessment <input type="checkbox"/> International plan, when applicable <input type="checkbox"/> Drug certificate of analysis and lot number <input type="checkbox"/> Drug stability information <input type="checkbox"/> Internal deadlines <input type="checkbox"/> Personnel availability	<input type="checkbox"/> Milestones <input type="checkbox"/> Independent safety monitoring <input type="checkbox"/> IND requirement or IMP information availability <input type="checkbox"/> Plan and terms for additional funds <input type="checkbox"/> List of dates for monthly update teleconferences <input type="checkbox"/> List of dates for quarterly steering committee meetings including annual meeting <input type="checkbox"/> Data lock plan	<input type="checkbox"/> Final clinical protocol <input type="checkbox"/> Final consent <input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> IND safe to proceed <input type="checkbox"/> Investigator brochure <input type="checkbox"/> Plan for drug packaging (PI pharmacy or Pharma partner) <input type="checkbox"/> Detailed independent safety monitoring plan, including draft charter and member list <input type="checkbox"/> IRB approval(s) <input type="checkbox"/> Submit Steering Committee roster <input type="checkbox"/> Submit Team Roster if different from Steering Committee <input type="checkbox"/> Quality management plan <input type="checkbox"/> Clinical monitoring plan	<input type="checkbox"/> Monthly animal/preclinical results <input type="checkbox"/> Recruitment status <input type="checkbox"/> Study outcome updates <input type="checkbox"/> Safety reports <input type="checkbox"/> FDA correspondence, when applicable <input type="checkbox"/> Minutes or recommendations from any independent oversight for safety <input type="checkbox"/> Any IB or protocol amendments

Abbreviations: FDA, US Food and Drug Administration; IB, investigator's brochure; IMP, investigational medicinal product; IND, investigational new drug; IRB, institutional review board; NIH, National Institutes of Health.

- NCATS coordinated funding opportunity announcements sought promising candidates for repurposing ideas from the academic community and put the most meritorious in contact with the companies.
- Access to patient populations through academic centers and to expertise on the new indication.
- New clinical projects that may not have been identified by the company alone.

The companies felt the access to funding via NCATS/NIH was extremely important for exploring new indications for their assets, as obtaining funding for a novel indication from the pharmaceutical company is often quite challenging, if not impossible. Private companies already have their prioritized portfolios. To add something new almost always requires the displacement of one or more of their existing/ongoing projects in which they have already invested. The opportunity to benchmark innovative outcome measures against standard outcome measures is the best way to transition to new standard measures. Such changes are particularly important when they improve the patient experience by reducing the duration of their involvement and/or the clinical evaluations themselves. These improvements can also reduce the number of subjects needed, thereby reducing the cost of the trials, which could ultimately lead to testing more drug candidates.

In closing, although the program did not demonstrate improved success rates for phase II clinical trials, more indications could be explored for less money under this model compared to the costs for industry. The phase II trials in this program support the potential of a nonsurgical treatment for calcific aortic valve stenosis as well as the treatment of cognitive impairment associated with schizophrenia. Additionally, testing innovative outcome measures that have the potential to reduce patient burden adds value for patients and future trials alike. These outcomes would suggest that bringing parties with complementary resources together through crowdsourcing and the use of template agreements and checklists is a collaboration model worth considering for future programs.

ACKNOWLEDGEMENTS

The authors would like to thank Bonnie Dunn, PhD, for creation of the checklists and Kyle Brimacombe for creating [Figure 1](#). The authors would like to thank the following individuals for helpful edits: Jeff Southerton, PhD, MBA (Azenova, LLC), Wayne C. Drevets, MD (Janssen Research & Development, LLC of Johnson & Johnson), and Pamela Hill (AstraZeneca).

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

REFERENCES

- DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J Health Econ.* 2016;47:20-33.
- Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov.* 2012;11(3):191-200.
- Cook D, Brown D, Alexander R, et al. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. *Nat Rev Drug Discov.* 2014;13(6):419-431.
- NIH, *NIH RePort*, in Reporter 2022. <https://reporter.nih.gov/search/B9Xu1HDwMUKpl1maeyaAPg/projects?>
- Kaufman AC, Salazar SV, Haas LT, et al. Fyn inhibition rescues established memory and synapse loss in Alzheimer mice. *Ann Neurol.* 2015;77(6):953-971.
- Nygaard HB, van Dyck CH, Strittmatter SM. Fyn kinase inhibition as a novel therapy for Alzheimer's disease. *Alzheimers Res Ther.* 2014;6(1):8.
- Smith LM, Zhu R, Strittmatter SM. Disease-modifying benefit of Fyn blockade persists after washout in mouse Alzheimer's model. *Neuropharmacology.* 2018;130:54-61.
- Tang SJ, Fesharaki-Zadeh A, Takahashi H, et al. Fyn kinase inhibition reduces protein aggregation, increases synapse density and improves memory in transgenic and traumatic tauopathy. *Acta Neuropathol Commun.* 2020;8(1):96.
- Toyonaga T, Smith LM, Finnema SJ, et al. In vivo synaptic density imaging with (11)C-UCB-J detects treatment effects of Saracatinib in a mouse model of Alzheimer disease. *J Nucl Med.* 2019;60(12):1780-1786.
- van Dyck CH, Nygaard HB, Chen K, et al. Effect of AZD0530 on cerebral metabolic decline in Alzheimer disease: a randomized clinical trial. *JAMA Neurol.* 2019;76(10):1219-1229.
- Mecca AP, McDonald JW, Michalak HR, et al. PET imaging of mGluR5 in Alzheimer's disease. *Alzheimers Res Ther.* 2020;12(1):15.
- Francis MM, Hummer TA, VoHS JL, et al. Functional neuro-anatomical correlates of episodic memory impairment in early phase psychosis. *Brain Imaging Behav.* 2016;10(1):1-11.
- Hummer TA, Francis MM, VoHS JL, Liffick E, Mehdiyoun NF, Breier A. Characterization of white matter abnormalities in early-stage schizophrenia. *Early Interv Psychiatry.* 2018;12(4):660-668.
- Chu LH, Annex BH, Popel AS. Computational drug repositioning for peripheral arterial disease: prediction of anti-inflammatory and pro-angiogenic therapeutics. *Front Pharmacol.* 2015;6:179.
- D'Souza DC, Carson RE, Driesen N, et al. Dose-related target occupancy and effects on circuitry, behavior, and neuroplasticity of the glycine Transporter-1 inhibitor PF-03463275 in healthy and schizophrenia subjects. *Biol Psychiatry.* 2018;84(6):413-421.
- Buschman, H. UC San Diego Skaggs School of Pharmacy and Janssen R&D Collaborate to Treat Chagas Disease. In *UC San Diego News Center. This Week Newsmagazine*; 2015.
- Buschman, H. UC San Diego Skaggs School of Pharmacy and Janssen R&D Collaborate to Treat Chagas Disease. In *UC San Diego News Center. This Week Newsmagazine*; 2016.
- Bio, R.S.F. Yahoo!Finance. In *Rancho Santa Fe Bio, Inc. Enters into Worldwide Exclusive License Agreement with Sanofi for Ataciguat*; 2021. <https://www.yahoo.com/now/rancho-santa-fe-bio-inc-090000039.html>
- Frail DE, Brady M, Escott KJ, et al. Pioneering government-sponsored drug repositioning collaborations: progress and learning. *Nat Rev Drug Discov.* 2015;14(12):833-841.

How to cite this article: Wegner CD, Mount BA, Colvis CM. A public-private collaboration model for clinical innovation. *Clin Transl Sci.* 2022;15: 1581-1591. doi:[10.1111/cts.13293](https://doi.org/10.1111/cts.13293)