Preliminary and Incomplete
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A New Incentive to Accelerate Vaccines for Epidemics

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January 14, 2020

ABSTRACT

Timely access to vaccines and other emergency medical countermeasures (MCMs) such as drugs, vaccines, and diagnostics can prevent infectious outbreaks from growing into large-scale health emergencies. Emergency MCMs are in short supply however because industry does not develop products for epidemics that may never occur. As disease outbreaks become more frequent, the global community cannot continue to rely on the goodwill of the private sector to develop vaccines and other emergency MCMs. Public funds currently provide push incentives—resources to reduce the cost of research and development - but very few pull mechanisms to support the manufacturing and clinical activities required for Phase III trials. A robust incentive is required to ensure that these products are available for testing when outbreaks occur. We identify unique characteristics of the market for vaccines to prevent epidemic infectious diseases, assess incentive schemes according to their ability to address these exceptional challenges, and propose a mechanism to engage industry.

ACKNOWLEDGMENTS

The authors are grateful to the Nuclear Threat Initiative for funding, to Jake Jordan and participants in the On-Demand Medical Countermeasures Workshop held in June 2019 in Washington DC for insightful comments, and to Sophie Smith for able research assistance.

Policy Challenge

Outbreaks of unfamiliar pathogens such as SARS, MERS, Ebola, and Zika can emerge rapidly with little warning. The very unpredictability and potential scale of these outbreaks undermines the business case to develop MCMs because industry does not develop large quantities of new medicines for diseases they cannot anticipate. Even so, when Ebola began to spread through West Africa in 2014, funders, developers, regulators, and clinicians demonstrated that they could develop and test vaccines quickly under challenging circumstances.[1] Within one year, Ebola vaccine trials went from zero to twenty on five continents, with Merck's candidate progressing to late stage development and deployment towards the end of the outbreak.[2]

This record reflects a one-time effort under urgent conditions. Responding to Ebola disrupted daily operations in every sector. Industry in particular incurred significant opportunity costs, reaped no commercial reward, and received little public relations benefit.[3] As disease outbreaks become more frequent, the global community cannot continue to rely on the goodwill of a handful of companies.[4] "Our business has a noble purpose," notes Merck CEO, Kenneth Frazier, "but the capital markets don't go to church on Sunday."[5]

Efforts to respond to Ebola in real-time revealed three critical factors that could facilitate outbreak preparedness: a robust pipeline of candidate vaccines, science preparedness initiatives to streamline outbreak research and response, and finally, a sustainable set of economic incentives to encourage industry participation.[6] Laudable progress has been made on the first two objectives. In 2017, the governments of India and Norway, the Bill & Melinda Gates Foundation, the Wellcome Trust, and the World Economic Forum came together to launch the Coalition for Epidemic Preparedness Innovations (CEPI).[7] CEPI supports and coordinates vaccine development for diseases that have epidemic potential but few market incentives.[8] CEPI pools donor funds and contracts with industry to develop vaccines through Phase 2 so that candidates might be available to test in an outbreak. Working with the WHO and other partners, CEPI has also identified key steps to enable a more streamlined and coordinated research response in the countries where outbreaks occur.[9]

What happens, however, after CEPI partners develop a candidate through Phase 2? In the event of a large-scale outbreak, the hope is that an experienced manufacturer like Merck would step in, as they did for Ebola, to take a candidate over the finish line. A private company may choose to do so for humanitarian reasons, but they would have redirect personnel and facilities away from other, more profitable projects to address an outbreak with an uncertain future. If this company manages to demonstrate efficacy under outbreak conditions, which is by no means assured, how will they recoup their investment? If the countermeasure is a highly effective vaccine, it could quell the outbreak. This is a win for society, but a loss for the company, which has just killed its own market. If the disease spirals out of control, demand goes up, but the company may get caught in a political battle for access, and a public demand to share intellectual property to expand the manufacturing base. If the outbreak ends abruptly, the company may be able to sell remaining doses to an emergency stockpile. No matter what the outcome, the business case is weak.

Currently, public funds provide push incentives (such as milestone grants) through a government agency like the Biomedical Advanced Research and Development Authority (BARDA) in the U.S., which coordinates the development of pandemic and biodefense medical countermeasures, and pipeline accelerators like CEPI and CARBx, which coordinate the development of epidemic vaccines and new antimicrobials respectively. However, public entities lack robust mechanisms to incentivize large, experienced manufacturers to bring candidates across the finish line. To fully realize the benefits of public investments to develop emergency MCMs, a robust incentive is required to engage industry to make these products available when they are needed. Without it, publicly funded development pipelines run the risk of becoming a highway to nowhere.[10]

Economic Considerations

Three essential features differentiate emergency MCMs from other products, which justify the call for a special funding mechanism. First, the demand for emergency MCMs is highly unpredictable. Given the volatility of outbreaks, it is difficult for a developer to know how much of what countermeasures will be needed when. And yet, to achieve the

highest social benefit, the decision to manufacture emergency MCMs must be made well before global demand is established. Unchecked, some diseases such as Ebola could become endemic as HIV did in the 1990s, engendering half a trillion dollars in medical spending from 1995 to 2015 according to one estimate.[11] On the other hand, targeted administration from a small stockpile could quell a global pandemic.

Second, emergency MCMs, vaccines in particular, suffer from an extreme version of the positive externality problems that undercut the market for vaccines. In the general case, consumer A's decision to become vaccinated benefits every unvaccinated person B that A comes into contact with because B will not contract the disease from A. Preventing A from contracting the disease prevents A from transmitting the disease to B as a by-product, an external benefit that B gets for free.[12] In an outbreak, ideally, only a small amount of emergency vaccine will be used to contain the spread of disease. The more successful the response, and the more effective the vaccine, the smaller number of doses required. Contrarily, poor vaccine efficacy, delayed response, and ineffective containment would all increase the market for the vaccine. Depending on the characteristics of the outbreak, demand could rise or fall in a rapid and relatively unpredictable way.

Emergency MCMs—vaccines in particular—can also eliminate their own market. Quelling an outbreak at the onset benefits everyone that would have otherwise been infected. This feature of emergency MCMs precludes the private market from providing any serious incentives for development and production. When the best social outcome determines the worst economic outcome for the developer, there is a strong argument for a non-market intervention.

Third, free-rider problems stem from the positive externalities associated with measures taken to quell an emergency early. These measures benefit not only the countries that implement them but also other countries that do not. Whether countries' motives for helping out in global emergencies stems from altruism or self-defense, these countries may have an incentive to sit back and let other countries pay for the intervention, free riding on other countries' efforts. Absent robust global coordination, delay and under provision will result.

Traditional Pull Mechanisms

Policymakers have sought to address failures in the market for specific drugs, vaccines and diagnostics by proposing additional incentives for developers. Most of the incentive schemes that have been tested to date are insufficient to address the unique challenges that emergency MCMs must overcome in the market.

Advanced Market Commitment The first of these, Advance Market Commitments (AMCs), have been gaining attention in the development community as a viable mechanism to pull socially desirable vaccines through development and into the market. In 2009, GAVI launched a $1.5 billion pilot to purchase a second-generation pneumococcal vaccine for the 73 GAVI-eligible countries (having low enough income to be eligible for GAVI support). As proposed in a series of papers by Michael Kremer,[13] an AMC sets aside a committed fund for a potential product before it is fully developed. A subsidy is paid from the fund for each dose of the product on top of a copayment by the end user (or a country or other donor on the patient's behalf). The transfer of the fund to the innovating firm is tied to how much of the product is sold. If the innovator develops a product that end users do not find useful, they will not make their copayment. With no product sold, no AMC subsidy has to be paid out. Beyond avoiding the wasting of AMC funds, this feature can result in a better product being produced because it incentivizes the innovator to go beyond fulfilling the letter of some target product profile (TPP), which might be hard to specify completely and correctly years in advance of development of an actual product. It has an incentive to tailor the product to suit end-users needs closely since, in addition to satisfying a TPP, the AMC requires the product to meet the market test.

AMCs hold promise for endemic disease vaccines. Pneumococcus is widespread in rich and poor countries alike, accounting for nearly one million child deaths worldwide from associated pneumonia and meningitis. The program was designed to enable a universal vaccination program for children. The volumes contemplated were sizable enough that a small subsidy from the AMC, on top of the country copayment, could constitute a fund large enough to incentivize investment in R&D and capacity. Early evidence on the performance of the pilot suggests the pneumococcus vaccine is highly

cost effective and the pilot sped capacity and adoption of the pneumococcus vaccine relative to comparison vaccines that were rolled out without AMC support. [14]

AMCs do not offer a good model for epidemic disease vaccines, because they link industry reimbursement to the number of doses sold. Unlike endemic disease vaccines, the social value of an epidemic vaccine can be inversely related to the volume used. In an ideal world, prompt reaction with an effective vaccine in an outbreak will contain the disease and squelch demand for the vaccine.

Patents Patent policies offer another lever, [15] although patent buyouts and extensions are unlikely to incentivize emergency MCM development. Because the private market often fails to generate adequate emergency MCMs, procurement is undertaken by public (government and NGO) entities. The "market" for the product then reduces to bilateral bargaining between the agency and the firm. Monopoly rights, which for typical products give the firm the ability to post a price that atomistic consumers then have to pay to purchase, may not reduce the bargaining leverage much. The buyer would still be able to bargain the price down near cost, leaving the firm with little profit margin. Similarly, extensions to patents in bilateral-bargaining situations may not incentivize much investment either.

One alternative is to offer firms extensions on patents for other, unrelated products in their portfolios, ones for which the patent is profitable for the firm. This alternative holds the greatest potential for loss of consumer surplus, since the firm would likely apply the extension to its most popular product. Extending the patent increases the period over which the firm is able to charge a monopoly price. The high price results in fewer consumers accessing the product and a loss of consumer surplus.

Priority Review Vouchers Priority review vouchers are another mechanism that have been tested to incentivize socially desirable development. [16] A priority review voucher expedites the review by the U.S. Food and Drug Administration (FDA) of a product, reducing the usual lag from around ten months to six months. The authors proposed that the vouchers be given to firms that develop medicines for neglected diseases to provide extra incentives to do so. The vouchers are transferrable and since their institution have been sold for prices up to $350 million. The authors suggest the

program is a sort of "free lunch," benefitting "consumers in both developing and developed countries at relatively low cost to the taxpayer."

Priority review vouchers show promise as a short-term solution, but more research is be needed before they could be considered as a long-run solution to the underfunding of emergency MCMs. First, the high prices for the vouchers indicate that FDA delays destroy substantial surplus. The sales price is a measure of how much firms would pay to avoid profit losses from the delay. However, the delay also results in untold loss of consumer surplus.[17] A better policy may be to allocate more resources to the FDA to shorten the lead time for drug review. Shorter delays would reduce the value of the priority review voucher and make it less useful as an incentive for emergency MCMs.

Proposal

To incentivize emergency MCM development beyond Phase 2, we propose a fixed reward that delinks reimbursement from the number of units sold. The reward is designed to support the scale up of Good Manufacturing Practice (GMP) facilities as well as the manufacturing and clinical operations required for Phase 3 trials.[18] The reward signals a stable commitment to industry partners that meet pre-specified criteria. To qualify, manufacturers would have to demonstrate appropriate expertise and capacity to scale up GMP facilities and to coordinate Phase 3 trials for a Phase 2 candidate for a disease that is on the WHO list of priority pathogens with pandemic potential.[19]

The development prize could be awarded in a staged fashion for qualified manufacturers. In the first stage, the fund administrator would set up a Memorandum of Understanding (MOU) with qualifying industry partners to provide GMP manufacturing facilities and expertise for a designated post-Phase 2 candidate. Insurance providers could develop an instrument that will allow industry to defray cost and risk to prepare a GMP facility to scale up manufacturing for Phase III trials. If there is an outbreak of sufficient scale (funders and their partners will need to identify a pre-agreed threshold), award money is released and Phase 3 scale-up manufacturing and testing commences. This marks the second funding stage. If outbreak conditions persist, (i.e. an emerging infectious disease becomes endemic, and/or other countries recommend broader vaccination programs), the manufacturer could exercise an option to negotiate a long-

term maintenance/continuous improvement contract. Whereas the first award is designed to delink reimbursement from the number of doses produced, this second award could be structured as a traditional AMC, similar to the pneumococcal vaccine contract with GAVI. Exhibit 1 summarizes the proposed funding mechanism in a flowchart.

Setting the Prize The prize must provide adequate incentives for firms to undertake the necessary risk-adjusted investment to reach the stockpile goal. Setting the prize amount is a delicate exercise because the agency may know the distribution of investment costs and risks of failure for historical cases but not for the specific product under consideration; those costs are yet to be realized, so can only be forecasted. The prize should reflect the social benefit of avoiding a wider, perhaps global, spread of the disease but should be tailored not to give too large a share of the potential social benefit to firms.

The prize should be tied to the counterfactual value of the product and thus may vary from candidate to candidate. The expected counterfactual value v equals the global harm that would be experienced in the absence of the product in each of various scenarios multiplied by the probability that each scenario emerges in the absence of the product. As a toy example, consider a disease that has an 80% chance of causing no deaths, and respectively a 10%, 5%, 3%, and 2% chance of causing 100, 1,000, 10,000, or 100,000 deaths in a period. The expected number of deaths is 2,360, times some estimate of the social cost of losing a human life, say $1 million, gives an estimate of about $2.4 billion. If the MCM could theoretically prevent half of these deaths, and that is the only benefit provided, the counterfactual benefit would be estimated to be $1.2 billion. Other benefits such as avoiding economic decline associated with the outbreak and medical expenditures would also add to the figure. One source estimates indirect income losses from a flu pandemic ranging from 12-40% of the direct loss from premature death.[20] Taking the midpoint of this range, 26%, and adding this level of avoided income losses to the $1.2 billion reduction in death yields a value of $v = \$1.5$ billion.

Of course, the prize (denoted z) should not be set at this amount because that would give away all the value to the firm. The optimal prize balances two considerations: increasing firms' investment incentives, thereby increasing the probability that a product is developed against reducing the transfer of public funds to private firms. The appendix

provides technical details behind the computation of the optimal prize z^* for a given level of the value v of the product.

The calculations are based on the assumption that a single, risk-neutral, profit-maximizing firm has a candidate phase 2 product. The firm decides whether or not to invest to take the product through phase 3 trials to have a chance at earning the prize. In making this decision, the firm compares expected revenue, equal to the probability of phase 3 success times the prize amount, to cost, equal to the firm's draw from a distribution of potential out-of-pocket investment expenditures x marked up by the cost of capital compounding over the period of time between when the expenditure is made and when the prize is earned.

The calculations require several parameters to be calibrated including the distribution of the cost of completing phase 3 trials for an epidemic-disease vaccine, the probability of success of those trials, and the firm's discount rate. Exhibit 2 shows the distribution of investment costs that we use. The lognormal distribution of expenditures x appears to fit well, and we calibrate its parameters based on the mean and standard deviation of investment costs from the literature. [21] The graphed lognormal density function has quite a long and fat right tail, with quite high investment costs quite likely. We take 85% from the literature to be a plausible estimate of the probability of success from phase 3 vaccine trials from the literature. [22] Assuming the out-of-pocket expenditures are made continuously at a constant rate over the duration of phase 3 trials and inputting recent estimates of the annual cost of capital for pharmaceutical firms and the average duration of phase 3 trials,[23] it turns out that the complicated calculations involved in continuous compounding of an investment-expenditure flow at the going rate of the cost of capital is equivalent to simply marking up out-of-pocket expenditures by $r = 23\%$. This provides a threshold which expected revenue from the prize must exceed to induce investment.

Using these calibrated parameter values, Exhibit 3 graphs the result for the optimal prize for a range of values of a successful product. The graph is increasing and concave, implying that as the value of the product grows, the optimal prize grows but not as fast. For ease of viewing, Exhibit 4 provides results for the optimal prize for selected values of the value of the product v in table form. The exhibit also adds columns of

results for several other outcome variables. The third column shows the overall completion probability, equal to the probability of investing multiplied by the probability of phase 3 success. The last column shows expected net social surplus. Algebraically, this equals the difference between the first two columns (this nets the prize payment to the firm z^* from the gross value of the product v) multiplied by the completion probability in the third column.

One of the rows of Exhibit 4 carries out the calculations for the value of the product from the toy model above, $v = \$1.5$ billion. The optimal prize in this case is $82 million. This moderate prize is sufficient to ensure that the firm invests more than 96% of the time. Multiplied by the 85% probability of phase 3 success conditional on investing, this is how we arrive at the overall completion probability of 82% shown in the table. Expected net social surplus is $1.166 billion, a substantial fraction of the $1.5 billion gross product value. Although a toy example, this suggests that there is considerable surplus to be gained from undertaking the prize scheme.

Discussion

Governance and Operation To operationalize this funding mechanism, numerous questions of governance and administration must be addressed in broader stakeholder forum to give scope to a broad set of political and practical considerations. Chief among these is the question of who could best implement a resource mobilization strategy and administer the development fund. Potential candidates include GAVI, CEPI, the WHO, and the World Bank. Whoever administers the fund will also have to work out questions of liability, intellectual property, access, and distribution of limited supplies in a large-scale outbreak.

Platform Incentives Special consideration must be given to incentives that promote platforms technologies that accelerate development times. Examples include nucleic acid vaccines, which could be leveraged to respond to a wide range of diseases, and other vaccine delivery vehicles that could shorten development times and simplify manufacturing requirements. Just as CEPI issued two separate calls: (1) a “just-in-case” list of disease-specific vaccines and (2) a “just-in-time” list of disease-agnostic platform approaches, this fund could consider proposals from both categories if and when strong

proposal do not satisfy both strategic objectives.

Competition For the sake of simplicity, we designed a prize for a single developer. However, a "winner-take-all" reward may reduce competition because other players may perceive the risk of failure to be too extreme. A "winner-take-some" approach may encourage more entrants, although it becomes more complicated to administer, raising questions about how to divide the prize among qualified candidates and how to manage subsequent entrants. It would also help limit excess market or bargaining power on the part of certain firms, preventing them from overclaiming that the disease is difficult or costly to invent and produce. If so, the money goes to providing full funding for the four other opportunities. This would provide firms with more incentive to honestly reveal that their segment is promising. Finally, a slight restriction of funds would set up a sort of race among firms to speed development and lead to slightly quicker formation of the stockpile. While excessive racing for tightly limited funds should be avoided, some incentives for speed might be desirable.

Push Versus Pull The target here—completing phase 3 trials—is considerably narrower than the whole development path sometimes considered when innovation incentives are discussed, narrow enough that the distinction between push and pull incentives begins to collapse, meriting some clarification. Pull funding differs from push in two important dimensions. First, for staged projects, each stage might involve its own push, while a single pull incentive might try to draw the product through the combination of stages. Second, even for a single-stage project, what may be of primary importance is not the timing of the payment (up-front for push versus back-end for pull) as whether the payment is conditional on success or some other contingency (conditional with pull incentives, unconditional with push).

In the present context, pull funding could differ from push in that multiple stages—say a phase 3 trial stage followed by a stockpiling stage—could be incentivized by a single pull at the end, say contingent on the creation of the specified stockpile. Perhaps more important, the pull scheme would provide the prize only if phase 3 trials ended with a success and only if the firm successfully put together the stockpile. By contrast, a push scheme might allocate the prize payment if phase 3 trials are undertaken regardless of their outcome.

While the term “prize” seems to indicate a pull mechanism almost by definition, one can imagine modifications that bring in push elements. For example, the prize for phase 3 trials could be conditional on successfully conducting valid trials independent of what is found about the product’s efficacy.

While arguments can be made both ways, we think that the strongest arguments are on the side of maintaining the prize as a pure pull. If multiple stages are involved, the firm may be in the best position to navigate the path, assessing risks at various stages and the option value of continuing. Regarding payment for undertaking a task versus successful completion, conditioning the payment on success helps solve the classic asymmetric information problems of moral hazard and adverse selection.

In this context, the moral-hazard problem is that the firm’s expenditure and effort in undertaking the project may be difficult for a principal buying the service to monitor. A profit-maximizing firm would like to obtain the prize with as little expenditure or effort as possible. If the firm is not monitored, it may be difficult to determine whether it is shirking on the conduct of phase 3 trials a push scheme might have contracted for. But such monitoring may be difficult for an outsider. It may be easier to simply verify that the successful outcome of phase 3 trials passes review by a reputable journal or board.

The adverse-selection problem is that the firm may have better information about just how promising its candidate from earlier trials is. The firm has been working with the product and may have access to unpublished data, where the principal may at best see published data on say phase 2 trials. The firm may have inside information about the likely prospects in phase 3 trials. If a generous payment is made regardless of the phase 3 outcome, even firms with unpromising candidates may have an incentive to sign up for the program to earn the payment. If the prize is only paid conditional on a positive efficacy finding from phase 3 trials, firms with less promising candidates would be deterred, avoiding possible waste of funds. The firms who may be in the best position to do so would have to make the determination of whether the investment in phase 3 trials is worthwhile.

The presence of competing firms may be more naturally handled by a pull mechanism. Any number of firms can freely enter the process; the first one or two, say, could receive a share or the whole prize. With push funding, some pre-qualification

process or rules for dividing the pie among multiple firms would have to be devised.

That said, some arguments for integrating push elements can be offered. If firms are thought to be more risk averse than the principal, there is scope for the principal to effectively insure firms by making a more certain up-front payment, reducing the dependence of the payment on the random success outcome. In most cases, we think that firms are less risk averse than principals. Large pharmaceutical manufacturers have numerous projects whose independent outcomes aggregate up to a less variable profit stream. In addition, individual stockholders can diversify their holdings.

Perhaps a stronger argument is that the principal offering the prize may have the strongest beliefs in the possibility of an outbreak and the need for a vaccine to combat it. If firms are less certain, they may be reluctant to invest. The firm cannot engage in phase 3 trials in the absence of at least a small outbreak because there are no test subjects otherwise. The firm would be reluctant to make initial investments if it thought an outbreak was unlikely and would be inclined to wait to see one happen, slowing its response time, leading the initial outbreak to be wider spread than otherwise.

Taking this argument seriously, we could amend our proposal to say that the prize should be structured as a pure pull unless the principal has unusually strong beliefs about the likelihood of an outbreak and/or the disease is such that delay in containing its spread is unusually costly. Then consideration should be given to structuring the prize more as a push with payments for phase 3 trials regardless of efficacy determination, perhaps even with some funds drawn out of the prize fund for undertaking preparatory investments.

Nonmarket Solutions Currently, the global community relies heavily on multinational pharmaceutical companies (MNCs) to complete the last leg of development.[24] The large capital costs required to build vaccine facilities and specialized expertise required to operate them have allowed MNCs to crowd out smaller firms in the later stages of development. While MNCs are best able to manufacture vaccines at the scale and specification required to achieve licensure, they are not a reliable development partner for public interest vaccines. Vaccines account for only 11-17% of overall sales within multinational firms, which means that development dollars are in constant competition with other opportunities in the market for pharmaceuticals.[25] Even when a

vaccine is profitable, an MNC may choose to terminate the project at any time.

The disincentives for MNCs to develop epidemic vaccines are even more daunting for the reasons described above. Efforts to set the prize will put a price on MNC participation for MCM development. This exercise may reveal that MNCs are not the most efficient way to develop MCMs because opportunity costs and ROI requirements inflate the price of participation. If further research reveals that the prize must be x amount or higher, policymakers must give serious consideration alternatives to working with MNCs.

One alternative is to invest in a public capacity for post Phase 2 MCM development. One problem with this approach is that it is difficult to recruit the expertise and to replicate the accumulated know-how required for late stage development, manufacturing, evaluation, and licensure. The public sector will have to build facilities, recruit, and retain talent from an already limited pool of experts. Properly managed, however, a public facility could offer a more efficient solution to MCM development over the long run because it will not need to overcome other opportunities in the market or to make a financial return on investment. Initial attempts to build public sector capacity in the US have met with limited success (CAIDMS, Ology), but other state-run examples such as the Instituto Butantan in Brazil, or NGO-led development initiative such as PATH's development of the Menafrivac vaccine, are instructive.

If and when next-generation manufacturing technologies allow new entrants to compete with MNCs on the cost, speed, and scale, policymakers may return to market-based solutions that leverage new capabilities at a more efficient price point.

Conclusion

The unpredictability of outbreaks undermines the business case to develop emergency MCMs. Absent public support, private investment would be close to zero. Emergency MCMs pose unique economic challenges that traditional incentive schemes fail to address. To overcome this challenge, we propose a prize that is designed to de-link reward from units sold, offering stable reimbursement to incentivize private sector cooperation. The objective of this fund is to encourage manufacturers to participate in development efforts to ensure that essential medicines are available to address large scale

health emergencies.

Key questions remain for future research. A natural extension of the mechanism proposed here to multiple suppliers would be to set up a race, where the first firm to meet the conditions of the prize (producing the 300,000 dose stockpile, say) wins the specified amount (reduced by the outside investment funding the firm received along the way). Would this extension offer suitable incentives for second and third developers? Are there better modifications to incentivize appropriate entry and investment? How can new incentives be used to generate continued innovation over an initial solution?

The paper assumed the main commitment problem lies in the difficulty of agencies to commit to making a large enough payment to incentivize research, development, and production of EMCs. How important is the opposite worry that a monopoly manufacturer can ask for an exorbitant price if it holds the key to a lifesaving product? It would be useful to look at historical examples to determine if manufacturers tended to gain excess profits or make donations below cost in emergency situations.

NOTES

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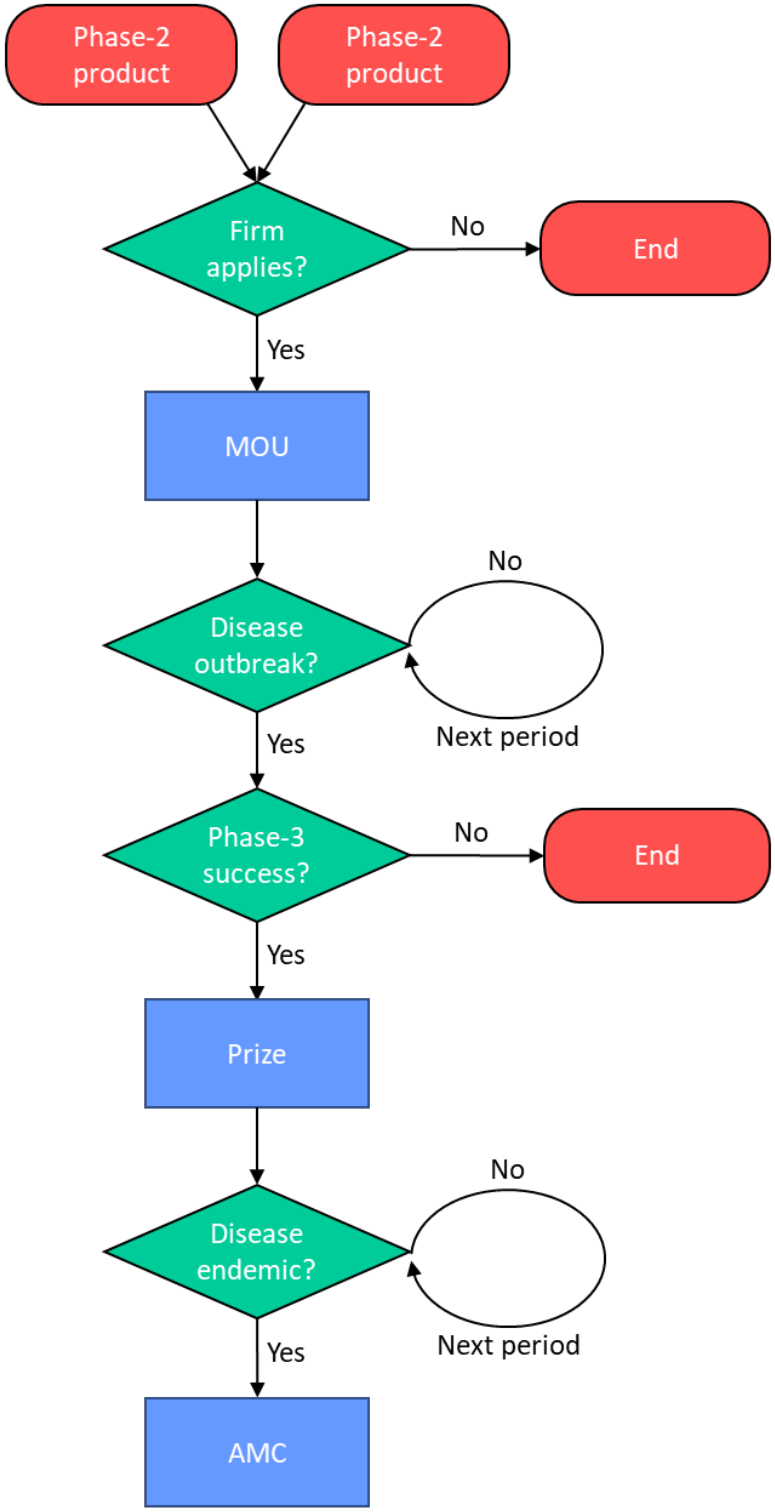
25 Ibid.

EXHIBIT 1

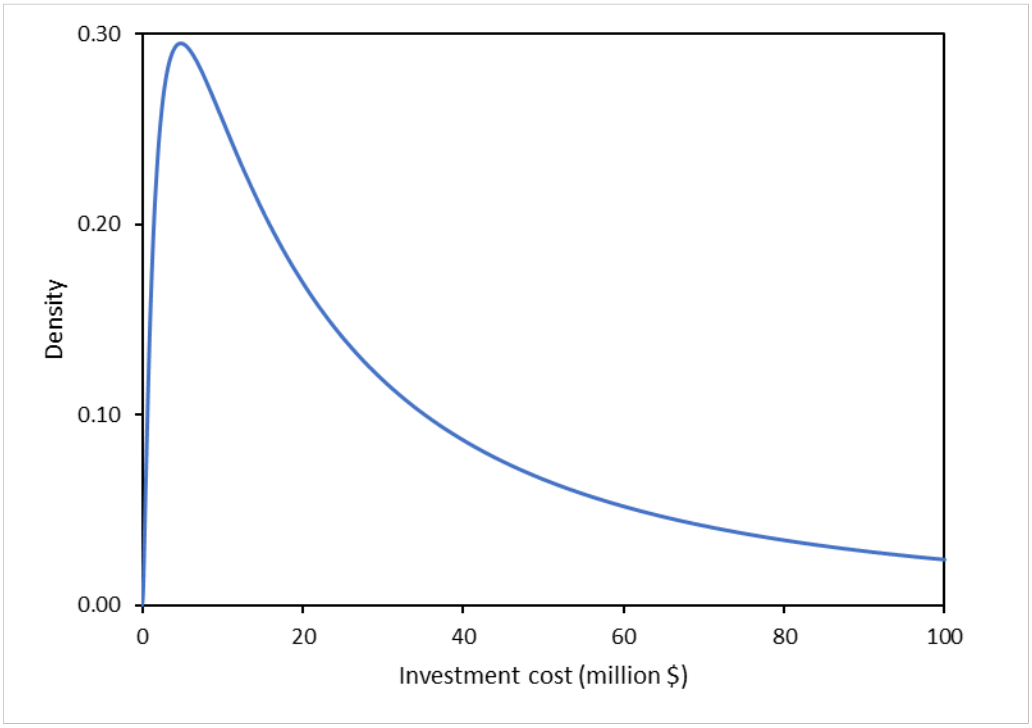
Flowchart for proposed funding mechanism



SOURCE Author synopsis of own proposal. **NOTES** Any number of firms may with promising phase-2 products may enter mechanism; we show two for concreteness. Blue rectangles show the key mechanism stages. "MOU" denotes Memoradum of Understanding and "AMC" Advance Market Commitment.

EXHIBIT 2

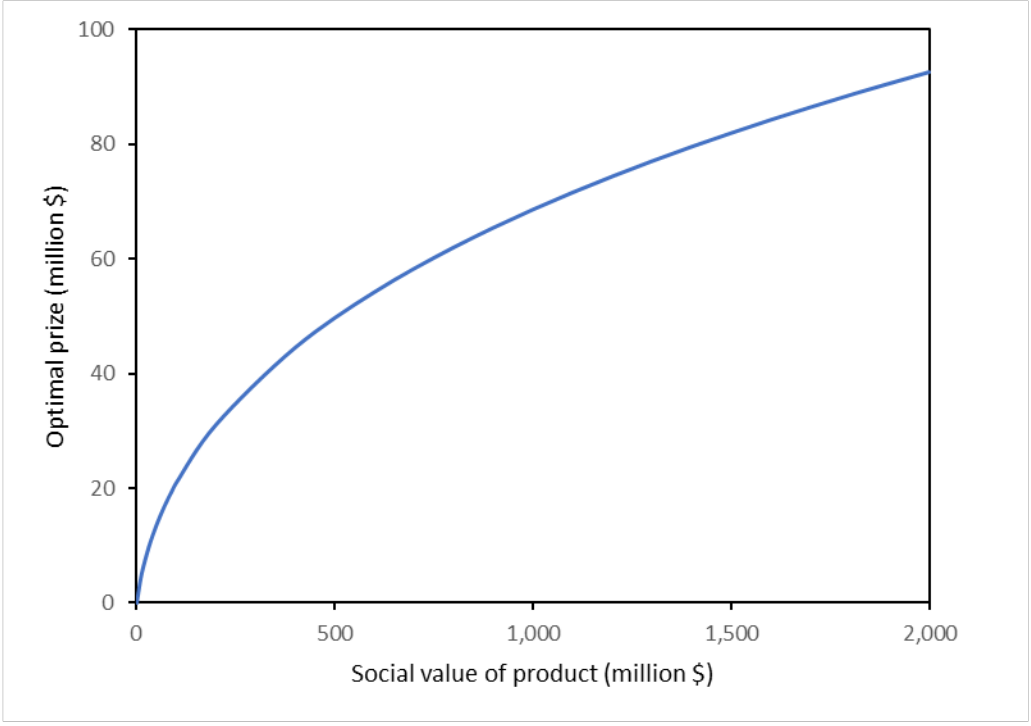
Distribution for phase-3 investment cost



SOURCE Author calculations for a lognormal random variable with parameters $\mu = 15.386$ and $\sigma = 1.353$ computed in Exhibit A1 in the appendix. **NOTES** The investment cost is denoted x in the appendix model. The probability density function drawn here, denoted $f(x)$ in the appendix, shows the relative likelihood of values of x.

EXHIBIT 3

Figure 3: Optimal prize compared to social benefit



SOURCE Author calculations based on model in the appendix. **NOTES** On the horizontal axis, we consider a grid of possible social values of the product. This is the variable denoted v in the text. The optimal prize, denoted z^*, maximizes the expected value of the social surplus net of payments to firms.

EXHIBIT 4

Optimal prize and other outcome variables for various levels of B, the social benefit from the product

Value of product, v (million $)	Optimal prize, z* (million $)	Completion probability	Expected net social surplus (million $)
0	0	0%	0
20	7	44%	6
40	12	55%	16
60	15	61%	27
80	18	65%	40
100	21	67%	53
500	50	79%	355
1,000	69	81%	757
1,500	82	82%	1,166
2,000	93	83%	1,578

SOURCE Authors' calculations as described in appendix.

Supplementary Appendix: Optimal Prize Size

Introduction

This appendix provides technical details behind the calculation of the optimal prize Z^* shown in Exhibits 4 and 5 in the text. Underlying the calculations is a principal-agent model in which the organization setting the prize plays the role of the principal and the investing firm plays the role of the agent.

Modelling Firm's Investment

To model firm investment, assume that a single firm has a vaccine that has successfully completed phase 2 trials. An outbreak of the disease has provided the firm with the opportunity to undertake phase 3 trials. The firm is faced with the decision of whether or not to invest in phase 3 trials. Investing involves out-of-pocket expenditure x but gives the firm the chance of obtaining the prize, z.

Out-of-pocket expenditure x is a continuous random variable with probability density function (pdf) $f(x)$, cumulative distribution function (cdf) $F(x)$, and support $[0, \infty)$. Assume the pdf is continuously differentiable and the cdf is logconcave. Bagnoli and Bergstrom (2005) show that this is a weaker assumption than logconcavity of the pdf. They prove that a random variable with a continuously differentiable, logconcave pdf has a logconcave cdf. The converse is not true: they prove that the cdf of a lognormal random variable is logconcave but the pdf is not. The lognormal will be a leading special case for us, which our assumption of logconcave cdf admits.

The investment cost is private information for the firm. The firm sees the realization x before undertaking investment; the principal does not see the realization, but the distribution $F(x)$ is common knowledge.

If the firm invests, with probability p phase 3 trials end in success and the firm obtains prize z. With probability $1 - p$, the phase 3 trials end in failure and no prize is paid.

The prospect of merely recovering its out-of-pocket expenditure is not sufficient to induce the firm to invest. This is true for two reasons. First, the firm faces a positive cost of capital, which must be covered with a profit margin. Second, the investment must

be undertaken well in advance of the prize payout. To put dollars spent early on the same footing as dollars earned later, the capital cost must be compounded over the period in between. Let r be the extra return required on out-of-pocket expenditure x over the investment period treated as the unit of time (whether it be one year, two years, or more) that would make the firm just willing to invest.

The firm, assumed to be risk neutral, undertakes investment if the expected prize exceeds the required return on investment, i.e., if

$$pz \geq (1 + r)x. \tag{A1}$$

Rearranging, the condition becomes

$$x \leq \frac{pz}{1 + r}. \tag{A2}$$

The probability that (A2) occurs—equivalently that the firm invests—equals $F(pz/(1 + r))$.

Modelling Principal's Prize Setting

To model the prize-setting behavior of the principal, assume that the principal obtains gross value v in monetary terms if phase 3 trials end in success. The principal prefers not to spend money, suffering a dollar of disutility for each dollar spent. Firm profit does not enter the principal's objective function. The principal could be a donor organization that cares about its mandate and budget but is indifferent to firm profits. If the principal is a government, the firm could be a pharmaceutical manufacturer in a different country, in which case again the principal may be indifferent as to its profits. The fact that the principal does not take into account the firm's welfare means that the principal is not fully benevolent.

The expectation of the principal's net surplus equals

$$F\left(\frac{pz}{1 + r}\right)p(v - z), \tag{A3}$$

the probability the firm undertakes investment times the probability of phase 3 success conditional on investment times net social surplus in the event of success. Imposing the

change of variables $\tilde{v} \equiv pv/(1+r)$ and $\tilde{z} \equiv pz/(1+r)$ and taking logs generates the following objective function, equivalent to (A3):

$$\ln(1+r) + \ln(\tilde{v} - \tilde{z}) + \ln F(\tilde{z}). \tag{A4}$$

Under the maintained assumptions, (A4) is concave in $\tilde{z}$ for all $\tilde{z} \in (0, \tilde{v})$. To see this, obviously the first term is constant in $\tilde{z}$. Direct differentiation can be used to verify that the second term is strictly concave in $\tilde{z}$ for all $\tilde{z} \in (0, \tilde{v})$. The last term is concave since F is logconcave.

The first-order condition for the optimal $\tilde{z}^*$, which maximizes (A4), can be written, after rearranging,

$$(\tilde{v} - \tilde{z}) f(\tilde{z}) - F(\tilde{z}) = 0. \tag{A5}$$

The concavity of (A4) is necessary and sufficient for the solution to (A5) to be a unique optimizer, $\tilde{z}^*$, of (A4). This implies (A3) has a unique optimum, z^*.

Comparative Statics

The implicit function theorem can be used to determine the effect of an increase in v on z^*:

$$\frac{\partial \tilde{z}^*}{\partial \tilde{v}} = -\frac{\partial(\text{A4})}{\partial \tilde{v}} \Big/ \frac{\partial(\text{A4})}{\partial \tilde{z}} \propto \frac{\partial(\text{A4})}{\partial \tilde{v}} = f(\tilde{z}^*) > 0. \tag{A6}$$

The second step follows from the concavity of (A4) in $\tilde{z}$, implying that (A5) is decreasing in $\tilde{z}$, in turn implying that the denominator is negative, implying that the fraction has the same sign as the numerator (as the symbol $\propto$ denotes). The third step follows from differentiating (A5) and the last step from the support of c including the positive real numbers. Now

$$\frac{\partial z^*}{\partial v} = \frac{\partial \tilde{z}^*}{\partial \tilde{v}} \cdot \frac{\partial \tilde{v}}{\partial v} \cdot \frac{\partial z}{\partial \tilde{z}} = \frac{\partial \tilde{z}^*}{\partial \tilde{v}} \cdot \frac{1+r}{p} \cdot \frac{p}{1+r} = \frac{\partial \tilde{z}^*}{\partial \tilde{v}}, \tag{A7}$$

implying $\partial z^*/\partial v > 0$ by (A6).

In words, we have just shown the intuitive result that an increase in the value of the product will lead the principal to set a higher optimal prize holds in the model.

Aside on Success Probability

Our simple model takes the success probability to be a single parameter p that is common knowledge for all actors in the model. Other authors have adopted a more complex treatment of this probability. For example, Gouglas, *et al*. (2018) assumes that p is itself a random variable, which they assume has a triangular distribution.

It turns out that our simple treatment does not impair the generality of our results as long as it is assumed that no actor is risk averse or has private information about p. We believe these assumptions are practically realistic. We also believe that other authors who have incorporated the probability of trial success into stochastic models of investment behavior have implicitly adopted these assumptions. Although they are not explicit about which assumptions on these matters they have adopted, as discussed below, it is unlikely they adopted any alternative.

To see that the simple assumption suffices, return to the firm's investment decision in (A1) and (A2). Let p be a random variable with mean $\bar{p}$. The analysis would be identical except that $\bar{p}$ would be substituted everywhere for p. The mathematical principle behind this result is that the probability enters linearly in expectation (A1). For linear functions of a random variable, the expectation of the function equals the function of the mean of the random variable. Moving to the principal's objective function in (A3), $\bar{p}$ should appear in the argument of F since this is inherited from (A2). After making this substitution, we see that (A3) is linear in p in the remaining place it appears, so the by the argument just made, the expectation over a random value of p is mathematically equivalent to the expression with mean $\bar{p}$ substituted there.

If one of the actors were risk averse, modeled as the actor's having a concave objective function, then by Jensen's inequality, it would not be correct to substitute the mean into the expectation. The expectation would have to be computed by integrating the concave function weighted by the density of p. The integral would be sensitive to the precise functional form adopted for the objective function. Sensitivity analysis or an extensive discussion of the precise functional form assumed would be merited. Since this discussion is absent from papers undertaking a similar modeling exercise as ours, we believe they have implicitly assumed risk neutrality.

If one of the actors were to have private information about p, this creates an asymmetry among the actors. The proper analysis differs depending on who has the private information and when they learn it. For example, the analysis would be different if the firm learned all the success probabilities for the entire sequence of trial phases up front than if it learned each right before the stage is undertaken. Since other authors have not specified these details, we suspect that their analysis is either inconsistent or makes the simple, consistent assumption of no private information. In any event, while it may add realism to assume the firm has private information about its costs, the same argument may not apply to success probabilities, about which the principal may have as much information as firms.

Calibrating Parameters

Let (m, s) denote the mean and standard deviation of x. Several studies provide estimates of the moments of the distribution of costs of bringing a product through various trial phases. To the best of our knowledge, Gouglas, *et al.* (2018) is the most relevant for our purposes because it uses the most recent data and covers the relevant product—vaccines against epidemic diseases.

The authors provide several versions of the estimates. We take the mean and standard deviation for the cost distributions from the first panel of their Table 3, the panel based on self-reports of costs from a survey of firms with a track record of previous product licensure. We judged these reports to be more accurate than those from the firms without a previous track record reported in the lower rows in their Table 3, guessing from the discussion in the article that the lower values reported by firms without a track record were due to their missing cost categories that experienced firms knew to be important.

Unfortunately, Gouglas, *et al.* (2018) do not report the cost distribution for phase 3 trials in their published paper or appendix, stopping at phase 2. We circumvent this problem by using information from an additional source. To clarify the discussion of the underlying calculations, we introduce subscripts on the parameters to distinguish the phase to which they apply. In particular, the mean and standard deviation of the cost distribution is denoted (m_2, s_2) for phase 2 trials, (m_3, s_3) for phase 3 trials, and (m_t, s_t) for trials for some arbitrary phase t. Exhibit A1 provides a summary of the calculations.

Using information from Wong and Jessup (2014), we can glean the ratio of the parameters between phase 2 and phase 3 trials. The ratio of (m_2, s_2) to (m_3, s_3) in that article provides scale factors that can be used to project the values of (m_2, s_2) from Gouglas, *et al*. (2018) to the values of (m_3, s_3) displayed in Exhibit A1. More specifically, according to Table 3 of Gouglas, *et al*. (2018), $m_2 = \$28.0$ million and $s_2 = \$26.2$ million. According to Table 2 of Wong and Jessup (2014), $m_3/m_2 = 1.5$ and $s_3/s_2 = 3.4$. We therefore obtain $m_3 = \$28.0 \text{ million} \times 1.5 = \$42.0 \text{ million}$ and $s_3 = \$26.2 \text{ millon} \times 3.4 = \$230.2 \text{ million}$.

An alternative approach would just be to take (m_3, s_3) directly from Wong and Jessup (2014). We are concerned about the applicability of their estimates for our purposes. First, those authors are focused on general pharmaceuticals rather than vaccines against epidemic diseases, which might have a different cost structure. More importantly, those authors explicitly omit the cost of manufacturing the tested product. Given the expense in setting up a plant to produce vaccines for phase 3 trials, we judged Wong and Jessup (2014) could be a severe underestimate. Validating this concern, comparing the overlapping estimates of the distributional parameters for phase 1 and 2 trials from Gouglas, *et al.* (2018) to those from Wong and Jessup (2014), we see the former are nearly an order of magnitude higher than the latter. On the other hand, there is no obvious reason why the ratios m_3/m_2 and s_3/s_2 should be biased scale factors since numerator and denominator both apply to general therapeutic classes and both omit manufacturing costs.

While Gouglas, *et al*. (2018) provide the mean, variance, and other statistics for the cost distributions, they do not specify the distribution's functional form. We argue that the lognormal distribution provides perhaps the best approximation. It has the useful feature that it does not produce negative values of cost that would need to be artificially truncated. By Bagnoli and Bergstrom (2005), it satisfies the assumption that the cdf $F(x)$ is logconcave. Furthermore, the lognormal with the given mean and standard deviation maps well into the other statistics given in their Table 3.

Textbook formulas can be used to convert moments (m, s) into the standard parameters (μ, σ) given for a lognormal distribution. To be clear, (m, s) are the mean and standard deviation for the lognormal random variable x, as distinct from (μ, σ), the mean

and standard deviation of $\ln x$, which has a normal distribution. Dispensing with subscripts no longer needed to distinguish among different trial phases, we can substitute $m = \$42.0$ million and $s = \$230.2$ million into the formulas

$$\mu = \ln\left(\frac{m^2}{\sqrt{m^2 + s^2}}\right) \tag{A7}$$

$$\sigma = \sqrt{\ln\left(1 + \frac{s^2}{m^2}\right)} \tag{A8}$$

to obtain $\mu = 15.386$ and $\sigma = 1.353$.

The remaining parameters to be calibrated are p and r. A credible estimate of p is provided by Table 2 of the comprehensive study by Wong, Siah, and Lo (2019). In particular, the entry $p = 0.851$ in the row for vaccine-lead indications seems the most relevant for our purposes.

To calibrate r, assume that the out-of-pocket expenditure x is made continuously at a constant rate over the duration of phase 3 trials. Table 4 of DiMasi, Grabowski, and Hansen (2016) shows that the average duration of a phase 3 trial is 45.1 months, or 3.76 years. They estimate annual capital costs for pharmaceutical firms of 10.5%, quite close to other estimates in the literature summarized in their Table 1. Substituting those numbers into a formula for compounding of continuous rate of expenditure, r must satisfy

$$1 + r = \frac{1}{3.76}\int_0^{3.76} e^{0.105t}\, dt. \tag{A9}$$

Solving (A9) yields $r = 23\%$.

Results

We are not aware of a closed-form solution to the first-order condition (A4). Instead, we apply numerical methods to maximize (A2) directly after substituting the parameters from the previous section. The results are reported in Exhibits 3 and 4 in the text.

Having calculated optimal prize size, other interesting variables can easily be computed as well. The third column of Exhibit 4 in the text shows the completion probability, which equals the probability that the firm invests, $F(pz^*/(1+r))$ times the probability of success p conditional on investment. The last column shows the expected net social benefit, which nets out the prize payment from v and incorporates the probability that the firm invests and the project succeeds. It equals the value of objective function (A2) evaluated at the optimal prize level z^* or, equivalently, the difference between the first and second columns of the exhibit multiplied by the third.

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Wong H-H, Jessup A. Examination of clinical trial costs and barriers for drug development. Washington (DC): U.S. Department of Health and Human Services, Assistant Secretary of Planning and Evaluation; 2014.

Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019; 20(2):273–86.

Exhibit A1

Calibration of Parameters for Optimal Prize

	Phase-2 trials (t = 2)		Phase-3 trials (t = 3)	
Parameter	**Value**	**Source**	**Value**	**Source**
m_t	28.0 mil	G	1.5 x m_2 = 42.0 mil	WJ
s_t	26.2 mil	G	3.4 x s_2 = 230.2 mil	WJ
μ_t	16.833	A	15.386	A
σ_t	0.793	A	1.353	A
p_t	0.571	WSL	0.851	WSL

SOURCES Provided in table according to following key. G stands for Table 3 of Gouglas, *et al*. (2018); WJ stands for for Table 2 of Wong and Jessup (2014); WSL stands for Table 2 of Wong, Siah, and Lo (2019); and A stands for author calculations based on equations (A7) and (A8).