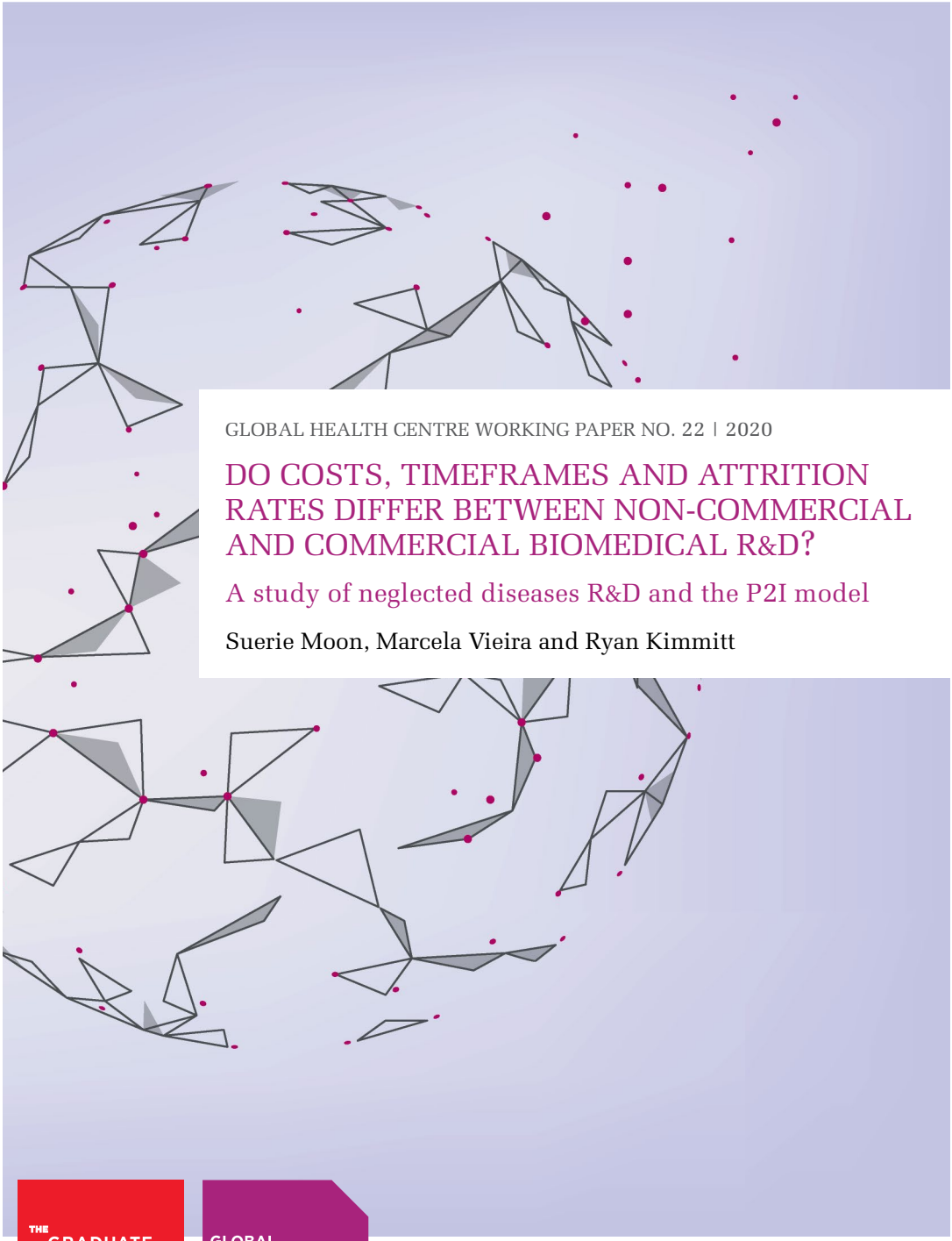

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DO COSTS, TIMEFRAMES AND ATTRITION RATES DIFFER BETWEEN NON-COMMERCIAL AND COMMERCIAL BIOMEDICAL R&D?

A study of neglected diseases R&D and the P2I model

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GLOBAL HEALTH CENTRE

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Abbreviations	
CPI-U	Consumer Price Index (for all urban areas)
CROs	Contract research organizations
DNDi	Drugs for Neglected Diseases initiative
EUR	Euros
LMIC	Low- and middle-income countries
LOA	Likelihood of approval
MMV	Medicines for Malaria Venture
NCE	New chemical entity
ND	Neglected diseases
P2I	Portfolio-to-Impact tool
PO	Participating Organization
PDP	Product development partnerships
R&D	Research & development
TDR	UNICEF- UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases
USD	United States Dollars

EXECUTIVE SUMMARY

Do costs, timeframes and attrition rates differ from commercial and non-commercial biomedical R&D? A study of neglected diseases and the P2I model

Introduction: The question of the costs and efficiency (i.e. timeframes and attrition rates) of biomedical research & development (R&D) has long been of interest to scholars, industry practitioners and policymakers alike. The past two decades have witnessed significant growth in non-commercial R&D initiatives, particularly for neglected diseases, which predominantly affect people in low- and middle-income countries (LMICs). We defined "non-commercial" R&D initiatives as those undertaken with a not-for-profit purpose. Understanding is limited, however, of the ways in which these alternate business models compare with traditional commercial R&D, particularly in terms of their overall costs, timeframes and attrition rates. This study compared existing non-commercial R&D initiatives to the averages used in the Portfolio-to-Impact (P2I) v2.0 model on these three parameters. The P2I averages are derived from historical data mostly from commercial R&D for a range of diseases. A literature review was conducted to compare P2I averages with other published estimates.

Data: We contacted 48 non-commercial R&D initiatives to request participation in the study, and received quantitative data from 8 organizations on 83 candidate products, and qualitative data through 14 interviews with 20 individuals from 12 organizations. Compared to data available on commercial initiatives and data points used to construct averages in the P2I Model, the sample size was very small and was better suited for hypothesis generation than drawing firm conclusions. We limited our analysis of the quantitative data to simple and complex new chemical entities due to data limitations. Qualitative data aimed to compare non-commercial R&D to commercial R&D in general.

Quantitative and qualitative results: Regarding costs, the collected quantitative data compared to P2I averages suggested that non-commercial R&D total costs are slightly higher for simple and slightly lower for complex new chemical entities (NCEs), with variation by phase.

The qualitative data identified many more reasons why non-commercial costs would be *lower* than commercial R&D, but did not shed light on the magnitude of the effects. The overall emerging hypothesis is that direct costs of non-commercial R&D are expected to be *equivalent or somewhat lower* than commercial. Indirect costs for commercial R&D are expected to be higher due to higher overhead and costs of capital.

Regarding **timeframes**, the quantitative data suggested that non-commercial R&D timeframes would be slightly *shorter* for simple NCEs and *equivalent* for complex NCEs. Yet the qualitative data identified many more reasons why non-commercial timeframes would be *longer* than commercial; the data did not shed light on the magnitude of the effects. The overall emerging hypothesis is that timeframes of non-commercial R&D are expected to be *equivalent or somewhat longer* than commercial.

Regarding **attrition** rates, the quantitative data was not adequate for analysis. The qualitative data uncovered more reasons why attrition rates might be higher in non-commercial R&D, but also provided a number of reasons why there might be no difference. Again, the magnitude of the effects are not quantified. The overall *very tentative* hypothesis that emerges is that attrition rates for non-commercial R&D would be *equivalent* to commercial R&D.

Discussion, study limitations and conclusions: The study found that non-commercial R&D differs in many significant ways from its commercial counterparts. However, it is possible that the sum of these differences cancelled each other out such that total costs, timeframes and attrition rates were largely equivalent to P2I averages. If non-commercial R&D is characterized by equivalent or lower direct costs, equivalent or longer timeframes, and equivalent attrition rates to commercial R&D, the final expected direct costs and quantity of products resulting from a pipeline of non-commercially-developed candidate technologies would largely be equivalent to those resulting from commercial R&D. In other words, the estimated parameters of the P2I v2.0 model are supported by this analysis. That said, there are a number of significant differences between non-commercial and commercial R&D that were highlighted by this study. We note that the P2I model relies heavily on technology archetypes (e.g. repurposed molecule vs. simple NCE vs complex NCE for drugs) to assign costs, timeframes and attrition rates to candidate products in the pipeline.

However, coding candidates into these archetypes was not straightforward, even for organizations that knew their own technologies very well. Furthermore, the P2I Model was found to be less well-suited for modelling the development of products in combination or regimens, or for products that do not follow a linear development process or require more than one study per phase of development.

In total, we identified 12 factors influencing costs, 12 factors influencing timeframes, and 9 factors influencing attrition rates for non-commercial R&D. Some of these echoed those already identified in the literature on commercial R&D, but many of them were specific to non-commercial initiatives. These many factors suggest that the P2I model may need to be modified when applied more narrowly: differences may get averaged out when the model is applied to a pipeline of nearly 450 candidates across a broad range of diseases (its intended use), but differences are significant in the narrower context of a single disease, technology type, or organization. The many variables that affect cost, timeframes and attrition rates also highlight that caution is merited when comparing any single trial, product or organization against averages, as there are many legitimate reasons behind divergence from the mean.

Finally, we re-emphasize that the small size and heterogeneity of the dataset means that these are *tentative* conclusions. Further quantitative research is needed to test these hypotheses against larger datasets. And further qualitative research is needed to deepen our understanding of the strengths and weaknesses of non-commercial R&D initiatives, and how well they function as alternatives to the traditional commercial model, particularly in disease areas with high commercial interest.

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1. INTRODUCTION

The question of the costs, timeframes and attrition rates of biomedical research & development (R&D) has long been of interest to scholars, industry practitioners and policymakers alike. Understanding these factors is important for assessing the productivity and efficiency of R&D efforts. It is also critical for guiding public and organizational policies that shape R&D.

These questions have recently gained increased salience in light of concerns about the potentially declining productivity of commercial R&D; missing technologies in areas of "market failure" or where standard market incentives are insufficient, such as antibiotics or products for neglected diseases of poverty and outbreak-prone pathogens; and the high and rising prices of medicines such as those for cancers or rare diseases. Improved understanding of the biomedical R&D process is essential to address these societal challenges.

Relatedly, the question has arisen as to whether different approaches to organizing, financing or incentivizing R&D – sometimes referred to as "alternate" or "new" business models of R&D – can address some of the shortcomings of the traditional approach. One area where there has been significant experimentation in alternate business models is the neglected diseases (ND) (alternately, neglected tropical diseases or poverty-related neglected diseases), which predominantly affect people in low- and middle-income countries (LMICs). It has long been recognized that commercial R&D models did not and would not generate innovative technologies for these diseases because the market incentive is inadequate to do so (1). In addition to (usually early-stage) research taking place in academic or public institutes, later-stage product development for NDs has received increased funding and attention since the turn of the millennium through the creation of about two dozen product development partnerships (PDPs) (2). With at least two decades of significant non-commercial R&D efforts behind us, it is an opportune moment to examine more closely how they compare to traditional commercial R&D on costs and efficiency.

The study presented here sought to contribute to the knowledge base by gathering and analysing evidence on the costs, timeframes and attrition rates of "non-commercial" R&D initiatives and analysing how they compared to averages in the P2I Model, derived from historical data mostly from commercial R&D.

We define "non-commercial" R&D initiatives as *those undertaken primarily with a not-for-profit purpose*. Often, the lead organizations of such initiatives are academic or governmental in nature, or non-profit PDPs. For-profit firms frequently play a role in these initiatives. Therefore "non-commercial" should not be interpreted as excluding the private sector. Rather, private firms frequently collaborate by providing not-for-profit partners with access to compound libraries, technical expertise, and/or products for use in testing, among other in-kind contributions. However, these initiatives are not part of the firm's core commercial portfolio or strategy, as they are not expected to generate significant (if any) market revenue. Furthermore, we prefer to use the broader term "non-commercial" rather than "non-profit" as in some cases a developer may earn profit or revenue on a product as a way to offset costs (e.g. through the US Priority Review Voucher), even if the overall nature of the initiative is non-commercial.

We relied on the database of pipeline technologies for NDs developed by the Portfolio-to-Impact (P2I) tool, a project of the UNICEF- UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR) (see further description under Methodology below). While the database does not include all non-commercial R&D initiatives – for example, it excludes biodefense projects that are largely publicly-funded – it is the most comprehensive database of which we are aware focusing on R&D for neglected diseases, which is by nature largely non-commercial.

The P2I model was initially developed in 2015–6 by TDR (3) and adapted in 2017–8 by Duke University and Policy Cures Research (4) to predict which ND products could reasonably be expected to reach the market from the existing pipeline, and the estimated associated costs. A description of the original modelling tool (5) and its adaptation and application to NDs is available elsewhere (4). This project was undertaken as part of a TDR-led consortium of organizations that conducted further analysis of the P2I model throughout 2019.

The underlying assumptions (i.e. on cost, length per development phase, and project attrition rates from preclinical to Phase 3) that drove the P2I model in both versions 1 and 2 were derived from historical data on health product development on all diseases, not only NDs. Given that non-commercial R&D (at least late-stage product development) is both relatively recent and small in scale, we assume that the vast majority of the data used to construct the P2I averages comes from commercial R&D. We conducted a literature review on costs, timeframes and attrition rates to allow for comparison with the averages built-in the P2I Model.

Finally, the specialized literature suggests that there are important differences between commercial and non-commercial R&D such as the PDPs (6–9) (see further description of the literature below). Our study sought to examine whether these differences mattered for the costs, timeframes or attrition rates for product development. We did not find any studies that had systematically examined this question across multiple products from different non-commercial R&D initiatives, and concluded that further data collection and analysis was needed.

This study did not compare the patient, population-level, equity or health system benefits offered by the products emerging from non-commercial vs commercial initiatives.

2 | LITERATURE REVIEW

Pharmaceutical firms, investors, and policymakers have an interest in understanding how effectively and efficiently R&D processes are working, and there is a considerable literature on costs, timeframes, and attrition rates of biomedical R&D.

Most of the literature focuses on the development of new chemical entities (NCEs) by pharmaceutical companies (commercial R&D), with a growing literature on biologics (including but not limited to vaccines).There is some analysis of specific non-commercial R&D initiatives (10–17), but we did not find any studies examining costs, timeframes or attrition rates across more than one initiative.

There is a wide range of estimates regarding costs, timeframes and attrition rates of biomedical R&D (see Tables 1, 2 and 3 below for a summary)[1]. This range can be explained by the broad variety of methods, data sources and time periods covered in the studies. Estimates also vary depending on other factors, including: the type of technology under development, the therapeutic area, diversity of the portfolio, the kind of data required for regulatory approval, the type and size of the organization leading the development process and the type of expenses that are included as R&D costs, among other factors (a detailed discussion follows in the Qualitative Results section of this report).

[1] A full version of the research syntheses on costs, timeframes and attrition rates in the pharmaceutical sector are available at the Knowledge Portal on Innovation and Access to Medicines at: https://www.knowledgeportalia.org/cost-of-r-d and https://www.knowledgeportalia.org/r-d-time-success.

Modelling tools are used to estimate how much it would cost and how long it would take to develop health products, as well as how many candidates need to be in each phase of development to result in one successful product. They are designed as portfolio management tools, more than to estimate individual projects costs, timeframes and attrition rates, but assumptions in modelling tools have been used as benchmarks for individual projects. The P2I model is one such tool. It has built-in assumptions on costs, timeframes and attrition rates used to calculate how much it would cost, how long would it take and how many products are expected to be launched in a given period of time. The Model considers four stages of product development: preclinical, phase 1, phase 2 and phase 3, with built-in assumptions for each of these phases. The assumptions vary according to 14 product archetypes. For the purpose of this literature review, we included in comparison tables (Tables 1, 2 and 3) only the assumptions for two archetypes: NCE-simple and NCE-complex. The assumptions for the other archetypes are available in the original papers. A brief synthesis of the most relevant recent studies and how they compare with P2I averages is presented below.

a. Costs

A number of studies have estimated the costs to bring a medicine to market, with averages ranging widely. The vast majority of the literature focuses on development costs (clinical stage), with less information available on research costs (discovery and preclinical stage). Almost all studies are related to new drugs, with less data available for other types of medical products and devices. And almost all data are from pharmaceutical companies, with only four papers providing some data from other types of organizations conducting product development. A summary is provided in Table 1 on the next page, with a focus on papers that provide costs broken down per phase.

Table 1: Recent estimates of new drug development costs by phase for commercial R&D and non-commercial R&D compared to P2I averages (millions of USD)

Paper	Period	Sample size	Capitalized/ rate	Preclinical	Phase 1	Phase 2	Phase 3
Mestre-Ferrandiz et al. (2012) (18)[1]	In clinical development between 1998–2002	97 projects conducted by pharmaceutical companies	No	$76.5	$236.3	$316.9	$235.9
			Yes, 11%	$207.4	$468.1	$501.6	$293.8
DiMasi et al. (2016) (19)	Compounds first test in human from 1995–2007 and R&D expenditures from 1990–2013	106 new drugs from 10 multinational biopharmaceutical companies of varying sizes	No	$430	$25.3	$58.6	$255.4
			Yes, 10.5%	$1,098	$49.6	$95.3	$314
Sertkaya et al. (2014) (20)[20]	2004–2012	Industry-sponsored trials conducted in the US	No	–	$ 3.4	$13.6	$21.8
Jayasundara et al. (2019) [21]	Drugs approved between 2000–2015	100 non-orphan drugs / 561 trials (only NMEs) – all sponsors (mostly industry)	No	–	$2.81	$7.0	$25.75
			Yes, 10.5%	–	$5.16	$11.11	$34.82
		100 new orphan drugs and / 602 trials (only NMEs) – all sponsors (mostly industry)	No	–	$4.27	$20.86	$20.02
			Yes, 10.5%	–	$9.61	$39.87	$30.35
DNDi (2019) (11) [3]	2003–2019	2 new chemical entities	No	$ 14.9	$ 4.3	$ 32.9	
P2I Model (NCE-Simple) (4)	2007–2014	3,655 candidates	No	$ 5.0	$2.2	$5.8	$32.8
P2I Model (NCE-Complex) (4)	2007–2014	18,851 candidates	No	$ 10.0	$7.4	$ 6.4	$36.1

Legend: White = commercial or mostly commercial; Yellow = non-commercial; Green = P2I Model averages

[1] Mestre-Ferrandiz et al. does not use the standard division of the R&D into phases, but instead use the following intervals: Interval 1. Pre-first toxicity dose, Interval 2. First toxicity dose to first human dose, Interval 3. First human dose to first patient dose, Interval 4. First patient dose to first pivotal dose, Interval 5. First pivotal dose to first core submission, Interval 6. First core submission to first core launch. For the purpose of this table, we considered interval 1 as preclinical, intervals 2 + 3 as phase I, interval 4 as phase II, interval 5 as phase III and interval 6 as approval. Total includes approval, not included in the table. (2) Original figures are broken down in 13 different therapeutic areas; we calculated a simple average to include all drugs. (3) We included a simple average of the costs provided for two new chemical entities. Preclinical includes discovery costs. Costs for phase II and III are combined and include registration costs. Total costs are only for two candidates and does not include cost of failures. Original figures are in euros; exchange rate: 1.12 USD/EUR.

Cost estimates available in the literature vary significantly. Differences in methodology, data sources, scope and period of analysis can account for some of those differences, while a lack of transparency in the underlying data limits the ability to compare studies. Some estimates are adjusted for inflation and others are not, and some include only out-of-pocket costs while others add cost of capital. Estimates might also differ in the extent to which they include the cost of failed projects. An analysis of the differences in estimates is beyond the scope of this paper. For the purpose of this project, it is worth nothing that P2I cost averages per phase are comparable to the low range of cost estimates available for commercial R&D estimated by Sertkaya et al. (20) and Jayasundara et al. (21), and much lower than the estimates by Mestre-Ferrandiz et al. (18) and DiMasi et al. (19). Estimates from DNDi (11), a non-commercial organization, are similar to the P2I Model averages.

b. Timeframes

The timeframes for drug development are generally calculated as an adjusted continuous timeframe, that is, the total amount of time from the beginning of preclinical testing to the regulatory approval of a drug. A continuous timeframe also allows for estimating capitalized costs over the duration of a drug's development. As per DiMasi et al. (1991) (22), phases are either truncated (if a phase's testing extends past the beginning of the next phase) or extended (if there is a gap between the end of one phase and the beginning of another). (See a more in-depth discussion of methodologies in the section Quantitative Results in this report.)

There are several timeframe estimates that have been published in recent years. Most of the literature focuses on the development of medicines and on the clinical development stage of the process. The literature is dominated by pharmaceutical industry data and projects related to the development of drugs, with some studies providing information disaggregated by therapeutic class. A summary of most recent studies and a comparison with P2I averages for NCEs is provided in Table 2. We did not find any study with development timeframes of NCEs by non-commercial R&D initiatives.

Table 2: Recent estimates of drug development timeframes by phase compared to P2I averages (in months)

Study	Sample Size	Time Period	Phase 1	Phase 2	Phase 3
Abrantes-Metz, Adams, Metz (2004) (23)	27,987 drug entities	1980–2004	22.1	34.0	44.9
DiMasi, Grabowski, Hanson (2016) (19)	106 new drugs	1990–2010	19.8	30.3	30.7
Martin (2017) (24)	>17,000 interventional studies	2006–2015	32	39	40
Wong, Siah, Lo (2019) (25)	406,038 data points	2005–2015	19.2	34.8	45.6
P2I Model (NCE-Simple) (4)	3,655 candidates	2007–2014	30	21.6	40.8
P2I Model (NCE-Complex) (4)	18,851 candidates	2007–2014	34.8	22.8	42

Compared to the identified published literature, averages from the P2I Model for NCEs are somewhat longer for phase 1, shorter for phase 2 and within the same range for phase 3 trials.

c. Attrition (success/failure) rates

Attrition rates – alternately referred to as either failure, or conversely, success rates – are considered a key parameter for understanding the efficiency of R&D, but methods to calculate these rates vary. Individual phase success rates have been calculated as the number of candidates that pass a trial in that phase, divided by the total number of candidates that entered the phase. As with costs and timeframes, available estimates for attrition rates are mostly for new drug development conducted by pharmaceutical companies. Table 3 below provides a summary of the studies and a comparison with P2I averages for NCEs.

Table 3: Recent estimates of phase success rates of drug development compared to P2I averages

Study	Sample Size	Time Period	Phase 1	Phase 2	Phase 3
Abrantes-Metz, Adams, Metz (2004) (23)	27,987 drug entities	1980–2004	81.0%	57.0%	57.0%
Kola and Landis (2004) (26)	10 pharmaceutical companies	1991–2000	68.5%*	38.0%	55.0%
Hay et al. (2014) (27)	850 pharmaceutical organizations	2003–2011	64.5%	32.4%	60.1%
Smietana et al. (2016) (28)	9,200 compounds in development	1996–2014	52.0%*	39.0%*	67.0%*
BIO (2016) (29)	9,985 phase transitions	2006–2015	63.2%	30.7%	58.1%
Wong, Siah, Lo (2019) (25)	406,038 data points	2005–2015	66.4%	48.6%	59.0%
P2I Model (NCE-Simple) (4)	3,655 candidates	2007–2014	60.0%	39.0%	69.0%
P2I Model (NCE-Complex) (4)	18,851 candidates	2007–2014	57.0%	20.0%	40.0%

*Exact figures are not given, but approximate data is taken from figures or calculated from given information.

Compared to the identified published literature, the P2I averages are lower than other estimates for complex NCEs (especially in phases 2 and 3) and in the same range for simple NCEs.

d. Non-commercial initiatives

We also reviewed the literature on non-commercial R&D initiatives. We did not find any study comparing costs, timeframes and attrition rates across different non-commercial organizations engaged in health product development. However, a growing body of literature exists on Product Development Partnerships (PDPs),[2] which are non-commercial organizations created from the mid-1990s to address market failures for unmet health needs (mostly for NDs). The goal of PDPs is to develop new, public health-oriented medical products tapping into the research and development assets and skills of multiple actors. By

[2] A full version of the research synthesis on Product Development Partnerships – PDPs is available at the Knowledge Portal on Innovation and Access to Medicines at: https://www.knowledgeportalia.org/product-development-partnerships.

providing an international framework for coordinating infectious disease research activities in the 1970s–80s, TDR laid the groundwork for the emergence of PDPs. PDPs are frequently referred to as "virtual organizations" (2) since they do not usually engage in hands-on R&D activities but instead coordinate and collaborate with partners who perform said activities.

Several studies analysed specific projects carried out by PDPs. Gordon, Røttingen, and Hoffman (2014) (30) provided a case study on the creation of the Meningitis Vaccine Project (MVP), and the development of the MenAfriVac vaccine, which involved multiple public and private partners including the WHO and PATH. Ubben and Poll (2013) (31) focused on the development process for the drug Eurartesim undertaken by Medicines for Malaria Venture (MMV) and its partner, emphasizing the collaborative strength in the PDP model. Luiza et al. (2017) (32) and Wells, Diap, and Kiechel (2013) (33) analysed the drug development process of ASMQ-FDC, an anti-malaria drug developed by the Drugs for Neglected Diseases Initiative and its partners. In terms of results, the Global Forum for Health Research (2008) (34) noted that PDPs have led 85% of the R&D for 106 neglected disease candidates since 2000. It has been noted that PDP drug development projects initially focused mainly on drug repurposing and more recently tested new chemical entities (NCE) in clinical trials (2), but have brought relatively few NCEs to market.

The literature on costs, timeframes and attrition rates for products developed by PDPs or other non-commercial R&D initiatives is nascent. DNDi published a study in 2014 calculating the costs of product development from its portfolio (10), with an updated study in 2019 (11). MMV published an analysis of one decade of discovery and development of new antimalarial medicines in 2017, including information on historical attrition rates (15). Odevall et. al, 2018 (16) published the history of the development of an oral cholera vaccine (Euvichol) led by the International Vaccine Institute. Gunn et. al, 2019 (14) analysed the vaccine pipeline of the European Vaccine Initiative (EVI), providing information on costs, timeframes and attrition rates as part of the same TDR-led project of which this is a part. Speich et al., 2018 (17) provided a detailed breakdown of the costs of two clinical trials for two different drugs conducted in academic settings in Switzerland. The table below summarizes the cost information available in these studies.

Table 4: Out-of-pocket R&D costs* for non-commercial initiatives (millions of USD or Euros)

Paper	Product / type	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Registration	Total
DNDi (2014) (10)	ASAQ / drug – fixed dose combination	–	–	–	–	€7m		–
DNDi (2014) (10)	NECT / drug – combination	–	–	–	–	€3.6m	–	–
DNDi (2014) (10)	SSG&PM / drug – combination	–	–	–	€9.3m		–	–
DNDi (2014) (10)	SCYX-7158 / drug – NCE	€17.7m	€4.4m	€3.6m	€12.6m (estimates)		–	–
DNDi (2014) (10)	Fexinidazole / drug – NCE	–	€7.2m	€4.4m	€14.2m (estimates)		–	–
DNDi (2014) (10)	Drugs – combination	–	–	–	–	–	–	€10–40m (estimate including failures)(1)
DNDi (2014) (10)	Drugs – NCEs	–	–	–	–	–	–	€100–150m (estimate including failures)(1)
DNDi (2019) (11)	NECT / existing drug without new formulation	–	–	–	€3.6m			€3.6m
DNDi (2019) (11)	SSG+PM / existing drug without new formulation	–	–	–	€9.5m			€9.5m
DNDi (2019) (11)	Pediatric Benzinidazole – existing drug without new formulation	€0.1m		–	€3.3m			€3.4m
DNDi (2019) (11)	ASAQ / existing drug with new formulation	€0.2m		€1.5m	€3.6m			€5.3m
DNDi (2019) (11)	ASMQ / existing drug with new formulation	€0.2m		€1.5m	€4.4m			€6.1m
DNDi (2019) (11)	Fexinidazole / drug – NCE	€7.2m		€4.4m	€43.8m			€55.4m
DNDi (2019) (11)	Acoziborole / drug – NCE	€22.6m		€5.2m	€30m (estimates)			€57.8m (estimates)

Table 4: continued

Paper	Product / type	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Registration	Total
DNDi (2019) (11)	Existing drugs without new formulation	Not applicable			€4–10m			€4–12m (estimate including failures)
DNDi (2019) (11)	Existing drugs without new formulation	€1–2m		€1–4m	€3–7m			€5–32m (estimate including failures)
DNDi (2019) (11)	NCEs	€10–20m		€4–6m	€30–45m			€60–190m (estimate including failsures)
University-sponsored (Speich et.al, 2018) (17)	Prednisone – Drug repurposed	–	–	–	–	$2.3m	–	–
University-sponsored (Speich et.al, 2018) (17)	Oxantel – Drug repurposed	–	–	–	$0.1m	–	–	–
IVI (Odevall et al, 2018) (16)	Euvichol – Vaccine	–	–	–	–	–	–	$19.7m
EVI (Gunn et al. 2019) (14)	Vaccines (average of 3 candidates)	–	€2.5m	€1.5m	–	–	–	–

*Figures are listed as in the original studies and have not been adjusted for inflation or exchange rates.

There is very little information available in the published literature on timeframes. The Speich et al. study (17) mentions that the prednisone phase 3 trial lasted for 59 months, while the oxantel phase 2 trial had a 2 month duration (for comparison, P2I averages for simple repurposed drugs are 25 months each for phase 2 and 3). The Odevall et al. study on the Euvichol vaccine (16) mentions that product development took a total of 6 years and 10 months from inception to registration. For comparison, P2I averages for the archetype "simple vaccine" adds up to 9.5 years from preclinical to Phase 3 (4). The study analysing EVI's vaccine pipeline provides information on timeframes for unprecedented vaccines (14), compared to P2I averages (4) in the table below.

Table 5: Timeframes for vaccine development for EVI (non-commercial initiative) compared to P2I averages

Study	Technology / archetype	Preclinical	Phase 1	Phase 2	Phase 3
EVI (Gunn et. al, 2019) (14)	Unprecedented vaccines	36 (N = 2)	17.4 (N = 10)	22.5 (N = 2)	–
P2I Model (4)	Vaccines unprecedented	39.6	24	44.4	42

Even less information was found for attrition rates. The DNDi 2019 study (11) uses average success rates calculated for anti-infectives R&D from a 2003 study by Nwaka and Ridley (35). The MMV study (15) provides information on their historical attrition rates for drug development. The EVI study (14) for vaccines also provides information on historical attrition rates. The table below compares these with P2I averages (4) for repurposed drugs and NCEs (combined average) and unprecedented vaccines. In comparison to estimates available for non-commercial R&D initiatives, the P2I Model assumes lower success rates in all clinical development phases, while preclinical is higher.

Table 6: Success rates for product development for non-commercial R&D initiatives compared to P2I averages

Study	Technology / archetype	Preclinical	Phase 1	Phase 2	Phase 3
Nwaka and Ridley (2003) (35)	Drugs (anti-infectives)	55%	70%	50%	65%
MMV (Burrows et. al, 2017) (15)	Drugs	50%	70%	76.5%*	67%
P2I Model (4)	Average of all NCEs and repurposed drugs combined	67%	59%	38%	59%
EVI (Gunn et. al, 2019) (14)	Unprecedented vaccines	–	70%	100%	–
P2I Model (4)	Vaccines unprecedented	41%	50%	5%	40%

*Average of phase 2a (78%) and phase 2b (75%).

3 | METHODOLOGY: DATA COLLECTION

This section offers a general description of the methodology for data collection for the study as a whole. For ease of comprehension, we offer more detailed descriptions of the quantitative and qualitative methods used to analyse the data in the results section that follows.

a. Data collection

We began with a review of the literature on the costs, timeframes and attrition rates for R&D (summarized above), and found that it focuses almost entirely on commercial R&D. We found only a few studies estimating some of these factors for specific non-commercial R&D initiatives, but none analysing more than one initiative. Therefore, we focused our efforts on generating a novel dataset.

We sought to collect two kinds of original data: 1) quantitative data on costs, timeframes and attrition rates and 2) qualitative data from non-commercial R&D initiatives and/or experts on such initiatives to explain existing costs, timeframes and attrition rates and reasons why these might or might not differ from commercial R&D.

We began our inquiry by selecting all not-for-profit organizations in the P2I database that were directly involved in conducting R&D of candidate products. We used a version of the spreadsheet "Candidates in the pipeline for neglected diseases, as of August 31, 2017" sent to us by the authors, which included a categorization of the organizations by developer type. Selected organizations included product development partnerships (PDPs), academic and research institutions and public research institutes and other public sector organizations.

There was a total of 443 candidate products and 285 organizations that fit these initial criteria. We decided to keep all the 16 PDPs given their organizational focus on non-traditional R&D. We checked the list of PDPs in the pipeline against two other PDP lists provided in the 2018 G-FINDER report on neglected disease R&D funding (36) and in Munoz et al.'s study of PDPs (2). For the other organization types, we further limited the study population to include only organizations that had at least one product that had reached Phase 3 in order to have adequate data on total development costs, timeframes and attrition rates. Most organizations only had products in Phase 1 or 2. Another 32 organizations were included after this second selection. It should be noted that the P2I database only contains candidates for neglected diseases.

The final list of organizations was then separated into 5 groups. The first group was PDPs that are currently using the P2I model to analyse their portfolios. The second group was PDPs that do not currently use or were not in the process of applying the P2I to analyse their portfolios. The third group was PDPs that are no longer in existence, in an attempt to utilize historical data from these partnerships. The fourth group was non-PDP organizations with an ND R&D initiative. The fifth group consisted of three additional organizations suggested to us through snowball sampling that did not fit into any of the previous categories. A complete list of organizations by group is available in Annex 1.

We contacted a total of 48 organizations to request participation in the research. We contacted each organization by email, with the initial request addressed to the organization's most senior executive (e.g. Chief Executive Officer, Executive Director, Managing Director) to ensure leadership was aware of and agreed to our interview request, as recommended by the ethical review process. In specific cases, where we had reason to know another employee would be relevant to or aware of our research project, we copied other individuals on the initial email. The senior executive often delegated the interview to one or more staff, such as the lead staff person responsible for R&D, finance, policy and/or external relations. Three individual experts identified through snowball sampling and not employed by a specific R&D initiative were contacted directly. For five organizations, we interviewed more than one staff person, with each individual having a different area of expertise or responsibility. In the case of non-response, follow-up emails were sent after 7–14 days in the relevant working language of the recipient (English, French, Portuguese, or Spanish). Organizations that did not reply to the follow-up email were considered as "Did not respond." A few organizations responded to the initial request but did not follow-through with an interview or quantitative data; these were also coded as "Did not respond." Of 48 contacted organizations, 23 did not respond, 12 declined and 13 participated in some way (not all participating organizations

provided both quantitative and qualitative data), a participation rate of 27%. In total, we obtained quantitative data regarding 8 organizations and 83 products, and qualitative data from 14 interviews with 20 individuals from 12 organizations. Information was returned on a total of 37 drug candidates (of which 13 NCEs, 8 repurposed drugs and 16 not specified), as well as 19 vaccine and 27 diagnostic candidates.

We developed a questionnaire to collect the quantitative data (Annex 2) on the costs, timeframes, and attrition rates for a given organization or project. The questionnaire requested information on project-level start dates, end dates, direct and in-kind cost estimates, funding sources, and reasons for termination or suspension (if applicable) for each clinical phase. Phases were classified as follows: 1/1a, 1b, 2/2a, 2b, 3/3a, 3b, and regulatory approval. Additional information on dates of obtaining authorization to start clinical development (e.g. IND – Investigational New Drug Application) or filing of patent applications was also solicited, as they are used in the literature as points of transition between development phases. Information regarding the organization's attrition rates were also requested.

We also developed a list of questions for the semi-structured interviews (Annex 3). Interviewees were provided with the consent form in advance of the interview (Annex 4), and upon request, the list of interview questions. We went over the consent form at the start of the interview, provided an opportunity to ask any questions, and shared a final copy of the consent form with both participant and researchers' signatures back to the participant for their records. All interviewees were informed they would not be quoted by name, they would have the opportunity to review their interview transcripts and correct them, and an opportunity to comment on the draft report before publication.

Finally, we gathered publicly available information on each organization's product portfolio and financial data. A small number of organizations had published quantitative data on costs, timeframes or attrition rates in reports or articles prior to the start of this study (10,15–17), and we included these in our sample. Some of the organizations in the TDR consortium published (11,14,15) and/or made available to us (12,13) quantitative data during the course of our study as part of their participation in this group, and we have also included these in our dataset. And a small number of organizations provided us with original data that had not yet been published, and/or provided disaggregated data underlying their published aggregates. We tried to use data from annual reports or other public sources to estimate costs, timeframes or attrition rates, but found it was not possible as the data was provided at a high level of aggregation; therefore, we relied entirely on data provided by the organizations themselves.

b. Limitations of the data

This study relies on a very small sample size, particularly for the quantitative data. Most organizations that responded to our request to participate in the study did not keep data in the same format in which we requested it, and informed us that it would either take further time and/or not be possible to gather and share such data. Only two organizations put their quantitative data into the requested format, such that the data we finally obtained was quite heterogeneous. Some organizations did not agree to share their data.

In the original research plan, we relied on receiving quantitative data from at least the organizations in the TDR consortium (which included 5 PDPs), which we did partially receive. This data covered a wide range of technology types (drugs, vaccines, diagnostics) and diseases, such that for any given archetype in the P2I model we had only a very small number of data points. In the quantitative analysis we ultimately decided to exclude vaccines and diagnostics, as the small sample size would have made it impossible to preserve the anonymity of the data sources. Therefore, the quantitative analysis should be seen as merely suggestive, providing hypotheses for further testing against a larger dataset in the future.

In part, we believe the limited dataset is likely due to hesitance to share data that is usually kept internal. For commercial R&D, costs are a tightly-held piece of information that are even sometimes claimed to be trade secrets. For non-commercial R&D, an organization might be uncomfortable sharing information that could compare unfavourably against benchmarks (despite the fact those benchmarks are derived largely from commercial R&D). In part, the limited quantity of data is also due to the short time period of this project. After receiving approval from both the WHO Institutional Review Board and the Graduate Institute's Research Office (April 2019) we had a total of seven months for data collection and analysis (the first draft was finalized in November 2019, with revisions in this final version in response to comments from the participants). As mentioned in the Conclusions, we plan to continue pursuing this line of research as part of a larger ongoing study.

In comparison, the amount of qualitative data is relatively more substantial (20 individuals from 12 organizations) though still limited. Several organizations participated in interviews, even if they did not share quantitative data. We were able to include consideration of vaccines and diagnostics, in addition to drugs, although the qualitative data was still limited. The interviewees covered not only a broad range of organizations, but also had varied professional backgrounds (R&D managers with and without industry background, finance, external affairs, expert consultants). They offered a diversity of responses to the questions on cost, timeframes and attrition rates. However, we focused our efforts on interviewing representatives of non-commercial R&D initiatives themselves, and the study would benefit from a more comprehensive set of interviews including from major funders, for-profit and non-profit partners, and other stakeholders, as well as non-commercial R&D initiatives beyond NDs.

As this is the first time such an analysis has been published (to our knowledge), we expect that establishing some initial hypotheses and findings will facilitate further data collection and analysis in the future.

4 | RESULTS: QUANTITATIVE

We created a quantitative dataset by combining data provided by respondents with publicly available information pertaining to the costs, timeframes, and attrition rates of non-commercial R&D initiatives. Among the 13 organizations who participated in the research project, 8 shared quantitative data on their R&D costs, timeframes and/or attrition rates or referred us to publications containing at least some of these data. We used the disaggregated information collected as well as recently published studies to calculate new figures. Due to the limitations of our dataset, we limit our analysis to only two P2I archetypes: simple and complex new chemical entities (NCE-Simple, NCE-Complex) (Annex 5). Only one organization provided information about diagnostics and two about vaccines (one only included aggregated totals for one product), and we decided to exclude these from the analysis as it would be impossible to protect the anonymity of the organizations.

a. Costs

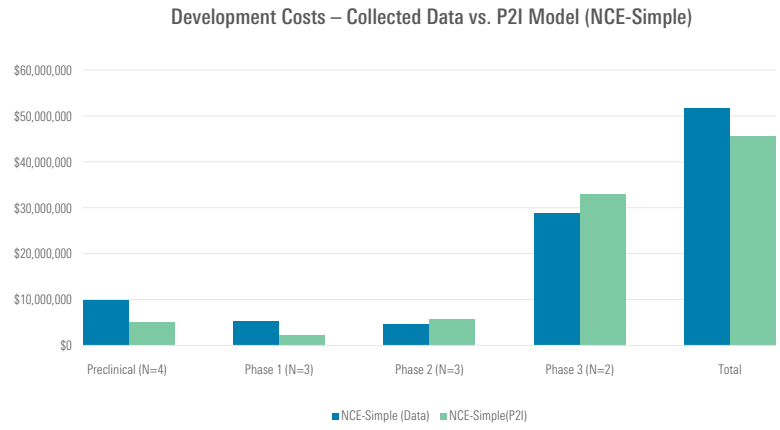
For cost calculations, several assumptions were made to standardize costs and allow comparison with the P2I v2.0 figures. First, for each phase, we assumed that money was spent at a steady rate across the time period, to the nearest month.[3] To calculate the phase costs per year, the total cost for the stage of testing was simply divided by the cumulative amount of years spent in that phase. For candidates with costs denominated in currencies other than USD, a yearly exchange rate from the year in which the cost was incurred was used[4] to make the conversion into USD. Totals were calculated in 2019 USD, which were then deflated to 2017 USD in order to facilitate comparison with the P2I v2 figures (which are in 2017 USD). To deflate the figures, the standard consumer price index was used (CPI-U, chained to 1982-1984 prices).[5]

[3] For example, if phase 1 testing for a product lasts for 27 months, the total amount of phase 1 costs are assumed to be equal for the first full month and 15th month (and every other month). If the trial started or ended in the middle of a month, the month would be weighted, and the cost per month would be the average amount equal to the proportion of the month where testing took place (one month was assumed to be 30 days). For example, the trial ending on the 12th of the month would be weighted as .4 months, and the monthly cost would be equal to the cost per month multiplied by the weight, in this case, .4.
[4] https://data.oecd.org/conversion/exchange-rates.htm
[5] US Bureau of Labor Statistics: https://www.bls.gov/cpi/tables/supplemental-files/historical-cpi-u-201905.pdf

Given the complexities of clinical development processes, several data points were treated as special cases. If data for candidates was provided with costs disaggregated by each year spent in the phase, these costs were not recalculated to find the yearly cost across the adjusted timeline period for that phase, they were left unadjusted until deflation to 2017 prices. For drug regimens, phase 1 and 2 costs were calculated as the costs to develop any novel candidate in the regimen. We split the costs for testing in a phase if there were multiple regimens featuring the same novel candidate in that phase. For example, if two regimens shared preclinical testing costs, those costs were distributed across both regimens equally. For combined Phase 2/3 trials, the timeline to calculate yearly costs used the same starting point for both Phase 2 and 3. In such cases, the end point for phase 2 was the end of the trial. The end of phase 3 was still counted as the first application to a regulatory authority.

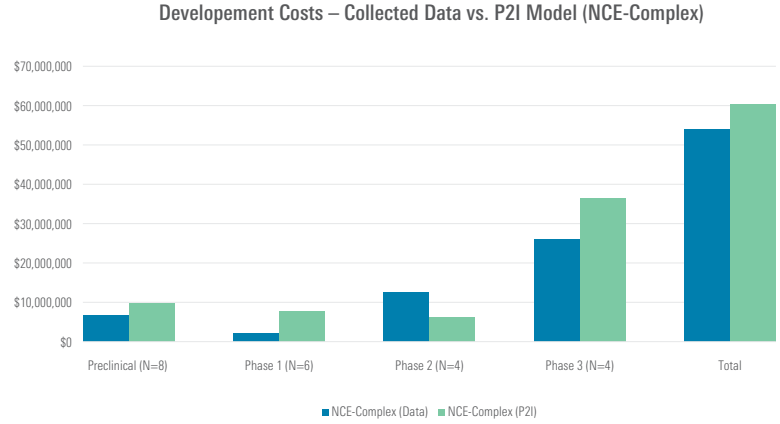
Our collected data on non-commercial R&D costs were in line with the P2I model estimates, with some variation. For simple NCEs, total costs for non-commercial were 13% higher than the P2I estimates (51.87 million USD for non-commercial vs 45.84 million USD for P2I). The largest differences were in preclinical and phase 1 – where the costs in our sample were more than double the P2I model estimates. Conversely, phase 2 and 3 trials were less expensive for simple NCEs in our data, but by a small margin. The sample size is too small for statistical significance or to generalize to non-commercial R&D more broadly; rather, the findings merely suggest a hypothesis that overall costs to develop simple NCEs are similar between commercial and non-commercial R&D initiatives.

Figure 1: Development Costs – Collected Data vs. P2I Model (NCE-Simple)



For complex NCEs, total costs were 8% less than the P2I model (53.98 million USD for non-commercial vs 58.93 million USD in P2I). In contrast with simple NCEs, for complex NCEs non-commercial preclinical and phase 1 costs were lower than the P2I model. Notably, phase 2 costs were much higher in our dataset (12.65 million USD vs 6.39 million USD in P2I). This could be in part because of the high proportion of phase 2/3 trials in the dataset, as well as the ratio of phase 2b to 2a tests being higher than the P2I data. Phase 3 costs were substantially lower than the P2I estimates, which may be explained by the fact that many pivotal trials were in phase 2. The opportunity to forgo phase 3 testing would drive up phase 2 costs while lowering phase 3 costs. The proportion of pivotal phase 2 tests may be different between P2I and our dataset. As with simple NCEs, the findings merely suggest a hypothesis that should be tested against a larger dataset – that overall costs to develop complex NCEs are similar between commercial and non-commercial R&D initiatives.

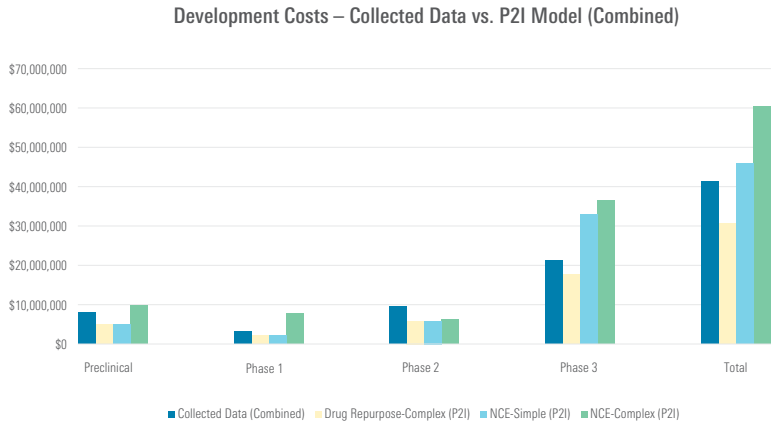
Figure 2: Development Costs – Collected Data vs. P2I Model (NCE-Complex)



Finally, we should note that between P2I version 1.0 and 2.0 there was a change in approach, such that three categories of archetypes (NCE-simple, -innovative, and -complex) were condensed down to two (NCE-simple, and -complex). However, some of the organizations that shared data with us used the older P2I v.1.0 terminology. In this case, we combined all products classified as either "NCE-innovative" or "NCE-complex" as "NCE-complex," in line with P2I v2.0. We also note that some of the candidates for which we received data were not in the P2I database and had not been assigned an archetype. Arguably, some of the combination

products actually required significant additional R&D investments and would better be classified as "NCE-simple" rather than "repurposed". Because approaches to coding by archetype were not uniform, and there is room for disagreement, we did a sensitivity test by combining all data on repurposed, NCE-simple, NCE-innovative (old code) and NCE-complex (new code) candidates, and compared against the P2I figures (See figure below).

Figure 3: Development Costs – Collected Data vs. P2I Model (Combined)



Archetype	Preclinical	Phase 1	Phase 2	Phase 3	Total
Collected Data (Combined)	$ 7,867,086	$ 2,984,988	$ 9,224,250	$ 21,242,590	$ 41,318,914
Drug-Repurpube-Complex (P2I)	$ 5,000,000	$ 2,210,000	$ 5,810,000	$ 17,610,000	$ 30,630,000
NCE-Simple (P2I)	$ 5,000,000	$ 2,214,390	$ 5,811,000	$ 32,818,000	$ 45,843,390
NCE-Complex (P2I)	$ 10,000,000	$ 7,435,829	$ 6,392,100	$ 36,099,800	$ 59,927,729

Total average costs in our dataset (41.3m USD, not including registration costs) lay between P2I's NCE-simple and NCE-complex (45.8m–59.9m USD), suggesting that non-commercial costs are largely in line with P2I parameters, even if there are some differences in coding. That said, as with all other calculations, we caution that this remains merely a hypothesis in need of further testing.

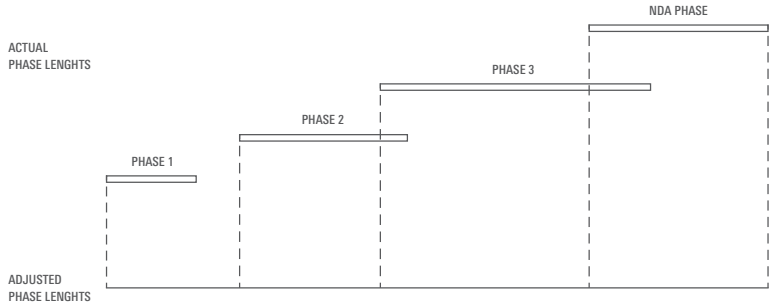
b. Timeframes

We calculated the total time spent in development as starting from the beginning of preclinical until the submission for regulatory approval (beginning of NDA stage) or the end of phase 3 testing, whichever is sooner. Preclinical times were measured from their start date (if provided in the questionnaire), or the first mention in the public domain of preclinical testing of an individual compound. Phase 1a and 1b trials were counted as phase 1. Phase 2a, 2b, and 2c trials were counted as phase 2, as were phase 2/3 tests. Phase 3a and 3b are both counted as phase 3 tests.

For timeframe calculations, an average of time per trial for each phase was taken to estimate the amount of time required for a given clinical phase. Because many candidates have multiple trials in each phase, the average of all trials was used rather than truncating or extending timeframes to create a continuous timeline per candidate. For some data points, early stage testing was aggregated for multiple drug candidates. This might happen, for example, if several different drug regimens counted preclinical testing for a single drug present in each of the regimens. For testing time that was allocated across candidates in this way, total time spent in a phase was divided by the number of candidates. Because it was not possible to identify start dates for each regimen in such cases, the total time in the shared phase was distributed equally across every candidate which was a part of that development time.

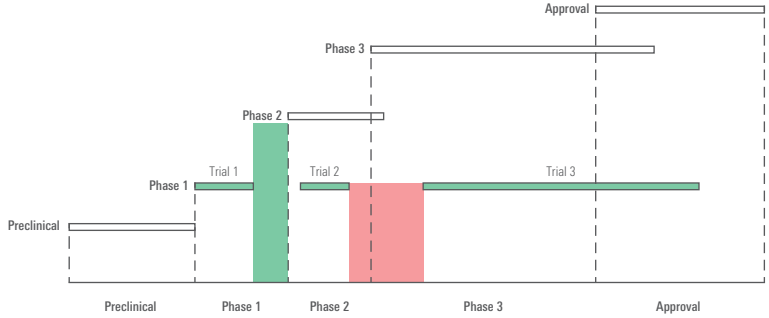
A more detailed description of the analytical methodology is merited here. Due to the non-linear nature of the development process in our dataset we made some adjustments in how we calculated phase lengths. DiMasi et al. (1991) (22) highlighted that the length of each phase is not always straightforward to calculate, as one phase may overlap with another, or conversely, there may be gaps between the end of one phase and the start of the next, as they illustrated in Figure 4.

Figure 4: Adjusted Phase Lengths (DiMasi et al. 1991) (22)



DiMasi et al. (22) calculated timeframe as the time spent in development from start to finish (e.g. Time = Date of NDA submission – Date of start of Preclinical/Phase X), effectively truncating the amount of time attributed to each specific phase. This method was not appropriate for our dataset, however, because many products involved multiple trials within each phase, and truncating phase times based on the starting date of the following phase would not accurately depict the amount of time spent in each phase. Furthermore, we only had three candidate products with data through the end of Phase III, but more candidate products in earlier stages of development. Due to the small number of data points we judged that average trial times per phase were more representative of the amount of time a candidate would spend in a phase.

Figure 5: Our approach to calculating trial times per phase

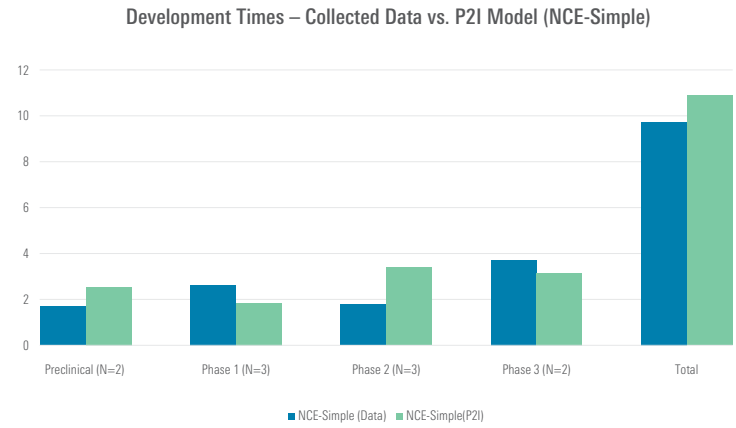


The cumulative amount of time spent in clinical testing for a given phase for each candidate is accorded to the phase length for that candidate. That is, if there is a phase 1 trial lasting 12 months, then phase 2 testing for the same candidate begins, then a new phase 1 trial is launched for 6 months, the cumulative time allotted to phase 1 for that candidate will be 18 months (Trial 1, Trial 2 and Trial 3 in Figure 5 are all Phase 1 trials). Secondly, we include gaps between the end of one phase and before the start of the next (green tint in Figure 5) as part of the previous phase. Returning to our prior example, if the first trial in phase 1 lasts 12 months and ends 3 months before the start of phase 2, the 3-month gap will be added into phase 1's timeframe. We do not include other gaps, such as those between different trials of the same phase, or any gap for a phase while later stage testing is already underway. This can be seen in Figure 5, where the time between trials 2 and 3 (red tint) would not be counted.

We calculate total time spent in development as the sum of time spent in preclinical, Phase 1, 2 and 3. This sum is likely to be larger (i.e. longer) than if we had adopted the DiMasi et al (same as P2I model) method of a continuous time frame. The disadvantage of this approach is that the two numbers are not directly comparable, but the advantage is that it makes more meaningful use of our original dataset.

For simple NCEs, timeframes between non-commercial R&D and P2I averages were roughly similar. Non-commercial R&D had shorter preclinical times (1.65 years vs 2.49 years in P2I), and longer phase 1 times (2.61 vs 1.80 years in P2I). Non-commercial R&D also had much shorter Phase 2 times (1.75 vs 3.38 years in P2I), while phase 3 times were slightly higher (3.67 vs 3.18 years in P2I). Overall our dataset suggested modestly faster timeframes for non-commercial simple NCE development, taking 9.67 years vs. 10.85 years in the P2I model.

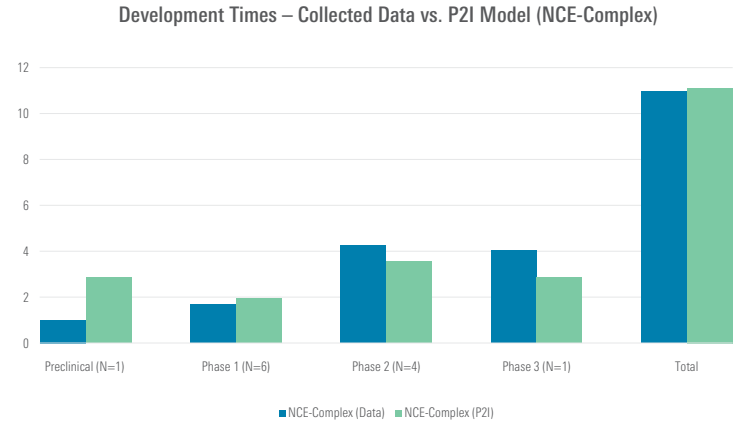
Figure 6: Development Times – Collected Data vs. P2I Model (NCE-Simple)



For complex NCEs, we found that non-commercial preclinical testing was much shorter (1.00 vs 2.87 years in P2I), phase 1 testing slightly shorter (1.67 vs 1.93 years in P2I), phase 2 longer (4.25 vs 3.51 years in P2I), and phase 3 longer (4.0 vs 2.8 years in P2I). Overall, non-commercial development time was nearly identical, at 10.92 compared to 11.11 years for the P2I model. Possible explanations for these differences could be a result of the ratio of phase 2a to phase 2b tests included in phase 2. The P2I model does not suggest what proportion of its phase 2 tests are 2a compared to 2b, but for our data set, there were many phase 2b tests, which may

have increased the amount of time in this phase. Preclinical time may have been shorter due to our decision to divide the time in this stage of development among multiple candidates, as that is how some data was shared with us. It is unclear how many preclinical studies in the P2I dataset would have been calculated in this way.

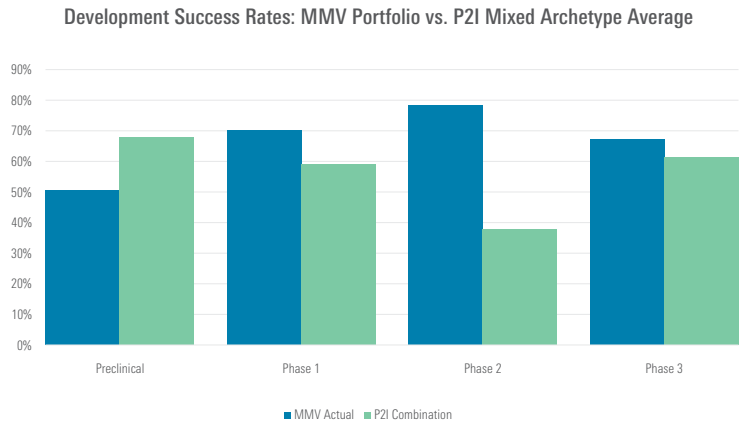
Figure 7: Development Times – Collected Data vs. P2I Model (NCE-Complex)



c. Attrition (success/failure) rates

Attrition data was the most difficult to obtain, and there did not appear to be a standard methodology nor practice of calculating such rates within participating organizations. As all non-commercial initiatives in our sample had relatively small portfolios (compared to large commercial firms), attrition rates might not be meaningful. We judged that the data we received could not be aggregated across organizations, nor was it adequate for hypothesis generation. We note, however, that MMV published its success rates by phase in a 2017 article (15), and merely for the sake of illustration we illustrate how these compare to P2I parameters (Figure 8). Further research is needed in this area.

Figure 8: Development Success Rates – MMV Portfolio vs. P2I Mixed Archetype Average



5 | RESULTS: QUALITATIVE

In order to develop a better understanding of the factors that drive the costs, timeframes and attrition rates of non-commercial R&D initiatives, and also potential differences with commercial R&D, we conducted in-depth semi-structured interviews with individuals with a high degree of familiarity about product development from the organizations included in the scope of the research. A list of the sample interview questions is available in Annex 3. A total of 14 interviews were conducted, with 20 individuals from 12 different organizations; most interviews lasted about one hour and were either conducted in person in Geneva or using an online platform. Out of those, 18 individuals provided their perspective based on projects conducted within their own organizations and two were experts with knowledge of a range of organizations. Interviews transcripts or notes were analysed and coded using NVivo12.

Below, we identify the main factors driving costs, timeframes and attrition rates in non-commercial R&D, and implications for how these may differ from commercial R&D. Quotes are linked to the Participating Organization (PO); quotes from different individuals affiliated with the same organization are not separated.

a. Costs

Interviewees were asked about the main factors that drove costs up or down in the different phases of product development within their own non-commercial R&D initiatives, and how they believed that factor would differ from commercial R&D. Most responses focused on a clinical stage of development rather than preclinical or earlier. A list of the factors that might push costs up or down for non-commercial R&D in comparison to commercial R&D is summarized below. Each factor is illustrated with selected interview quotes to provide further explanation. The quotes have been lightly edited for grammar and/or brevity.

i. Type of technology or product:

The type of product under development was frequently cited as a major factor accounting for wide variation in costs for each phase of development, which is also the main factor emphasized by the P2I model. For example, respondents mentioned that developing repurposed drugs costs much less than developing new chemical entities (and among repurposing projects, those involving a new formulation would cost more than those without one).

> *"We are mostly working with drugs which are already available for other diseases. So to get a bit of a shortcut, what we do is we work with drugs which are used for veterinary health, which have undergone a great deal of preclinical research. So we would save a long part of the drug discovery and development pipeline. Of course, we know that there is not billions in funding to develop a new drug for NTDs so we have to find strategies to make these costs lower." (PO 09)*

Implication: Non-commercial R&D may focus (more than commercial) on repurposing existing drugs which means overall R&D costs are likely to be **lower**, ceteris paribus. However, commercial R&D also works on repurposing drugs and direct R&D costs are likely to be **equivalent** for non-commercial and commercial R&D working on the same type of product.

ii. Trial location in LMIC vs HIC:

Most interviewees highlighted the location of the clinical trial in high or low and middle-sincome countries (LMICs) as a factor. In general, interviewees agreed that running trials in HICs is more expensive than in LMICs, mostly due to differences in the costs of infrastructure and personnel. Some interviewees highlighted factors that might drive costs up in LMICS. Factors that drive costs up in LMICs were related to building local capacity by training human resources and building research infrastructure to run the clinical trials, as well as the state of local infrastructure such as roads, electricity or telecommunications – particularly in rural areas. Even with these additional costs, however, several interviewees estimated that overall total costs would still be lower in LMICs than HICs.

> *"The infrastructure doesn't necessarily exist in the regions in which we operate. In trial networks, the regulatory environment, the technical capability of the sites conducting research etc. is very different, but it doesn't necessarily affect costs because it could be that it's cheaper in some sense, but it will have implications either, I would say, either on time or money to conduct that kind of research." (PO 2)*

"To work in a remote area, we have to rent boats or we have to buy cars. It is complicated to do monitoring and the cost of course is increasing because the conditions are very, very difficult." (PO 3)

"We're working with local investigators and building capacity. At the same time. So instead of flying in teams to do these clinical trials, we both work with local institutions, and capacity strengthening is part of this. But overall, I don't know, but my feeling is it's probably a lower cost way of working than just flying in teams of experts from all around the world." (PO 12)

Depending on where a disease is endemic, there may be limited options for where a trial can be run regardless of the availability of infrastructure.

"If you had a choice you could do it somewhere else. But for some of the diseases, it's not a choice. You have to do it where the patients are." (PO 3)

Implication: Non-commercial R&D has focused on neglected diseases which means clinical trials must usually take place in LMICs, which means costs are likely **lower** than commercial R&D, *ceteris paribus*.

iii. Standard of care and trial size:

A significant driver of costs is the number of patients enrolled in a trial (trial size) particularly in Phase 3; a key driver of trial size is the standard of care – more precisely, the number of participants required to demonstrate a statistically-significant difference with a comparator product. Interviewees highlighted than NTD trials generally required smaller numbers of patients (ranging in the hundreds) because the standard of care was generally not high. For example, if the current standard of care is not very effective (e.g. cure rate of 50%) it might be easier to demonstrate the candidate product is more effective (e.g. cure rate of 70%), and a regulator more likely to accept this degree of improvement over the status quo. If the currently available treatment is highly effective (e.g. cure rate of 90%), it would require a larger sample to demonstrate with statistical significance that the candidate product is non-inferior or superior (e.g. a cure rate of 95%) and to obtain regulatory approval.

"We do mostly pilot or proof of concept studies which are done on a smaller number of patients. In oncology studies it is two thousand patients, we are 100, 200, or more for cohorts but it's not thousands of patients in clinical trials." (PO 1)

"Some diseases are much more complicated than others. I think the first thing is that probably we don't need to have so many patients – usually far more in oncology. Since current therapeutic options are often poorly effective or adapted, we can make a difference quite quickly." (PO 3)

"The regulatory environment can be such that – the suffering is so great that the cost benefit reasoning regarding approval may be more swift in these areas. And the WHO assessment may factor that type of ethical reasoning in their policy guidance and their requirements for what they would need to see in the dataset. So it's not just that demonstrating superiority to standard of care is easier, but also that the cost-benefit equation is a little bit different." (PO 2)

Conversely, for commercial firms competing in a therapeutic area where there is a higher standard of care, the size and costs of trials would be higher.

"If there's a lot of product launched and if there is an established standard of care, and if for commercial reasons, you actually need to differentiate versus the other standard of care to get the price – because when you go to get market access in Germany, you apply for a price, they will actually price you based on the fact that your product is superior to standard of care – or not – in the given patient population that you have defined. And you know, they define superiority. If you have superiority, it's free pricing. If you don't have superiority, it's equal -- they will kind of match you with the price of the standard of care. And if you are inferior well then you're in trouble." (PO 7)

One interviewee highlighted that, as more products for NTDs have been successfully developed in recent years, raising the standard of care, future costs for R&D may be higher.

"The interesting question is what you describe as a successful study, and how this can change over time. Currently in malaria we need drugs that have a 95% cure rate at 28 days, so anything new with say 92% is a failure. However, with malaria treatments at one stage success was 90% at 14 days, and then 95% and now 95% at day 28. Whilst the current drugs work – the bar gets higher with time, and if the current drugs fail then the bar will get lower again." (PO 8)

"The increase of efficacy that we've seen over the last couple of years into new treatments, for the future, will lead to significantly larger trials which obviously will have a major impact on the costs of clinical trials." (PO 10)

Implication: Non-commercial R&D is largely done in therapeutic areas with great unmet need in which the standard of care is relatively low, which means the number of patients in clinical trials should be lower, implying costs should be **lower** than commercial R&D, ceteris paribus.

iv. Number of arms of the trial:

A greater number of arms in a trial was also mentioned as a factor that would drive costs upward, for both non-commercial and commercial initiatives. The development of combinations or regimens combining products with different mechanisms of action has been emphasized as a strategy to combat the emergence of resistance by target pathogens, such as TB, HIV or malaria. Developing combinations requires more arms in a trial. Adding a different formulation, such as a pediatric formulation, could also require an additional arm in a trial.

> *"Combination drugs are much more expensive to develop, because you need to develop first model components until phase two, then you need to combine them. And it's inherently more risky and more costly to prove the combination rule for a combination product in a phase 3. And then in phase 3, you essentially have to demonstrate that the combination is more effective than any of its ingredients alone. So that trial has to have many arms in it. That is a huge study, that phase 3 study. It's something that makes things much more expensive, for sure." (PO 2)*

> *"You might change the clinical trial protocols as you're going through -- so you then decide to add a pediatric formulation… we're working on an adult formulation, and then we separately do a clinical trial for pediatric. Sometimes there's an overlap between the two, which can be both cost saving compared to if you do them separately, but they might be more expensive because they add on to the cost that we may have anticipated at the beginning." (PO 3)*

Implication: Since non-commercial and commercial R&D both develop combination products, costs would not **necessarily be higher or lower**, *ceteris paribus*.

v. Organizational costs:

A cost driver mentioned by almost all interviewees was the difference in organizational costs between for profit and not-for-profit. Factors that drive costs higher in commercial R&D initiatives included: costs of capital (sometimes conceptualized as costs to borrow, raise funds in capital markets, or opportunity costs of internal funds), which non-profits do not incur or calculate; marketing costs, which most non-profits do not incur; and higher bricks-and-mortar costs for firms, as compared to PDPs operating on a "virtual" or "networked" model.

> *"Obviously the cost of FTE is a big difference from pharma. One figure is that the average FTE is about 250-260K. And we are at half of that, so of course it is one driver…this is for sure, we don't have the same salaries and the same overhead costs." (PO 3)*

> *"Costs in pharma are higher because of overhead, but pharma costs are not transparent." (PO 5)*

> *"I do think it's interesting also to see how relatively small and nimble organizations like PDPs or like biotechs compare to large R&D organizations…the sales and marketing machines that these big companies have -- that obviously also has to be recouped somehow." (PO 10)*

> *"I would think there are two main areas where there are differences. One is the kind of overhead costs and what you load onto your cost of trials, and I think non-commercial are, in my view, should be leaner. And what do I mean by that? So, for example, pharma will do a trial and they will do an innovative type of project where they will introduce some analytics on top of the trial, thinking this will add value and maybe they want to try it. In that sense this trial will get more and more expensive. There is an overhead there. Yes, that's a minor one. But then there are two or three other drivers in commercial trials that are very important. One is, you know, sometimes they also use the trial to build physician networks and relationships that will support the launch of the product. So, there is a lot of money in "medical affairs," in which the personnel visits to get to know the main investigators at sites. That would be leaner in a non-commercial trial." (PO 7)*

Implications: Non-commercial R&D is largely done by not-for-profit organizations, which means costs would be **lower** than commercial R&D, *ceteris paribus*.

vi. Lower input prices for non-profit organizations:

Related to lower operational costs (see previous), another difference mentioned by several interviewees is possible lower prices for inputs, including discounts offered by contract research organizations (CROs), in-kind contributions, and/or donated products for testing. Firms may be more willing to provide lower or no-cost inputs to non-commercial initiatives as part of a corporate social responsibility strategy.

> *"We negotiate partnerships with CROs around the world to do the trials. As we are a non-profit dedicated to global health, I do believe we generally should be able to get significantly lower cost proposals from the partners that participate.… I would say from what we've heard, for instance from the CRO – we're talking probably 30% less or so. But honestly that is really just a guesstimate." (PO 10)*

> *"What actually happens is, with a lot of commercial suppliers like CROs, when we go to them, we will get a better price because we are more flexible on when the study will be done. In other words, it doesn't have to be done tomorrow, we probably have better planning for that because we have less projects. And secondly, don't forget that all the CROs also see themselves as doing something good in terms of corporate social responsibility. And that usually means once you've explained our mission, then usually people will give us much better prices than they would give a big company. For CSR reasons, you know, everybody we work with – if they catch the vision – is going to try and do the best they can." (PO 8)*

Most of the non-commercial organizations pointed out they received significant in-kind contributions but did not include these in their cost of product development, frequently pointing to the difficulty in attributing economic value to the different types of in-kind contributions. One publicly available figure comes from DNDi, which estimated that in-kind contributions comprise about 12.5% of their R&D costs (11). One interviewee also noted that in-kind contributions from commercial partners, when monetized, is done using the costs of the commercial partners, which may be higher than if the same was done directly by the non-commercial organization.

> *"Even if we had what a pharma company does for us properly costed out, perfectly, so you could extract out their overall contribution, e.g. what was their registration contribution – it would be costed at their cost, not our cost. In-kind contribution declarations, which is the only thing we can go by, is calculated by what it cost them. And for the same piece of work that is done by their team and our team there are actually very different costs, because of the cost per FTE – we estimate ours to be half of theirs." (PO 3)*

Another factor raised by one interviewee is access to already-developed products for use as a comparator in clinical trials, which could lower costs if the product can be obtained via donation – or impede the research if a non-profit organization cannot pay the full market price.

> *"We have historical collaboration with the pharmaceutical companies. Because we cannot buy the drugs, it is too expensive for us, they give it to us for free and we have a contract/collaboration agreement with them. If the company does not want to collaborate, to give the medicines to us, it is not sure that we can do the study. (…) if it is a project in which the company is not interested, and it has already happened, then we buy the drug, so it is more expensive for us. We try to avoid buying." (PO 1)*

Implications: Non-commercial R&D would frequently benefit from lower input costs, thus total R&D costs would be **lower** than commercial, *ceteris paribus*.

vii. Involvement of affected community in product development:

The involvement of the affected community in the clinical trials was also raised by one interviewee.

> *"We have a rigorous community engagement effort, which leads to costs that pharma does not have. We have more credibility. We have experience in engaging communities that is necessary to conduct clinical trials. Community involvement adds a significant budget, pharma recognizes it is not in their expertise and they do not want to take responsibility for it." (PO 5)*

Implications: Non-commercial R&D would, arguably, be more likely than commercial to involve community engagement as part of the research, and thus total R&D costs would be **higher**, *ceteris paribus*.

viii. Specifics of the disease/indication:

A number of interviewees highlighted disease-specific factors that influenced R&D costs. As noted in the literature review (20), R&D costs are lower on average for certain therapeutic areas (e.g. dermatology, endocrine) than for others (e.g. pain and anesthesia, ophthalmology) with anti-infectives at the higher end of the spectrum. All the non-commercial initiatives interviewed for this study addressed infectious disease, thus, our emphasis below is to highlight variations within anti-infectives in cost drivers.

a. Scientific understanding of the disease:

Several interviewees noted that the state of scientific understanding of a disease was critical, with R&D costs and risks likely to be higher when basic understanding was lower – as is often the case for neglected diseases that have attracted relatively little basic research funding or attention. The existence of correlates of protection or biomarkers of disease progression or cure, for example, could all significantly reduce R&D timeframes and costs.

> *"Let's take vaccines. As an example, I would say that the main cost driver for vaccines is whether there exists a correlate of protection in phase 3, or if you have to go for a prevention of disease endpoint. And that very much depends on whether there is a precedent or not. In the case of Group B strep vaccines, there isn't really a good correlate of protection or biomarkers where there's an endpoint. So we would likely have to go for the phase 3 program with prevention of disease – a huge trial. That is then in the order of hundreds of millions of dollars for the phase 3 program only. Whereas in the pneumococcal conjugate vaccine space there is simple blood measures in phase 3 that you can use to tell whether it's working or not. And there is only a fraction of the cost in that trial. I think those are the main drivers and that very much depends on the disease. Whether there exists some kind of biomarker that has been validated to correlate with outcomes, or not." (PO 2)*

Implication: Non-commercial R&D costs are likely to be **higher** than commercial, ceteris paribus, as the state of scientific understanding of neglected diseases is usually less than others.

b. Predictive model and attrition profile:

Interviewees also highlighted that for some diseases it was more feasible to reduce risk earlier in the R&D process.

> *"Sometimes we have been lucky with attrition because we identified a compound at an early stage quickly and the model is very predictive in the animal model, and we were pretty sure, at the end of phase one, that it was okay, and the risk of failure was limited." (PO 3)*

> *"Another factor that has possibly not been mentioned, is the attrition profile. For a lot of parasitic diseases you are able to get quite a lot of confidence whether or not your drug will work at early stages in its development. And so you can take your attrition early, which will save you a lot of money further down the line. I think that's true of parasitic diseases, it's probably true of bacterial diseases as well." (PO 3)*

Implication: Non-commercial R&D costs **not necessarily higher or lower**, as compared to commercial.

c. Duration of treatment and/or disease progression:

Interviewees also pointed out that the duration of treatment and/or disease progression also influenced costs and timeframes. For example, a two-year treatment regimen for MDR-TB means that trials – even for shorter regimens – must run for at least several years to gather adequate data.

Implication: Non-commercial R&D costs **not necessarily higher or lower**, as compared to commercial.

d. Prevalence or incidence of the disease:

Several interviewees raised the challenge of recruiting an adequate number of patients for certain diseases, such as rare diseases or those nearing elimination. Challenges in finding patients could require opening new trial sites for recruitment, increasing the costs and time-frames.

"Depending on how difficult it is to recruit the patients, how rare they are, the cost will be very different trial to trial." (PO 7)

"If I looked at the standard pharma company and at how much they have trials in oncology versus trials in diabetes, there's a huge difference. Because for oncology at the moment, there's huge competition, especially for a rare patient population, in a very prominent center, like Cleveland Clinic or MD Anderson, and the cost of acquisition for one patient in the trials is enormous. If you look at something like diabetes, it will be lower. So can you imagine for infectious diseases, it will be even lower because there is not such a big competition for the patients." (PO 7)

Implication: Non-commercial R&D costs **not necessarily higher or lower**, as compared to commercial, as both can address relatively rare diseases.

Table 7: Factors influencing costs for non-commercial (vs commercial) R&D

Costs pushed upward	Indeterminate	Costs pushed downward
Infrastructure building and training at LMIC trial sites	Number of arms of the trial	Type of technology (i.e. simpler)
Involvement of affected community in product development	Duration of treatment or disease progression	Trial location in LMIC (vs HIC)
Limited scientific understanding of the disease	Prevalence or incidence of the disease	Organisational costs (i.e. non-profits)
	Predictive model and attrition profile	Advance over standard of care easier to show with smaller trial size
		Lower input prices for non-profit organizations

There were more factors that would push costs for non-commercial R&D down vis-à-vis commercial models. However, as the qualitative data does not tell us about the magnitude of the effect, no firm conclusions can be drawn.

b. Timeframes

As with costs, interviewees were also asked about the main factors impacting timeframes in different phases of product development. Where the same factor was mentioned as driving both longer timeframes and therefore higher costs, for the sake of brevity we did not explain that factor again here but rather refer the reader back to the discussion under Costs. A summary list of the factors that might make timeframes longer or shorter when comparing non-commercial and commercial R&D is available in Table 5.

i. Availability of funding:

The most frequently raised factor lengthening timeframes of non-commercial R&D was the need to raise funds, sometimes for each development phase. The challenge was especially acute between phases 2 and 3, which are typically the most expensive and more difficult to secure the necessary funds. Interviewees noted that having core funding allowed projects to move faster, as opposed to having project funding alone.

> *"[The companies] they have more money, they will put more means to do it faster. Maybe they will be able to put more in the monitoring, which will finish faster. We have 2–3 people to do the monitoring, it's not 50. The industry will pay scientific writers for study reports, we cannot pay – it is too expensive. You see that there is still a question of means. We believe that the companies could go faster to do the final study report." (PO 1)*

> *"I think one factor that is quite complex is the timeline. Because this actually is also a factor of money. If you're in a commercial firm and they really want to achieve something and they have a commercial end they'll throw a lot of time, money and resources at it, which can speed up the process. It doesn't necessarily increase your hit-to-lead, but you find out more quickly whether something can move forward, or not." (PO 3)*

> *"Some of our delays could be incurred because we're waiting for a funder, or the funder is waiting for additional resources. You wouldn't think this, but there was a three-month delay on one of our projects because they were waiting for the next fiscal year so that they could use 2019 money rather than 2018 money. Since we're not internally funded, we lose efficiency, because we can't rapidly push through everything unless we have the funding already lined up." (PO 6)*

"It took about 5 years to really get funding for this project. But it's not that I've followed it every day, I mean, I know the field, I know where to obtain funding possibilities, so it was really also put on ice for some years. Commercial R&D they could have immediately spent the funds, while we are really facing this valley of death. We can move compounds up to a certain point, but then we really need partners who help us take the compound further." (PO 9)

"Maybe it took 2 or 3 years to get enough funding to start a phase 3 trial because we needed to go out to donors and convince them to jointly fund which is a significant amount of money, and that delays development and obviously comes as an expense. Whereas a commercial manufacturer, generally when they get on the development path they do have the financial capabilities – once the data comes in and the go/no-go decision is taken – to immediately start working on phase 3." (PO 10)

"I think timeframes could be shorter with commercial partners, just because of funding availability. What you see for a lot of PDPs, most of the time there is no available funding for the next trial. So what you have to do is already during your current trial, write applications. But then for most of the vaccine trials in TB for example, there are time gaps between finalizing, for example, a phase 1 or phase 2a trial and going to the next trial just because you need to re-engage with the funders, you need to negotiate, you need to put in grant proposals to try and match different funding sources to each other. There you can easily get a delay of one, one and a half years between trials, if you're lucky… Commercial partners, if they really believe in their products and they really see they got results for a commercial disease, they just take the money and next day, basically, they go ahead with it." (PO 11)

Implication: Non-commercial R&D timeframes are **longer**, *ceteris paribus*.

ii. Decision-making processes:

Another factor frequently raised was the decision-making process both within an organization and the involvement of external partners and donors. The involvement of donors in decision making seemed to vary considerably between different donors, with a few being very much involved in technical decisions and most less involved. Interviewees noted that external involvement in no-no go decisions, for example, could slow down the R&D process.

"With funders like Gates or the Wellcome Trust there are go/no-go criteria and often you have to have a decision gate meeting around that. Instead of going from phase one to phase two, phase two to phase three. It means we have to have all the data available for them, present it to them, and then there's a period of time where they decide we've passed, and then there's another period of time where we're preparing the next documents for the next round of funding. So they're funding our salaries while we're waiting." (PO 6)

"Some of the donors want to get involved in the decision-making process. You need to have a good system of stage gating to decide your investments. Normally you could do them internally with your own governance, but now you have more and more external parties wanting to get into this process. This might generate months of delay for one project…one year minimum." (PO 3)

"That is what some people call the white space, essentially when nothing is really happening – it is just that you are trying to come to a conclusion about what to do. And I think that the white space is longer in this area where there are more parties involved." (PO 2)

"We have seen with some of our former partners, just the processes for decision making can be quite heavy." (PO 8)

Implication: Non-commercial R&D timeframes are **longer**, *ceteris paribus*.

iii. Negotiating access to candidate compounds:

The challenge of negotiating access to candidate compounds was raised as a factor that lengthens timeframes, especially for compounds owned by different companies when an organization is trying to develop a regimen or combination product.

"Negotiating access to constructs like drugs or vaccines can be something that delays the programs, if the commercial partner is not interested to participate. For natural reasons they want to make a return on whatever assets they have, right? They also are hesitant in giving access to that construct, and those types of negotiations take a very long time. In a commercial contract between two commercial players they quickly agree whether or not to merge or to out-license. The same type of business dynamic [with non-commercial] I don't think necessarily applies. They may go for one trial and then the next thing they are getting cold feet, and things like that…I think it is a problem that the non-commercial sector is facing." (PO 2)

"The other point is the instability of the private sector as well. This drug started at [commercial organization] then they were taken over by somebody else, who were taken over by somebody else, who were taken over by [another commercial organization]. And so, actually even for us to get this license we've had to go back through this labyrinthine corporate takeover… we were able to pull that out and not have to deal with that nonsense at the end. But it took time." (PO 12)

"If a drug gets stuck in a portfolio with partners who have difficulties raising funds, you have very interesting compounds that could be stuck and unavailable, literally. In the worst case there are examples of delays of almost 10 years. That's a bit of an outlier and sort of an extreme case, but we've seen quite a number of compounds moving hands when companies and biotechs were being taken over and delayed or shelved because the new owner was not (or no longer) interested in the disease." (PO 10)

Implication: Non-commercial R&D timeframes are **longer**, *ceteris paribus*.

iv. Development of regimens:

See above under Costs, "iv. Number of arms of the trial".

Implication: Non-commercial R&D timeframes **not necessarily shorter or longer**.

v. Regulatory/ethical review:

Some mentioned the time necessary to obtain authorization to run clinical trials.

"Trying to get global approvals for complex clinical trial protocols takes many years if you're looking at products where you have countries like Kenya, Tanzania, South Africa, India and the Philippines together. It takes sometimes 6–12 months for first approvals of protocols. I think if there would be some similarity in a project, and there would be a way for regulators to get together on approvals, you could significantly reduce timeframes for everyone, commercial/non-commercial. So some form of global collaboration between regulators would make a massive difference." (PO 10)

Implication: Non-commercial R&D requiring trials across multiple LMICs may mean **longer** timeframes than commercial R&D, *ceteris paribus*.

vi. Related trials:

One factor raised by two interviewees was coordination between portfolios of different organizations. If there are multiple organizations involved in product development for the same indication, there might be a pause before moving to the next phase while awaiting results of the other trials in order to evaluate which candidate is the best to move forward.

> *"There currently are at least two other candidates from other organizations out there that are in phase 1 for the same class. One question is, given the limited resources you have, do you want to develop all of these individually and until what time in the development pipeline. Or do you want to first look at which one is the best, and focus basically all your efforts, as a group of organizations combined, into this and develop the best one, putting money behind it?" (PO 10)*

Implication: Non-commercial R&D initiatives would be more likely to engage in collaborative approaches with other organizations (as opposed to the competitive dynamic among commercial initiatives), and therefore have **longer** timeframes, *ceteris paribus*.

vii. Combined Phase 2/3 trials:

One interviewee pointed out that it was possible to save a significant amount of time by combining Phase 2/3 trials, where appropriate.

Implication: Non-commercial R&D timeframes **not necessarily shorter or longer**, as both commercial and non-commercial could seek to conduct combined Phase 2/3 trials.

viii. Organization scale or maturity:

Interviewees pointed out that organizations with greater experience and expertise in conducting R&D would be able to run trials more quickly. Since many non-commercial R&D initiatives are relatively small and/or less established than commercial firms, they would have less access to expertise and/or experience. However, small/medium enterprises may face the same challenges as PDPs in this regard.

"PDPs may need capacity building funding in order to just stand up those organizations, building the capability so that they can actually embark on doing the job that is needed. This of course means that they are typically less mature. And there is a time before they can actually get really good at what they do and conduct clinical trials efficiently and things like that." (PO 2)

"Recently with advances in data technologies and digital, pharma companies and startups and CROs have invested a lot into optimizing operations of clinical trials to drive faster timelines…It's not just that you optimize the speed of recruitment, but because of the speed of the trial, actually you pull the revenues forward. Because if your asset has a certain patent lifetime, the faster you get this on the market, the more revenue, the faster you get the revenue. So that's actually a bigger driver than just the cost. And they've figured this out and they're doing everything possible, if they're a mature and savvy organization, to pull the trials as fast as they can. (…) when you apply some of these tools, let's say optimizing sites and country selection, that's typically within 15 to 20% even 25% faster trial timelines that you achieve." (PO 7)

"We work with some partners that are startups, or small and medium enterprises and usually they have good technical expertise on a new technology, and an R&D focus. But they haven't necessarily commercialized the product or manufactured any similar product in the past or distributed. They don't necessarily have a network. And I guess the more mature the manufacturer, the larger the company, the more it has experience, already developing, but also commercializing products, the more efficient they're going to be. And so the costs are going to go down, and then the length of phase also, and I guess, because of that the likelihood of success." (PO 4)

Implication: Non-commercial R&D **longer**, as organizations are generally smaller, have less experience or access to product development expertise compared to (at least larger) commercial firms.

ix. Capacity building:

The issue of capacity building in non-commercial R&D was also raised by a number of interviewees. (See also under Costs "b. Trial location in LMIC vs HIC")

> *"There is an aspect that the traditional R&D projects don't have, which is that we often have to build the clinical sites and expertise. Most of the time there is a plugin strategy to existing sites. But with our diseases we have to build this. I mean, not only get the authorization, but build the site, train the people and basically establish a new clinical trial infrastructure from scratch." (PO 3)*

Implication: Non-commercial R&D **longer**, *ceteris paribus*, as more likely to require and include capacity building as part of the R&D process.

x. Specifics of the disease or indication:

a. Duration of treatment and/or disease progression:
See above under Costs "viii. (c) Duration of treatment and/or disease progression".

Implication: Non-commercial R&D timeframes **not necessarily shorter or longer**.

b. Seasonality of disease incidence: One interviewee noted that diseases that arise seasonally, such as influenza or malaria, could require longer timeframes for patient recruitment.

> *"Infectious diseases that have a seasonality to them – if the trials are delayed, they may extend over two seasons. And when that happens, a massive delay is incurred. And I think that is a typical situation if you don't have enough events to make the trial or too few patients, then you have to go to the next season." (PO 2)*

Implication: Non-commercial R&D timeframes **not necessarily shorter or longer**.

c. Prevalence or incidence of the disease:
See above under Costs, "viii.(d) Prevalence or incidence of the disease".

Implication: Non-commercial R&D timeframes **not necessarily shorter or longer**.

Table 8: Factors influencing timeframes for non-commercial (vs commercial) R&D

Timeframes longer	Indeterminate	Timeframes shorter
Lower availability of funding	Need to develop regimens of multiple products (rather than single products)	
Slower decision-making processes	Combined Phase 2/3 trials	
Longer time to negotiate access to candidate compounds	Duration of treatment and/or disease progression	
Longer regulatory/ethical review	Seasonality of disease incidence	
Multiple simultaneous related trials, longer time to reach conclusions	Prevalence or incidence of the disease	
Smaller organization scale or less mature organization		
Time for capacity building in LMICs		

There were a number of factors that would lengthen timeframes for non-commercial R&D vis-à-vis commercial models, or that were indeterminate. Notably, in none of the interviews did a respondent argue that non-commercial R&D would move faster. As the qualitative data does not tell us about the magnitude of the effect, no firm conclusions can be drawn on whether non-commercial R&D would generally take the same amount of time or more than commercial R&D.

c. Attrition (success/failure) rates

Interviewees were also asked about the main factors that drive attrition rates up or down in the different phases of product development. This question generated a wide range of responses, and (as noted in the quantitative results section) different organizations took quite different approaches to conceptualizing – let alone calculating – attrition rates. There is also reasonable disagreement as to whether or when a higher attrition rate is undesirable. Some interviewees argued that it is beneficial for an organization to "fail early and fail fast" – that is, to have a high(er) attrition rate in preclinical or Phase 1. Too low of an attrition rate could also suggest an organization is not taking enough risk, particularly in the earlier and lower-cost phases of R&D.

Below we briefly explain factors that seemed most salient for understanding differences between non-commercial and commercial R&D, which are summarized in Table 6.

i. Type of technology or product:

The degree of complexity of the technology could influence attrition rates, for example, as repurposing drugs would likely have lower attrition rates than developing new molecular entities.

> *"Obviously, if you work on entirely new classes of drugs, your attrition rate should be higher. So the way we explain it to people who do portfolio management is that our attrition rate actually tracks quite well to the industry standard for anti-infectives. But since pretty much every one of our molecules is a new target, under normal circumstances, you would expect our attrition rate to be much higher. So we think we are doing better, not because we have a lower attrition rate, but just because we have more novelty and we keep the same attrition rate." (PO 8)*

Implication: Non-commercial R&D would **not necessarily have higher or lower** attrition rates, as both non-commercial and commercial R&D develop simpler and more complex technologies and have both novel and established targets.

ii. Standard of care:

See Costs "iv. Standard of care and trial size".

Implication: Non-commercial R&D likely to have **lower** attrition rates because it is more likely to focus on diseases with relatively low standard of care, *ceteris paribus*.

iii. Testing for multiple indications:

The number of possible indications for a compound was mentioned as a factor that could drive attrition rates lower, as a compound might fail for one indication but work for another.

> *"So big companies often have a multi-indication strategy for one asset. They will take something like TNF alpha, and they will try first in mature arthritis, and then they'll start to go into psoriasis, and candidiasis, into different therapy areas and by default that a little bit de-risks. Because in principle you already have safety data on this and also all the human data and then you're moving into just expanding into the next indication." (PO 7)*

Implication: Non-commercial R&D would **not necessarily have higher or lower** attrition rates, as both non-commercial and commercial R&D may test a compound for multiple indications.

iv. Combinations or regimens:

Depending on how attrition rates are calculated, developing regimens or combination products could lead to either higher or lower attrition rates, as illustrated by two different interviewees below. These conflicting views are a reminder that there remains a range of approaches to conceiving of and calculating attrition rates.

> *"In phase 3, you essentially have to demonstrate that the combination is more effective than any of its ingredients alone. So that trial has to have many arms in it. That is a huge study. It is something that makes things much more expensive, for sure. Then on the risk side it is also more expensive because you have to come up with three good monotherapies existing at the same point in time so that you can actually put them in a combination. That is just less likely. So the probability of success for such a program is much lower than for other programs." (PO 2)*

> *"For regimen development, the combination studies happen for the first time in phase two. It is one study that has multiple arms, looking at different combinations. It might be that one arm may be terminated based on study results. However, the other study arms will remain. It is really hard to capture the attrition rate for the specific arms. So what we've done is looked at the entire study and consider it as one study, and not calculating attrition within each arm of the study. So it changes the way we calculate attrition." (PO 10)*

Implication: Non-commercial R&D would not necessarily have higher or lower attrition rates, as both non-commercial and commercial R&D seek to develop regimens or combinations.

v. Reluctance to stop the project:

Another issue raised by a few of the interviewees was the reluctance to stop a project as a factor that leads to longer timeframes and potentially more costs, and ultimately, higher later-stage attrition. In general, this was raised as an issue affecting mostly non-commercial organizations, either due to emotional attachment to the project (e.g. if the employees are more personally involved) or due to the need to keep the project running to receive funding.

> *"It seems to be a commonly held belief, whether it's true or not – that within industry there's a stronger governance system in place. And in publicly funded projects, some things can last many years when in actuality they should have been closed down. Yeah, because people, it could become almost like a kind of personal crusade, as it were." (PO 12)*

"This could be potentially a bit contentious but these organizations that are funded in order to do this type of work are very reliant on donor funding for their survival. This inherently leads to a dynamic where they want to keep their projects alive. They may not necessarily look at the projects as rational as a pharma company would, and keeping research projects alive could be a good thing, but it can also detract and divert resources that could be used better in other projects. So that is a dynamic in the system that exists, and everybody is aware of it, but it is also something that sometimes can delay, and make things more expensive." (PO 2)

On the other hand, it was pointed out that having independent scientific advisory committees and/or an outside funder to provide an arms-length perspective would guard against this type of bias in decision-making. Furthermore, one interviewee argued that commercial firms are also reluctant to stop a project but for different reasons, such as if a product is not ideal in comparison to others but is still potentially profitable.

"In a general sense it is true that if a company is putting in its own money, they've done some research as to why they want to work in certain areas. Often it is a challenge, we find that they are so convinced that the product that they are developing is the right one, it becomes hard for us to say it's not going to work." (PO 4)

Implication: Non-commercial R&D would **not necessarily have higher or lower** attrition rates, as reflected in competing views expressed among interviewees.

vi. Use of optimization tools:

One interviewee raised the point that some optimization tools for product development that could improve attrition rates might not be available for non-commercial organizations due to their high-costs or to the nature of the diseases they usually work on.

"I think in commercial trials, pharma companies are investing more and more into artificial intelligence, other methods, predictive analytics of toxicity to get smarter in which molecules they pick. (…) big companies have all these artificial intelligence systems that help to tell, to predict toxicity, to predict other things. I haven't seen that maturity in the non-commercial entities, because they simply don't have the resources." (PO 7)

Implication: Non-commercial R&D would have **higher** attrition rates, as they have less access to optimization tools.

vii. Differing non-commercial vs commercial reasons for attrition:

Interviewees highlighted a number of ways in which (non-scientific) reasons for attrition would differ in a non-commercial vs commercial initiative. For a non-commercial entity, cited reasons for higher attrition rates included: focusing on earlier-stage basic research, lack of funding, high cost to manufacture the end product, or greater willingness to share data to facilitate a "fail early, fail fast" strategy.

> *"This is the unique role of the public sector, costs are higher and the probability of success is lower in basic research – pharma picks it up later" (PO 5)*

> *"[Candidate x] was removed from our pipeline a couple of years ago, and then we decided to bring it back. And that was solely a funding decision, it wasn't about the data itself." (PO 10)*

> *"If you look at the highly profitable diseases like oncology, then budget for clinical studies with similar molecules is never really an issue, since there is no global portfolio responsibility. So you would never have this question that we have to choose between two molecules which are equally exciting and might work clinically, since one company would work on each. In neglected disease we often have to choose between two molecules from different companies." (PO 8)*

> *"We have treatments out there, which cost 30 cents for a child, these are already too expensive for some countries … otherwise the Global Fund would not have to subsidize it. So, we don't want the prices for new medicines to be higher. And so in neglected diseases non-commercial the concern is how can we get the cost of goods down so that when we launch a medicine, it's actually affordable. That's why we spend a lot of time trying to reduce the cost of goods early on in clinical development trying to make sure that the final drug will be affordable." (PO 8)*

"There have been very high early attrition rates, as in a lot of the projects being stopped or revised or being thrown back to the drawing board, because these people are researchers who are able to share and willing to share their pre-publication data very early on. We've looked at this, and in the last 10 or so years, our partners have probably worked on 60 to 80 different concepts. And from those, only probably five or six advance eventually to the clinic stage. First of all, it's a very, very efficient system…the scientists value it very much because they can actually see that if you do a preclinical head-to-head comparison between six or eight different candidates, and yours comes out last, then most of the scientists themselves reach a conclusion: we should probably go back to the drawing board and not further pursue that. And that's a very, very cost effective and efficient way of down-selecting and up-selecting different compounds." (PO 11)

Cited reasons for potentially higher attrition rates in commercial initiatives differed, and included: profitability (linked to patentability or competing products), or having ample resources to take risks.

"We won't suffer attrition for commercial reasons (like competition, market or patentability), which is a factor in commercial pharma. I've always wondered how that would impact the attrition profile. So the difference working here is, for example, even in discovery, one of the commercial decision gates would be: could you patent the drug or not? We obviously don't apply this gate." (PO 3)

"A commercial organization…sometimes you're forced to use an active comparator instead of a placebo. And by default, that increases the risk of your trial, but if it's actually successful then you actually can command much higher pricing. (…) So that could drive your attrition up, right? Because it's like, Okay, I'm taking a risk in this cardiac thing, but I mean, if I win it, these are kind of multi-billion dollar revenues if I don't, okay, I just lost, I don't know, a few hundred million, so it might be worth it." (PO 7)

"In industry, I suspect there's a lot more in the earlier stage where you just set up a lot of horses and see what's coming out to the front of the pack and start moving." (PO 12)

Implication: Non-commercial R&D would **not necessarily have higher or lower** attrition rates, as the reasons for stopping a project may differ between non-commercial and commercial initiatives.

viii. Specifics of the disease or indication:

a. Scientific understanding of disease:

The degree of scientific understanding of a disease was raised as a factor that influences high attrition rates especially in earlier stages of the development process.

> *"Attrition rates are very high, they have not yet advanced a model from the [X] trial presented over 10 years ago. This could have potentially been advanced if pharma had made it a priority" (PO 5)*

Implication: Non-commercial R&D likely to have **higher attrition rates** because it works in diseases with limited scientific understanding, *ceteris paribus*.

b. Prevalence or incidence of the disease:

The size of the at-risk population, and the degree to which a product can or cannot be tailored to a subset of the population could also influence attrition.

> *"You can target drugs for more precision type medicine. I don't think that is available to us in the non-commercial space because we are targeting broad populations, we need solutions that work across broader populations. So I think that commercial can have slightly higher success rates because they can target more narrow target population that is more likely to respond to a particular treatment." (PO 2)*

Implication: Non-commercial R&D likely to have **higher attrition rates** because the target population is broad, *ceteris paribus*.

There were more factors that would raise attrition rates for non-commercial R&D vis-à-vis commercial models, than would lower them, but most of the factors raised by respondents were indeterminate. As the qualitative data does not tell us about the magnitude of the effect, no firm conclusions can be drawn on whether non-commercial R&D would be characterized by higher, lower or equivalent attrition rates as commercial R&D.

Table 9: Factors influencing attrition rates for non-commercial (vs commercial) R&D

Attrition rate higher	Indeterminate	Attrition rate lower
Limited availability or use of optimization tools	Type of technology or product	Lower pre-existing standard of care means easier to demonstrate benefit of candidate product
Limited scientific understanding of disease	Testing for multiple indications	
Wide prevalence or incidence of the disease means broad target population across which a drug must be shown to be effective	Combinations or regimens	
	Reluctance to stop the project	
	Differing non-commercial vs commercial reasons for attrition	

6 | LIMITATIONS OF THE STUDY AND DIRECTIONS FOR FUTURE RESEARCH

This is an observational, descriptive and analytic study of non-commercial R&D initiatives. The main limitations of the study are the small non-random sample size and the short period of time in which the study was conducted, which can partially explain the limited amount of quantitative data received. As a result, we have sought to be cautious in drawing inferences from the data.

Given the nascent nature of the area, with almost no prior literature focusing on costs, timeframes or attrition rates of non-commercial R&D initiatives, we see the merits of this study as generating hypotheses for further testing against a larger sample of quantitative data, and for providing intuition regarding reasons underlying any significant differences between non-commercial and commercial initiatives.

We also recognize that respondents may have had incentives to report costs, timeframes or attrition rates that were favourable to their organizations. Although we sought to check quantitative data against publicly available sources, in general very little relevant data was in the public domain or it was only available at a high level of aggregation.

It is also important to highlight that many non-commercial R&D initiatives arose because the commercial model did not meet important global public health needs. This study did not compare the patient, population-level, equity or health system benefits offered by the products emerging from non-commercial vs commercial initiatives – only the costs and timeframes to develop those products. A fuller comparison could take both into account.

For future research, it may be useful both to expand the dataset on NCEs and also dedicate special attention to improving our understanding of non-commercial vaccine and diagnostics R&D, recalling that we excluded vaccines and diagnostics from our quantitative analysis due to very little data, and were only able to examine a small sample for simple and complex NCEs.

Finally, in future research it would be useful to interview a broader range of stakeholders. Our interviews focused on practitioners with direct knowledge of non-commercial R&D initiatives involved in product development for NDs, usually employees of the initiatives themselves. A more thorough picture is likely to emerge through interviews with additional non-commercial initiatives, and a broader range of their partners and funders.

7 | DISCUSSION AND CONCLUSIONS

The quantitative and qualitative data combined paint a complex, if grainy, picture. Keeping in mind the very small sample of quantitative data, the following hypotheses emerge from the analysis:

Regarding **costs**, the quantitative data suggested that non-commercial R&D costs about the *same* overall as P2I averages for NCEs. The qualitative data identified many more reasons why non-commercial costs would be *lower* than commercial R&D, but did not shed light on the magnitude of the effects. The overall emerging hypothesis is that direct costs of non-commercial R&D are expected to be *equivalent* or *somewhat lower* than commercial. Indirect costs for commercial R&D are expected to be higher due to higher overhead and capitalization costs.

Regarding **timeframes**, the quantitative data suggested that non-commercial R&D timeframes would be *shorter* for simple NCEs and *equivalent* for complex NCEs in comparison to P2I averages. Yet the qualitative data identified many more reasons why non-commercial timeframes would be longer than commercial; the data did not shed light on the magnitude of the effects. The overall emerging hypothesis is that timeframes of non-commercial R&D are expected to be *equivalent or somewhat longer* than commercial.

Regarding **attrition** rates, the quantitative data was not adequate for analysis. The qualitative data uncovered more reasons why attrition rates might be higher in non-commercial R&D, but also provided reasons why they might be lower or there might be no difference. Again, the magnitude of the effects are not quantified. The overall *very tentative* hypothesis that emerges is that attrition rates for non-commercial R&D would be *equivalent* to commercial R&D.

The study found that non-commercial R&D might differ in many significant ways from its commercial counterparts. However, it is possible that the sum of these differences cancel each other out such that total costs, timeframes and attrition rates would be largely equivalent to commercial R&D. If non-commercial R&D is characterized by equivalent or lower costs, equivalent or longer timeframes, and equivalent attrition rates to commercial R&D, the final expected direct costs and quantity of products resulting from a pipeline of non-commercially-developed candidate technologies would be equivalent to those resulting from commercial R&D. In other words, the estimated parameters of the P2I v2.0 model are supported by this analysis, keeping in mind the differences between P2I averages and other estimates available in the literature for commercial R&D.

In sum, the emerging overall hypothesis is that non-commercial R&D is comparable to commercial initiatives in efficiency, as indicated by direct costs, timeframes and attrition rates.

We note that the P2I model relies heavily on technology archetypes (e.g. repurposed molecule vs. simple NCE vs complex NCE for drugs) to assign costs, timeframes and attrition rates to candidate products in the pipeline. However, coding candidates into these archetypes was not straightforward, even for organizations that knew their own technologies very well. Both in the literature and in our interviews, technology type is only one of many variables that influenced costs, timeframes or attrition rates.

This study identified a number of significant differences between non-commercial and commercial R&D. In total, we identified 12 factors influencing costs, 12 factors influencing timeframes, and 9 factors influencing attrition rates; many of these echoed those already identified in the literature on commercial R&D, but many of them were specific to non-commercial initiatives. These many factors suggest that the P2I model may need to be modified when applied more narrowly. In other words, these differences may get averaged out when applied to a pipeline of nearly 450 candidates across a broad range of diseases (the intended use of the model), but may be magnified in the narrower context of a single disease, technology type, or organization. The many variables that affect cost, timeframes and attrition rates also highlight that caution is merited when comparing any single trial, product or organization against average benchmarks, as there are many legitimate reasons behind departure from the mean.

Finally, we re-emphasize that the small size and heterogeneity of the dataset means that these are tentative conclusions. Further quantitative research is needed to test these hypotheses against larger datasets. And further qualitative research is needed to deepen our understanding of the strengths and weaknesses of non-commercial R&D initiatives, and how well they function as alternatives to the traditional commercial model, especially beyond the neglected diseases where commercial interests are higher.

As this short study forms part of an ongoing 5-year research project (2019–2023), we hope to tackle some of these research needs in the future.

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9 | ANNEXES

Annex 1.
List of non-commercial R&D organizations contacted by group

Group 1: PDPs that are currently using the P2I model to analyse their portfolios
DNDi – Drugs for Neglected Diseases initiative
EVI – European Vaccine Initiative
FIND – Foundation for Innovative New Diagnostics
MMV – Medicines for Malaria Venture
TB Alliance

Group 2: PDPs not currently using the P2I model to analyse their portfolios
CONRAD
FHI360
GDAC – Global Dengue + Aedes transmitted diseases Consortium
HIV Vaccines Trials Network (HVTN)
IAVI – International AIDS Vaccine Initiative
IDRI – Infectious Disease Research Institute
IPM – International Partnership for Microbicides
IVCC – Innovative Vector Control Consortium
IVI – International Vaccine Institute
PATH
Sabin Vaccine Institute
TBVI – TuBerculosis Vaccine Initiative

Group 3: PDPs that are no longer in operation
Aeras
Consortium for Parasitic Drug Development (CPDD)
South African AIDS Vaccine Initiative (SAAVI)

Group 4: Organizations with projects addressing neglected diseases
Instituto Nacional de Salud
Justus-Liebig-Universitat Giessen
Universidade Federal de Goias
Universitat de Barcelona
US Centers for Disease Control and Prevention
French National Agency for Research on AIDS and Viral Hepatitis (ANRS)
Inserm
Institut Pasteur Lille
Chengdu Institute of Biological Products
Fundacao Butantan
NIAID
US National Institutes of Health
Fundação Oswaldo Cruz
Weill Cornell Medical College
Université des Montagnes
Stanford University
University of California Berkeley
Brandeis University
University of Stellenbosch
Swiss Tropical & Public Health Institute
University of Basel
Canadian Institutes of Health Research
McGill University
WHO/TDR

Group 5: Other Organizations
Bill and Melinda Gates Foundation (BMGF)
Unitaid
McKinsey and Co.

Annex 2.
Questionnaire for quantitative data collection

INSTRUCTIONS	
This questionnaire is based on the Portfolio-to-Impact (P2I) Model developed by the World Health Organization. For more information about the Model, please refer to: Terry et al (2018) and Young et al (2018)	
Attrition Rates Tab. Use this tab for information about attrition rates (probability of sucess) from one phase to the next in the development process (preclinical to phase 3).	
Open question	Use the space below the questions to provide information about how the organization uses attrition rates to analyse its portfolio.
Attrition rates table	Use the table to provide the attrition rates used by your organization. If possible, break down rates by product archetype. If not, provide information for the portfolio as a whole.
Project Tabs. Use one tab per project for each project in product pipeline history. Include all products that have reached at least the preclinical phase, including those that have been terminated or suspended. If you chose to provide information about some projects, but not all, please let us know that not all candidates from the portfolio were included.	
Project	Name of the project/candidate/product in the development process
Disease	Select from drop-down list. If "other", please specify in the "additional comments" field.
Archetype	Select from drop-down list. Refer to the list of archetype definitions on this page. If you are not sure, leave this field blank and use "additional comments" field to provide any relevant information.
Additional comments	Add any clarification from above fields or any additional relevant information
For diagnostics and vector control products	The Model considers that diagnostics and vector control products have different product development and regulatory pathways, and the development stage for these products was broken down into concept and research; feasibility and planning; design and development; and clinical validation and launch readiness. Please use "preclinical stage" field to provide information regarding "concept and research; "phase 1" field to provide information regarding "feasibility and planning"; "phase 2" field to provide information regarding "design and development" and "phase 3" field to provide information regarding "clinical validation and launch readiness".
Preclinical stage	**Preclinical (after lead optimization)**
Start date	Start date of preclinical stage. Date format: day / month / year
End date	End date of preclinical stage. Date format: day / month / year
Estimate of direct costs	Estimate of direct costs for the preclinical stage
Estimate of in-kind costs	Cash-estimate of in-kind contributions of preclinical stage, if available. If not available, leave blank
Currency	Specify the currency denomination of costs from the drop-down menu. If other, please specify in the "additional comments" field
Funding sources	Specify the names of the funders for the preclinical phase
Main reason(s) for termination/suspension of development (if applicable)	If the project was terminated or suspended, select the reasons from the drop-down list, if applicable. In case there is more than one or "other", please use "additional comments" field to specify. Leave blank if the project continued to the next phase.
Additional comments	Add any clarification from above fields or any additional relevant information

INSTRUCTIONS (continued)	
Clinical stage	
Date of submission of the authorization to start clinical trials	Date of submission of the first authorization to start clinical trials, eg. Investigational New Drug Application (IND) by the US Food and Drug Administration, Investigational Medicinal Product Dossier (IMPD) by the European Medicines Agency, or equivalent. Date format: day / month / year
Date of obtaining the authorization to start clinical trials	Date of obtaining of the first authorization to start clinical trials, eg. Investigational New Drug Application (IND) by the US Food and Drug Administration, Investigational Medicinal Product Dossier (IMPD) by the European Medicines Agency, or equivalent. Date format: day / month / year
Regulatory Agency	Specify which agency issued the authorization to start clinical trials
Additional comments	Add any clarification from above fields or any additional relevant information
Clinical stage – Phase 1a	**If phase 1 testing was not split into 1a/1b testing, use this section for 1a for phase 1 (entire phase) tests. If more than one trial was conducted for the same phase, please use colums on the side to add information about the additional trial(s)**
Start date	Start date of phase 1/1a. Date format: day / month / year
End date	End date of phase 1/1a. Date format: day / month / year
Estimate of direct costs	Estimate of direct costs of phase 1/1a
Estimate of in-kind costs	Cash-estimate of in-kind contributions of phase 1/1a, if available. If not available, leave blank
Currency	Specify the currency denomination of costs from the drop-down menu. If other, please specify in the "additional comments" field
Funding sources	Specify names of the funders for the phase
Main reason(s) for termination/suspension of development (if applicable)	If the project was terminated or suspended, select the reasons from the drop-down list, if applicable. In case there is more than one or "other", please use "additional comments" field to specify. Leave blank if the project continued to the next phase.
Add any additional relevant information	Add any clarification from above fields or any additional relevant information
Clinical stage – Phase 1b	
Start date	Start date of phase 1b. Date format: day / month / year
End date	End date of phase 1b. Date format: day / month / year
Estimate of direct costs	Estimate of direct costs of phase 1b
Estimate of in-kind costs	Cash-estimate of in-kind contributions of phase 1b, if available. If not available, leave blank
Funding sources	Specify name of the funders for the phase
Main reason(s) for termination/suspension of development (if applicable)	If the project was terminated or suspended, select the reasons from the drop-down list, if applicable. In case there is more than one or "other", please use "additional comments" field to specify. Leave blank if the project continued to the next phase.
Additional comments	Add any clarification from above fields or any additional relevant information

INSTRUCTIONS (continued)	
Clinical stage – Phase 2a	**If phase 2 testing was not split into 2a/2b testing, use this section for 2a for phase 2 (entire phase) tests. If more than one trial was conducted for the same phase, please use colums on the side to add information about the additional trial(s).**
Start date	Start date of phase 2/2a. Date format: day / month / year
End date	End date of phase 2/2a. Date format: day / month / year
Estimate of direct costs	Estimate of direct costs of phase 2/2a
Estimate of in-kind costs	Cash-estimate of in-kind contributions of phase 2/2a, if available. If not available, leave blank
Currency	Specify the currency denomination of costs from the drop-down menu. If other, please specify in the "additional comments" field
Funding sources	Specify names of the funders for the phase
Main reason(s) for termination/suspension of development (if applicable)	If the project was terminated or suspended, select the reasons from the drop-down list, if applicable. In case there is more than one or "other" please use "additional information" field to specify. Leave blank if the project continued to the next phase.
Additional comments	Add any clarification from above fields or any additional relevant information
Clinical stage – Phase 2b	
Start date	Start date of phase 2b. Date format: day / month / year
End date	End date of phase 2b. Date format: day / month / year
Estimate of direct costs	Estimate of direct costs of phase 2b
Estimate of in-kind costs	Cash-estimate of in-kind contributions of phase 2b, if available. If not available, leave blank
Currency	Specify the currency denomination of costs from the drop-down menu. If other, please specify in the "additional information" field
Funding sources	Specify names of the funders for the phase
Main reason(s) for termination/suspension of development (if applicable)	If the project was terminated or suspended, select the reasons from the drop-down list, if applicable. In case there is more than one or "other", please use "additional comments" field to specify. Leave blank if the project continued to the next phase.
Additional comments	Add any clarificaiton from above fields or any additional relevant information

INSTRUCTIONS (continued)	
Clinical stage – Phase 3a	**If phase 3 testing was not split into 3a/3b testing, use this section for 3a for phase 3 (entire phase) tests. If more than one trial was conducted for the same phase, please use colums on the side to add information about the additional trial(s).**
Start date	Start date of phase 3/3a. Date format: day / month / year
End date	End date of phase 3/3a. Date format: day / month / year
Estimate of direct costs	Estimate of direct costs of phase 3/3a
Estimate of in-kind costs	Cash-estimate of in-kind contributions of phase3/3a, if available. If not available, leave blank
Currency	Specify the currency denomination of costs from the drop-down menu. If other, please specify in the "additional comments" field
Funding sources	Specify names of the funders for the phase
Main reason(s) for termination/suspension of development (if applicable)	If the project was terminated or suspended, select the reasons from the drop-down list, if applicable. In case there is more than one or "other", please use "additional comments" field to specify. Leave blank if the project continued to the next phase.
Additional comments	Add any clarification from above fields or any additional relevant information
Clinical stage – Phase 3b	
Start date	Start date of phase 3b. Date format: day / month / year
End date	End date of phase 3b. Date format: day / month / year
Estimate of direct costs	Estimate of direct costs of phase 3b
Estimate of in-kind costs	Cash-estimate of in-kind contributions of phase 3b, if available. If not available, leave blank
Currency	Specify the currency denomination of costs from the drop-down menu. If other, please specify in the "additional comments" field
Funding sources	Specify names of the funders for the phase
Main reason for termination/ suspension of development (if applicable)	If the project was terminated or suspended, select the reasons from the drop-down list, if applicable. In case there is more than one or "other", please use "additional comments" field to specify. Leave blank if the project continued to the next phase.
Additional comments	Add any clarification from above fields or any additional relevant information

INSTRUCTIONS (continued)	
Regulatory stage	
Was there any accelerated drug development regulatory approval pathway?	"Yes" or "No". If "yes", specify which one. Eg. "orphan drug designation", "priority review", "fast track" by US Food and Drug Administration, or equivalent.
Data of submission	Date of submission of request for accelerated drug development/regulatory approval pathway. Date format: day / month / year
Date of obtaining	Date of obtaining accelerated drug development/regulatory approval pathway. Date format: day / month / year
Regulatory agency	Specify which agency issued the accelerated drug development/regulatory approval pathway.
Estimate of direct costs	Estimate of direct costs for obtaining accelerated drug development/regulatory approval pathway
Estimate of in-kind costs	Cash-estimate of in-kind contributions for obtaining accelerated drug development/regulatory approval pathway, if available. If not available, leave blank
Currency	Specify the currency denomination of costs from the drop-down menu. If other, please specify in the "additional comments" field
Funding sources	Specify names of the funders for the phase
Additional comments	Add any clarification from above fields or any additional relevant information
Regulatory approval	
Date of submission of first regulatory approval	Date of submission of the first regulatory approval. Date format: day / month / year
Date of obtaining the first regulatory approval	Date of obtaining the first regulatory approval. Date format: day / month / year
Regulatory agency	Specify which agency issued the first regulatory approval
Estimate of direct costs for the first regulatory approval	Estimate of direct costs for obtaining the first regulatory approval
Estimate of in-kind costs for the first regulatory approval	Cash-estimate of in-kind contributions for obtaining the first regulatory approval, if available. If not available, leave blank
Currency	Specify the currency denomination of costs from the drop-down menu. If other, please specify in the "additional comments" field
Funding sources	Specify names of the funders for the phase
Additional comments	Add any clarification from above fields or any additional relevant information

INSTRUCTIONS (continued)	
Additional information	
Was there any patent application filed?	"Yes" or "No", and if "yes", specify application/patent number
Date of filing of the first patent application	Date of submission of the first patent application. Date format: day / month / year
Data of grant of the first patent application	Date of grant of the first patent application. Date format: day / month / year.
Patent office	Specify at which patent office the first patent application was filed.
Estimate of direct costs for the first patent application	Estimate of direct costs for filing the first patent application
Estimate of in-kind costs for the first patent application	Cash-estimate of in-kind contributions for filing the first patent application, if available. If not available, leave blank
Currency	Specify the currency denomination of costs from the drop-down menu. If other, please specify in the "additional comments" field
Funding sources	Specify names of the funders for the phase
Additional comments	Add any clarification from above fields or any additional relevant information
End of questionnaire	

Description of archetypes from Terry 2018 and Young 2018 (Portfolio-to-Impact P2I Model)

Archetypes		Description	Examples
Vaccine	Simple	Platform has been used to develop other vaccines	Hepatitis A, Hepatitis B, Polio
	Complex	Requires completely novel approach; no platform; no existing research	Pneumococcal conjugate vaccine (PCV), Meningitis B
	Unprecedented	Vaccines targeting diseases that would require the development of innovative platforms and a better understanding of the basic biology and of immune protection	Candidate vaccines for HIV, TB, and malaria
New Chemical Entity (NCE)	Simple	Validated target or mechanism of action	Primaquine
	Innovative	Novel target or mechanism of action with understanding of disease pathogenesis	Ibrutinib
	Complex	Novel target or mechanism of action without understanding of disease pathogenesis	Imatinib
Repurposed Drug	Simple	Drug has sufficient safety data to start development in Phase II	Azithromycin, Doxycylcine
	Complex	Drug requires some Phase I clinical trials to verify safety in humans	Moxidectin
Biologic	Simple	Validated target or mechanism of action	IL-17 antibody
	Complex	Novel target or mechanism of action	Natalizumab
Diagnostics	Assay development	Development of a diagnostic assay	Lateral flow tests, Quantitative molecular tests
	Simple technical platform development	Development of a technological platform that enhances current technology	Hypersensitive malaria rapid diagnostic test (RDT)
Vector control products		Vector control products	

Attrition Rates

Does the organization use attrition rates to analyse its portfolio?
If yes, do you use historical (real) data or do you use an estimate? Please explain the approach you use.

Type answer here.

Attrition Rates

Project Group (e.g. by disease & technology)	Archetype	Preclinical	Phase 1/1a	Phase 1b	Phase 2/2a	Phase 2b	Phase 3/3a	Phase 3b
	Vaccine-simple							
	Vaccine-complex							
	Vaccine – unprecedented							
	NCE-simple							
	NCE-innovative							
	NCE-complex							
	Drug repurpose-simple							
	Drug repurpose-complex							
	Biologic-simple							
	Biologic-complex							
	Diagnostic-assay dev.							
	Diagnostic-simple platform dev.							
	Other products. Specify.							
	All portfolio							

Use this space to add any clarification or any additional relevant information you wish to add

Type answer here.

Project Description for Project 1 to 10

Project description	
Project	
Disease	
Archetype	
Additional comments	
Preclinical stage	
Start date	
End date	
Estimate of direct costs	
Estimate of in-kind costs	
Currency	
Funding sources	
Main reason(s) for termination/suspension of development (if applicable)	
Additional comments	
Clinical stage	
Date of submission of the authorization to start clinical trials	
Date of obtaining the authorization to start clinical trials	
Regulatory agency	
Additional comments	
Clinical stage – Phase 1/1a	
Start date	
End date	
Estimate of direct costs	
Estimate of in-kind costs	
Currency	
Funding sources	
Main reason(s) for termination/suspension of development (if applicable)	
Additional comments	

Project Description (continued)

Clinical stage – Phase 1b	
Start date	
End date	
Estimate of direct costs	
Estimate of in-kind costs	
Currency	
Funding sources	
Main reason(s) for termination/suspension of development (if applicable)	
Additional comments	
Clinical stage – Phase 2/2a	
Start date	
End date	
Estimate of direct costs	
Estimate of in-kind costs	
Currency	
Funding sources	
Main reason(s) for termination/suspension of development (if applicable)	
Additional comments	
Clinical stage – Phase 2b	
Start date	
End date	
Estimate of direct costs	
Estimate of in-kind costs	
Currency	
Funding sources	
Main reason(s) for termination/suspension of development (if applicable)	
Additional comments	

Project Description (continued)

Clinical stage – Phase 3/3a	
Start date	
End date	
Estimate of direct costs	
Estimate of in-kind costs	
Currency	
Funding sources	
Main reason(s) for termination/suspension of development (if applicable)	
Additional comments	
Clinical stage – Phase 3b	
Start date	
End date	
Estimate of direct costs	
Estimate of in-kind costs	
Currency	
Funding sources	
Main reason(s) for termination/suspension of development (if applicable)	
Additional comments	
Regulatory stage	
Was there any accelerated drug development/regulatory approval pathway?	
Date of submission	
Date of obtaining	
Regulatory agency	
Estimate of direct costs	
Estimate of in-kind costs	
Currency	
Funding sources	
Additional comments	

Project Description (continued)

Regulatory approval	
Date of submission of first regulatory approval	
Date of obtaining the first regulatory approval	
Regulatory agency	
Estimate of direct costs for the first regulatory approval	
Estimate of in-kind costs for the first regulatory approval	
Currency	
Funding sources	
Additional comments	
Additional information	
Was there any patent application filed?	
Date of filing of the first patent application	
Date of grant of the first patent application	
Patent office	
Estimate of direct costs for the first patent application	
Estimate of in-kind costs for the first patent application	
Currency	
Funding sources	
Additional comments	
End of questionnaire	

Annex 3.
Sample interview questions

Research Project:
"Analysing the data from the Portfolio-to-Impact (P2I) R&D modelling tool for non-commercial R&D"

Research Site: Global Health Centre, Graduate Institute of International and Development Studies

Principal Investigator: Suerie Moon, Director of Research at the Global Health Centre
Assistant Investigator: Marcela Vieira, Project Coordinator at the Global Health Centre

Sponsor: Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization

Sample interview questions

1. What is your role within the organization, and how would you describe your level of familiarity with the costs, timeframes and attrition rates of your organization's product development portfolio?
2. What are the main drivers of costs (higher or lower) per development phase?
   Timeframes (shorter or longer) per development phase?
   Attrition rates (higher or lower) per development phase?
3. How does the cost, timeframe and attrition rates of research and development vary between the different products developed?
4. How might costs or time be saved and attrition rates improved?
5. How does your organization decide whether a candidate technology will move from one development phase to the next?
6. Optional (if time): How do you believe your organization's costs, timeframes and attrition rates compare to commercial R&D?
7. Is there anything else the research team should understand regarding the costs, timeframes and attrition rates of product development for your organization?
   Is there anyone else, within or outside your organization, whom you would recommend we interview?
8. Clarification of questions from the questionnaire or from information obtained via webpages, annual reports or other public source.

Annex 4.
Informed consent form

Consent to Participate in a Research Study

Project: Analysing the data from the Portfolio-to-Impact (P2I) R&D modelling tool for non-commercial R&D

You are being asked to participate in a research study conducted by Dr. Suerie Moon and Ms. Marcela Vieira (research team) at the Graduate Institute of International and Development Studies, Geneva, Switzerland. Please take the time to read the following information carefully before you decide whether you want to take part. Please feel free to ask any questions about the research study and your role as a participant. All participants will receive a copy of this consent document.

Purpose, procedures, and participant selection: The purpose of this research study is to improve understanding of how the costs and timeframes of non-commercial R&D initiatives compare to current R&D averages included in the P2I Model. This research project will conduct an analysis of the data generated by the TDR Portfolio-to-impact (P2I) tool applied to non-traditional research and development (R&D) activities, particularly the product development partnerships (PDPs). The questionnaire and interview phase of the study will include participants from non-commercial R&D initiatives.

Participation in this study is voluntary and there are no direct benefits for participation, aside from the research itself and its implications for public policy. As a participant, you can refuse to answer any question you choose. You are also free to terminate the interview at any time, at your discretion and at any moment throughout the research process, without any consequence or inconvenience. The transcript or notes from the interview will be shared with you for review prior to finalization; you will be given the opportunity to change the wording of your own interview text. For the sake of research integrity and reducing bias in the sample, you will not be able to withdraw your data after submitting the questionnaire and/or when reviewing the interview transcript or notes.

Duration and location of interview: We estimate the interview will take between 30–60 minutes, depending on the length of responses. For interviewees located in Geneva, we will come to your office or host you at the Graduate Institute for the interview. The interview will be conducted by a member of the research team in a quiet, private location such as a closed office space. For interviewees located outside of Geneva, we will conduct the interviews over the Zoom webinar platform, which is password protected.

Anonymity: We appreciate the sensitivity of the issues being discussed. To offset any risks that may emerge from your participation, we fully commit to preserving your anonymity and the anonymity of your organization. Commitments to ensure anonymity will be maintained by ensuring recordings are not shared; that transcripts are anonymised and details that can be used to identify participants are removed from transcripts or concealed in write-ups. The questionnaire and any audio recording from your interview will be securely stored and any transcript of the interview will be fully anonymized. Neither your name nor that of your organization will be used in any published documents by the researcher without your express permission to do so.

Data security: All project data will be stored securely on the Graduate Institute's server and only accessible to the immediate project team (PI: Suerie Moon, Researcher: Marcela Vieira, Research Assistant: Ryan Kimmitt). The shared drives are protected through access controls, and all data access is logged and audited on a regular basis.

Sharing results: Prior to finalization, copies of both the draft full research report and shorter manuscript will be shared with you as a study participant, and you will be given the opportunity to comment. For the sake of research integrity and reducing bias in the sample, you will not be given the opportunity to withdraw your data when reviewing the research report and manuscript. A full research report will be published and a shorter article will be submitted to an open-access publication so that the findings will be widely and publicly available.

Important Contact Information:

Institution: Graduate Institute of International and Development Studies, Geneva
Chemin Eugène-Rigot 2, 1202 Genève, Switzerland

Principal Investigator: Dr. Suerie Moon
Director of Research, Global Health Centre and Visiting Lecturer
Graduate Institute of Geneva, Switzerland. Bureau P2–712
Maison de la Paix, Chemin Eugène-Rigot 2, CP 1176, 1211 Geneva, Switzerland
Email: suerie.moon@graduateinstitute.ch . Phone: +41 22 908 5845

Sponsor: Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization, Avenue Appia 20, 1211 Geneva 27, Switzerland

Informed consent form for representatives of non-commercial R&D initiatives

Research Project: Analysing the data from the Portfolio-to-Impact (P2I) R&D modelling tool for non-commercial R&D

Participant's Statement:

I, _____ (print name of participant), have read the foregoing information, and have understood the risks and benefits of participation in the research study. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction. I understand I will have the opportunity to comment on data from the interview and drafts of the research products. I understand I will not be quoted by name in the published results. I understand I will not be able to withdraw my data when reviewing the transcription or notes from the interview and/or the draft research report and manuscript.

I consent voluntarily to participate in this study YES/NO
I consent to having the interview audio recorded YES/NO

Participant's signature: _____

Date (day/month/year): _____

Researcher's Statement:

I,_____ (print name of researcher), confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily. A copy of this Informed Consent Form has been provided to the participant.

Researcher's signature: _____

Date (day/month/year): _____

Annex 5.
Quantitative dataset – costs and timeframes

Costs:

Product	Archetype	Preclinical	Phase 1	Phase 2	Phase 3	Approval	
product1	NCE-Simple	–	–	306,218.88	–	–	
product3	NCE-Simple	9,297,225.35	6,344,956.31	7,143,567.87	39,248,868.91	3,568,732.31	
product4	NCE-Simple	21,663,258.49	6,683,146.14	6,505,415.70	18,602,179.49	2,265,400.90	
product18	NCE-Simple	4,819,883.00	3,089,008.00	–	–	–	
product21	NCE-Simple	4,268,261.00	–	–	–	–	
product12	NCE-Complex	9,273,787.50	2,127,529.82	2,145,711.86	14,291,496.00	6,190,738.00	
product13	NCE-Complex	9,273,787.50	2,127,529.82	44,177,411.00	34,752,274.00	–	
product14	NCE-Complex	9,273,787.50	2,127,529.82	2,145,711.86	32,900,448.00	–	
product15	NCE-Complex	9,273,787.50	2,127,529.82	2,145,711.86	22,370,301.00	–	
product16	NCE-Complex	9,034,768.00	2,105,961.00	–	–	–	
product17	NCE-Complex	3,081,809.00	3,016,688.00	–	–	–	
product19	NCE-Complex	3,528,923.00	–	–	–	–	
product20	NCE-Complex	1,615,753.74	–	–	–	–	
product10	Repurposed Drug – Simple	–	–	–	2,300,000.00	–	
product11	Repurposed Drug – Simple	–	100,000.00	–	–	–	
product2	Repurposed Drug – Simple	–	–	–	5,475,151.12	–	
Global Average Drugs (NCEs + Repurposed)		$ 7,867,086	$ 2,984,988	$ 9,224,250	$ 21,242,590	$ 4,008,290	$ 45,327,204

Table of costs converted and adjusted to 2017 USD. Archetype averages were calculated by taking the sum of costs for each archetype in a phase, and dividing by the amount of candidates in that archetype that incurred a cost in that phase. Costs incurred in a phase shared among multiple product candidates were divided equally among them. The number of candidates incurring costs per archetype per phase is the N value below the average. Total global average was calculated by adding the averages in the different phases. Methodology and assumptions are more detailed described in the full research report.

		Preclinical	Phase 1	Phase 2	Phase 3	Approval	Total
	NCE Simple	$10,012,156.96	$5,372,370.15	$4,651,734.15	$28,925,524.20	$2,917,066.61	$51,878,852.07
		N=4	N=3	N=3	N=2	N=2	
	NCE Complex	$6,794,550.47	$2,272,128.05	$12,653,636.65	$26,078,629.75	$6,190,738.00	$53,989,682.91
		N=8	N=6	N=4	N=4	N=1	

Conversion Assumptions:
"Smooth" spending across entire timeframe
OECD yearly exchange rate
Phases dated at start of first trial in that phase
1/2, 1a, 1b are phase 1. 2a/2b 2/3 are Phase 2, 3a/3b/3c are phase 3
CPI-U Index, Chained to 1982–1984
Projected costs were estimated in 2019 dollars and deflated to 2017 dollars

Yearly costs calculated by multiplying the percentage of the year a candidate was in a phase (weight), the yearly cost incurred in that phase (total cost in phase divided by amount of years in that phase), and the conversion rate for the year incurred. Sum of all yearly costs is the total cost in dollars, which was then adjusted to 2017 dollars.

Historical Interest Rates: OECD monthly

USD : Euro									
2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
1.09	1.12	1.06	0.89	0.81	0.80	0.80	0.73	0.68	0.72
2010	2011	2012	2013	2014	2015	2016	2017	2018	10-Year
0.76	0.72	0.78	0.75	0.75	0.90	0.90	0.89	0.85	0.81

Euro : USD									
2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
0.92	0.89	0.94	1.13	1.24	1.24	1.25	1.37	1.46	1.39
2010	2011	2012	2013	2014	2015	2016	2017	2018	10-Year
1.32	1.39	1.29	1.33	1.33	1.11	1.11	1.13	1.18	1.39

CPI-U Chained 1982–1984									
2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
172.2	177.1	179.9	184	188.9	195.3	201.6	207.3	215.3	214.5
0.033	0.028	0.016	0.022	0.026	0.033	0.031	0.027	0.037	-0.004
2010	2011	2012	2013	2014	2015	2016	2017	2018	2019*
218.1	224.9	229.6	233	236.7	237	240	245.1	251.1	255.7
0.017	0.030	0.020	0.015	0.016	0.001	0.013	0.021	0.024	0.018

*An estimate for 2019 is based on the change in the CPI from second quarter 2018 to second quarter 2019

Timeframes:

Product	Archetype	Preclinical	Phase 1	Phase 2	Phase 3	Approval	Total
product1	NCE-Simple	–	–	1.38	–	–	–
product18	NCE-Simple	1	0.83	–	–	–	–
product21	NCE-Simple	–	–	–	–	–	–
product4	NCE-Simple	2.3	3.59	–	3.68	–	9.5
product3	NCE-Simple	–	3.98	1.78	3.67	–	13
product6	NCE-Simple	–	0.25	2.08	–	–	-
product12	NCE-Complex	4.25	2	2	3.83	0.67	16.95
product15	NCE-Complex	4.25	2	2	2.83	–	–
product13	NCE-Complex	4.25	2	11	1.83	–	–
product14	NCE-Complex	4.25	2	2	4	–	–
product16	NCE-Complex	–	1	–	–	–	–
product17	NCE-Complex	1	1	–	–	–	–
product19	NCE-Complex	2.83	–	–	–	–	–
product20	NCE-Complex	1.83	–	–	–	–	–
product2	Repurposed Drug – Simple	–	–	–	3.75	–	–
product5	Repurposed Drug – Simple	–	–	–	5.17	–	–
product7	Repurposed Drug – Simple	–	–	–	1.41	–	–
product8	Repurposed Drug – Simple	–	–	–	1.08	–	–
product9	Repurposed Drug – Simple	–	–	0.50	3.7	–	–

Timeframes were calculated by finding the cumulative amount of time in testing per archetype, then dividing by the number of candidates in the same archetype that had testing in that phase.Time incurred in a phase shared among multiple candidates was divided equally among them. Any testing that was ongoing as of 1-11-19 without a predicted end date was not used in the analysis (marked yellow in table). Individual project totals were calculated from initial of preclinical phase to obtaining of regulatory approval and is not the sum of individual phases. Total global average is a simple sum of averages in each phase. Methodology and assumptions are more detailed described in the full research report.

	Preclinical (N=2)	Phase 1 (N=3)	Phase 2 (N=3)	Phase 3 (N=2)	Total
NCE Simple	1.65	2.61	1.75	3.67	9.67
	N=2	N=3	N=3	N=2	
	Preclinical (N=1)	**Phase 1 (N=6)**	**Phase 2 (N=4)**	**Phase 3 (N=1)**	**Total**
NCE Complex	1.00	1.67	4.25	4.00	10.92
	N=1	N=6	N=4	N=1	

	With ongoing testing	With ongoing testing				
	NCE-Complex	**Preclinical**	**Phase 1**	**Phase 2**	**Phase 3**	**Approval**
Cumulative Time		22.67	10.00	17.00	12.50	0.67
Candidates in Phase		7	6	4	4	1
Time per candidate		3.24	1.67	4.25	3.13	0.67
	NCE-Simple					
Cumulative Time		3.30	8.65	5.24	7.35	–
Candidates in Phase		2	4	4	3	–
Time per candidate		1.65	2.16	1.31	2.45	–

	No ongoing testing	With ongoing testing			
	NCE-Complex	**Preclinical**	**Phase 1**	**Phase 2**	**Phase 3**
Cumulative Time		1	10	17	4
Candidates in Phase		1	6	4	1
Time per candidate		1	1.67	4.25	4
	NCE-Simple				
Cumulative Time		3.30	7.82	5.24	7.35
Candidates in Phase		2	3	3	2
Time per candidate		1.65	2.61	1.75	3.67

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