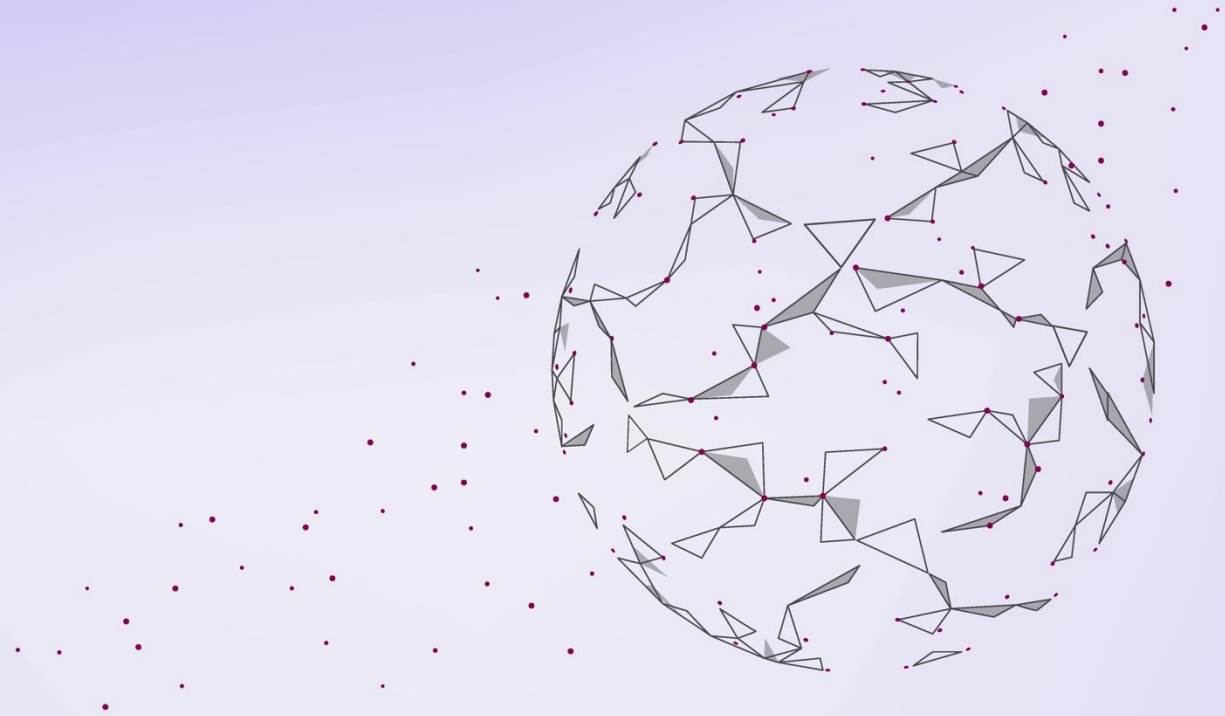

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NON-COMMERCIAL PHARMACEUTICAL R&D: WHAT DO PDPS SUGGEST ABOUT COSTS AND EFFICIENCY?

Research team: Suerie Moon, Marcela Vieira, Ryan Kimmitt

DECLARATIONS

- **Funding:**
  - → UNICEF – UNDP - World Bank -WHO Special Programme for Research and Training in Tropical Diseases' (TDR)
  - → Swiss National Science Foundation

- **Declaration of interests:**
  - → Suerie Moon was Secretary of the Board of Directors of the Drugs for Neglected Diseases initiative (DNDi) during the time of this study

BACKGROUND

- Significant growth in non-commercial research and development (R&D) initiatives, particularly for neglected diseases
- Limited understanding of the ways in which they compare with traditional commercial R&D
- Few studies providing data on costs, timeframes, and attrition rates for specific non-commercial R&D initiatives/projects, but none analysing more than one initiative

METHODOLOGY

- **STUDY GOAL**

→ Improve the understanding of how the costs, timeframes and attrition rates of non-commercial R&D initiatives compare to commercial R&D using averages from the TDR P2I Model

→ Definitions:

→ Non-commercial “initiatives undertaken primarily with a not-for-profit purpose” (lead organizations are academic or governmental in nature, or non-profit PDPs. For-profit firms can play a role in these initiatives).

→ “non-commercial” rather than “non-profit” as a developer may earn profit or revenue on a product as a way to offset costs

METHODOLOGY

- **STUDY DESIGN**

→ Mixed-method, observational, descriptive and analytic study

→ Literature reviews to compare P2I averages with other published estimates.

→ Two kinds of original data:

  → Quantitative data associated with individual R&D projects managed by non-commercial R&D initiatives (written questionnaire)

  → Qualitative data: interview with non-commercial R&D initiatives and/or experts on such initiatives to explain the data and reasons why these might or might not differ from commercial R&D

METHODOLOGY

- Selection of the study population: database of pipeline technologies for neglected diseases developed by Duke University and Policy Cures Research
- We contacted 48 non-commercial R&D initiatives and received quantitative data from 8 organizations on 83 candidate products, and qualitative data through 14 interviews from 12 organizations
- Data was collected between June and September 2019
- Data was aggregated and anonymized

P2I MODEL

- Portfolio-to-Impact (P2I) tool, developed by the WHO/TDR and refined by Duke University and Policy Cures Research
- Aims to predict which products could be expected to reach the market from the existing neglected diseases pipeline, and the estimated costs
- Underlying assumptions (i.e. on cost, timeframes, and attrition rates from preclinical to Phase 3) were derived from historical data on health product development on all diseases, not only NDs.
- Over 25,000 data points from Parexel's R&D cost sourcebook and further refined and validated by interviews.
- Non-commercial R&D (at least late-stage product development) is both relatively recent and small in scale,
- We assume that the majority of the data used to construct the P2I averages comes from commercial R&D.

P2I MODEL

Archetype		Description
Vaccine	Simple	Platform has been used to develop other vaccines
	Complex	Requires completely novel approach; no platform; no existing research
New Chemical Entity (NCE)	Simple	Validated target or mechanism of action
	Innovative	Novel target or mechanism of action with understanding of disease pathogenesis
	Complex	Novel target or mechanism of action without understanding of disease pathogenesis
Repurposed Drug	Simple	Drug has sufficient safety data to start development in Phase II
	Complex	Drug requires some Phase I clinical trials to verify safety in humans
Biologic	Simple	Validated target or mechanism of action
	Complex	Novel target or mechanism of action
Diagnostics	Assay development	Development of a diagnostic assay
	Simple technical platform development	Development of a technological platform that enhances current technology

Young et al. 2018. “Developing New Health Technologies for Neglected Diseases: A Pipeline Portfolio Review and Cost Model.” Gates Open Research 2 (August): 23. https://doi.org/10.12688/gatesopenres.12817.2.

LITERATURE REVIEW – COSTS

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

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LITERATURE REVIEW – TIMEFRAMES

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

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LITERATURE REVIEW – ATTRITION RATES

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%

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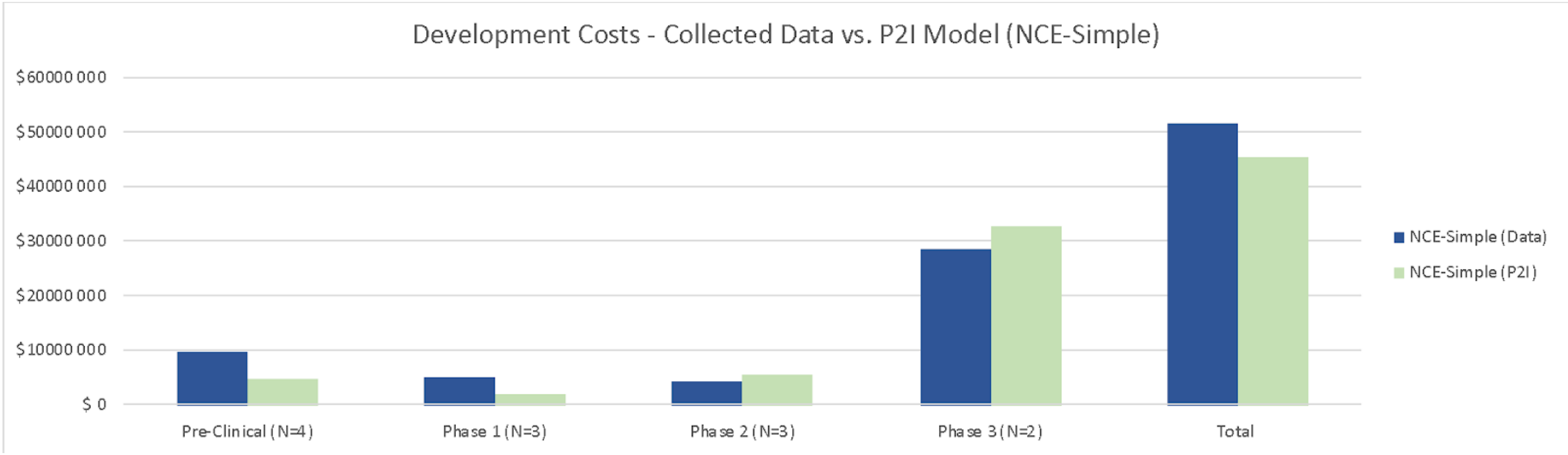
QUANTITATIVE DATA – Data collection

- Combination of data provided by respondents with publicly available information
- Data anonymized and combined by product archetype
- Due to limitations in our dataset, analysis limited to:
  - 1 technology type: drugs (excluded vaccines and diagnostics)
  - 2 P2I archetypes: NCE-Simple and NCE-Complex

QUANTITATIVE DATA – COSTS: NCE Simple



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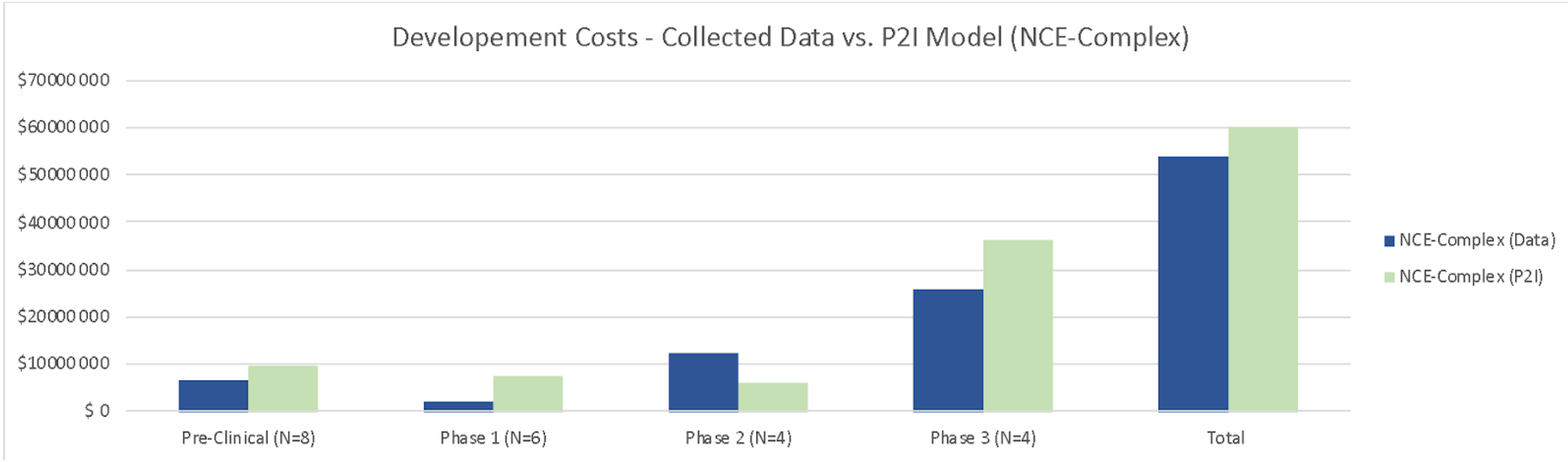
QUANTITATIVE DATA – COSTS: NCE Complex



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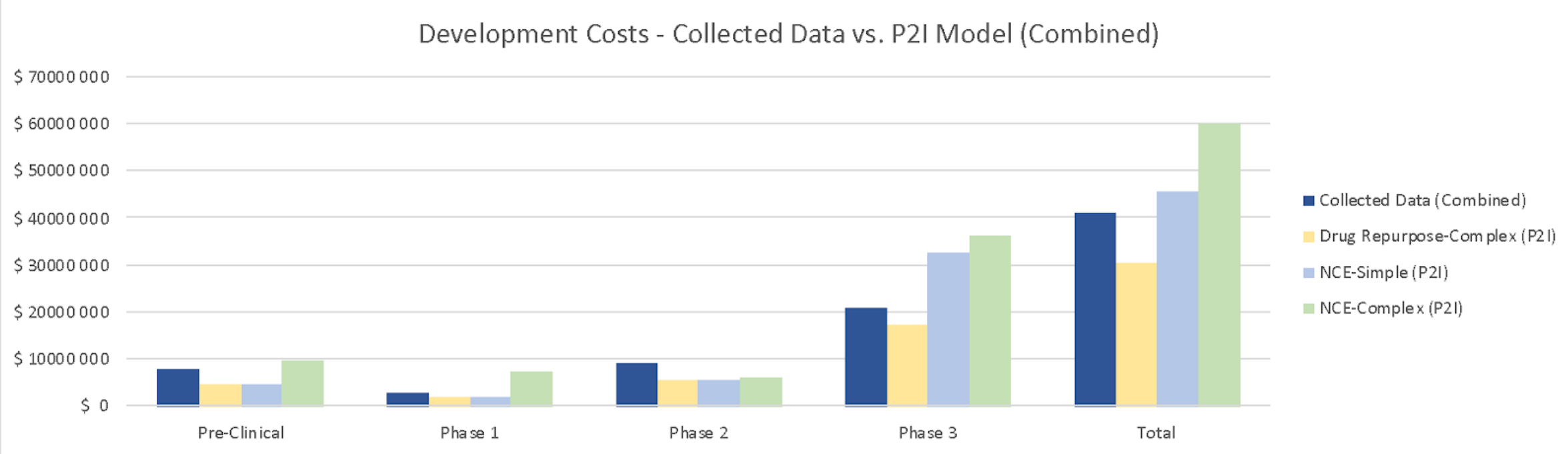
QUANTITATIVE DATA – COSTS: Sensitivity Analysis



Archetype	Pre-Clinical	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 Repurpose-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

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QUANTITATIVE DATA – RESULTS: COSTS

- Quantitative data on non-commercial R&D costs were largely in line with the P2I model estimates, with some variation by phase
  - 13% higher for NCE-Simple (51.87 million USD for non-commercial vs 45.84 million USD for P2I)
  - 8% lower for NCE-Complex (53.98 million USD for non-commercial vs 58.93 million USD in P2I)

- Findings suggest a hypothesis that overall costs to develop simple and complex NCEs are similar between non-commercial R&D initiatives and P2I.

QUALITATIVE DATA – COSTS

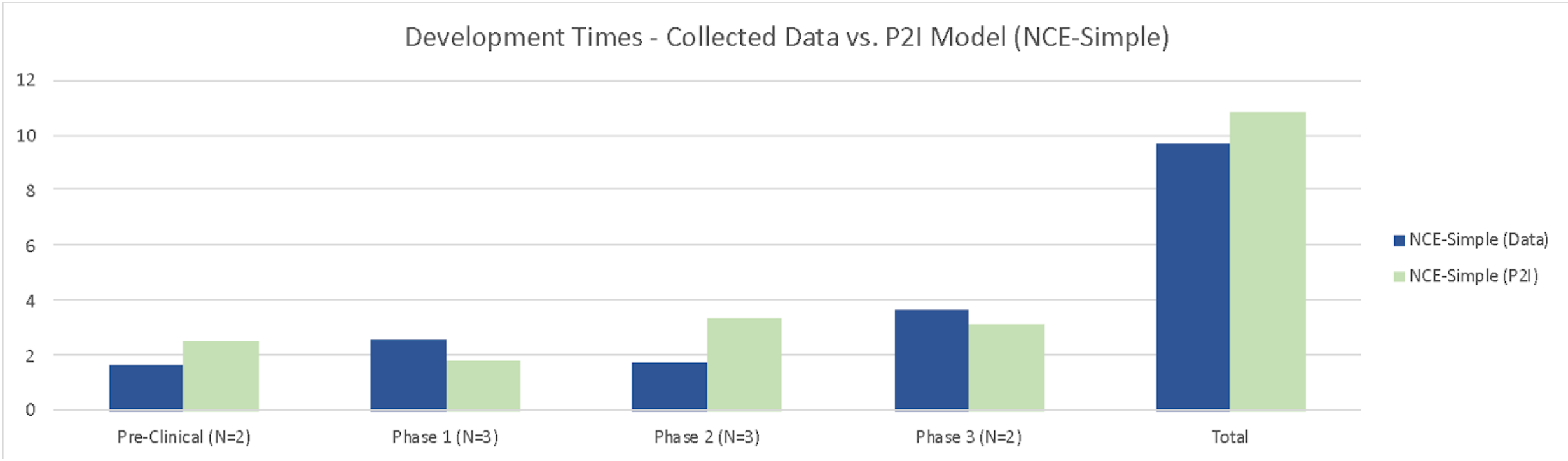
Costs pushed upward	Indeterminate	Costs pushed downward
Infrastructure building and training at LMIC trial sites	Number of arms of the trial	Type of technology (i.e. simpler)
Involvement of affected community in product development	Duration of treatment or disease progression	Trial location in LMIC (vs 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

QUALITATIVE DATA – RESULTS: COSTS

- The qualitative data identified 12 factors that drove costs up or down in the different phases of product development within non-commercial R&D initiatives.
  - 3 factors pushed costs upward,
  - 5 factors pushed costs downward
  - 4 factors were categorized as indeterminate as they would affect both non-commercial and commercial R&D in the same way

- The qualitative data does not tell us about the magnitude of the effects and no firm conclusions can be drawn on whether non-commercial R&D would generally cost the same, less or more than commercial R&D.

QUANTITATIVE DATA – TIMEFRAMES: NCE Simple



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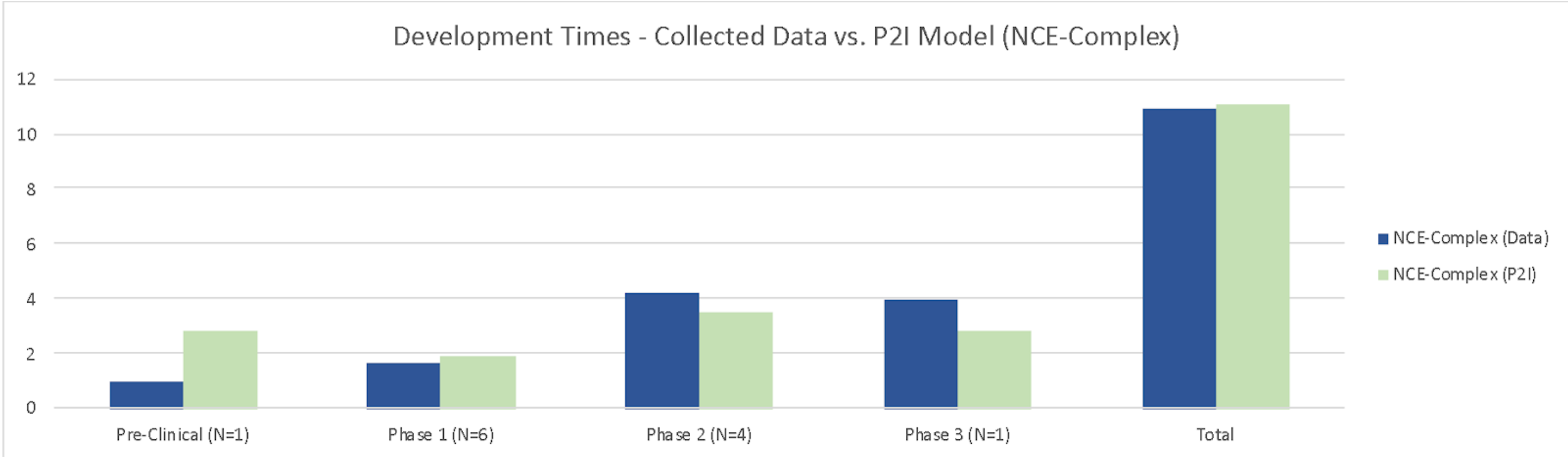
QUANTITATIVE DATA – TIMEFRAMES: NCE Complex



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QUANTITATIVE DATA – RESULTS: TIMEFRAMES

- Quantitative data on non-commercial R&D timeframes were largely in line with the P2I model estimates, with some variation by phase
  - NCE Simple - modestly faster timeframes for non-commercial (9.67 years vs. 10.85 years in the P2I model)
  - NCE Complex - nearly identical (10.92 year for non-commercial and 11.11 years for the P2I model)

- Findings suggest a hypothesis that overall timeframes to develop simple and complex NCEs are similar between non-commercial R&D initiatives and P2I.

QUALITATIVE DATA – TIMEFRAMES

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		

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QUALITATIVE DATA – RESULTS: TIMEFRAMES

- The qualitative data identified 12 factors that drove timeframes up or down in the different phases of product development within non-commercial R&D initiatives.
  - 7 factors likely to lengthen timeframes
  - 0 factor likely to shorten timeframes
  - 5 factors categorized as indeterminate

- The qualitative data does not tell us about the magnitude of the effect and no firm conclusions can be drawn on whether non-commercial R&D would take generally the same amount of time or more than commercial R&D.

QUANTITATIVE DATA – ATTRITION RATES

- Quantitative data on non-commercial R&D attrition/success rates 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.
- We judged that the data we received could not be aggregated across organizations, nor was it adequate for hypothesis generation.
- Further research is needed in this area.

QUALITATIVE DATA – ATTRITION RATES

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	

QUALITATIVE DATA – RESULTS: ATTRITION

- The qualitative data identified 9 factors that drove attrition rates up or down in the different phases of product development within non-commercial R&D initiatives.
  - 3 factors likely to push attrition rates higher
  - 1 factor likely to push attrition rates lower
  - 5 factors categorized as indeterminate

- The qualitative data does not tell us about the magnitude of the effect and 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.

RESULTS: SUMMARY

- Quantitative data suggested that non-commercial R&D for NCEs is largely in line with P2I averages regarding total costs and timeframes, with variation by phase.
- Qualitative data identified more reasons why non-commercial R&D costs would be lower than commercial R&D, timeframes would be longer and attrition rates would be equivalent or higher, though the magnitude of effect is not known.
- Overall emerging hypothesis:
  - direct costs of non-commercial R&D are expected to be equivalent or somewhat lower than commercial
  - timeframes are expected to be equivalent or somewhat longer
  - attrition rates would be equivalent

CONCLUSIONS

- Limitations:
- small non-random sample size
- short period of time in which the study was conducted
- respondents may have incentives to report costs, timeframes or attrition rates that were favourable to their organizations
- study did not compare the patient, population-level, equity or health system benefits offered by the products emerging from non-commercial vs commercial initiatives
- did not analyse “portfolio management” role

- Merits:
- almost no prior literature focusing on costs, timeframes or attrition rates of non-commercial R&D initiatives
- generating hypotheses for further testing against a larger sample of quantitative data
- providing intuition regarding reasons underlying any significant differences between non-commercial and commercial initiatives.

- Emerging hypothesis:
- non-commercial R&D is comparable to commercial initiatives in efficiency, as indicated by direct costs, timeframes and attrition rates.

DATA AVAILABILITY

- **Published study (open for peer review)**
  - → Vieira, Marcela, Ryan Kimmitt, and Suerie Moon. 2021. “Non-Commercial Pharmaceutical R&D: What Do Neglected Diseases Suggest about Costs and Efficiency?” F1000Research 10 (March): 190. https://doi.org/10.12688/f1000research.28281.1

- **Underling quantitative data**
  - → Zenodo: Quantitative data: costs and timeframes_ non-commercial pharmaceutical R&D. https://doi.org/10.5281/zenodo.4519709

- **Underlying qualitative data**
  - → Confidential to protect participant confidentiality as required by the Ethics Review Committee
  - → Selected quotes from the interviews are available in the full research report at the Graduate Institute Institutional Repository at https://repository.graduateinstitute.ch/record/298834

FORTHCOMING STUDY

- Vieira, Marcela, Ryan Kimmitt, Danielle Navarro, Anna Bezruki, and Suerie Moon. Forthcoming. “Advancing Innovation and Access to Medicines: The Achievements and Unrealized Potential of Product Development Partnerships.” In Partnership Effectiveness. Routledge.

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