SUPPLEMENTAL DATA FILE

ASSESSING THE NET FINANCIAL BENEFITS OF EMPLOYING DIGITAL
ENDPOINTS IN CLINICAL TRIALS

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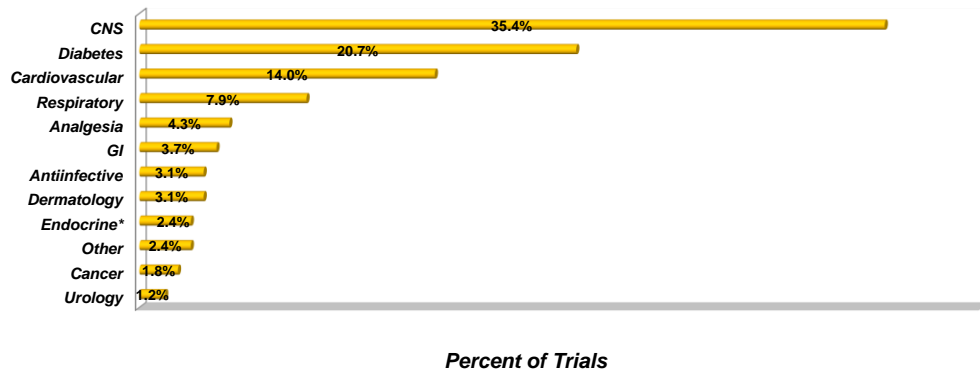[8] Genentech Inc.
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I. DATA AND METHODS SUPPLEMENT

Among the variables in the DiMe Library of Digital Endpoints dataset examined for our analyses were the ClinicalTrials.gov identifying number (NCT number), if one existed, the trial study phase, trial indication, date the trial was first registered, digital endpoint, digital endpoint positioning (primary, secondary, exploratory, label claim, other), digital technology type, product type (drug, biologic, device) and trial sponsor. We placed each endpoint record in a broad therapeutic area depending on the listed indication.

The variables in the ClinicalTrials.gov registry that we examined included NCT number, trial study phase, trial start date (the actual date on which the first participant was enrolled in the study), trial primary completion date (date on which the last participant in a clinical study was examined or received an intervention to collect final data for all primary outcome measures), trial enrollment, trial condition (i.e., indication), intervention type (drug, biologic, device, and other types), intervention name, sponsor class (industry, NIH, other federal agency, other governments, network, other sponsor types), lead or collaborator (whether the sponsor class value is for the lead sponsor or is a collaborator, sponsor name, study type (interventional, observational, observational with patient registry, and expanded access), number of countries involved (overall and by region), and the number of trial sites (overall and by region). Data from the DiMe Library of Endpoints and the ClinicalTrials.gov datasets were merged for analysis by the NCT identifier.

II. DIGITAL ENDPOINT LANDSCAPE AND MODEL PARAMETERIZATION: FIGURES AND TABLES

Figure S1. Therapeutic Class Distribution for Trials with Digital Endpoints

CNS 35.4%
Diabetes 20.7%
Cardiovascular 14.0%
Respiratory 7.9%
Analgesia 4.3%
GI 3.7%
Antiinfective 3.1%
Dermatology 3.1%
Endocrine* 2.4%
Other 2.4%
Cancer 1.8%
Urology 1.2%

Percent of Trials

* Excludes diabetes trials

n = 164 trials

Figure S2. Distribution of Number of Countries per Trial in ClinicalTrials.gov and DiMe Digital Endpoints Data
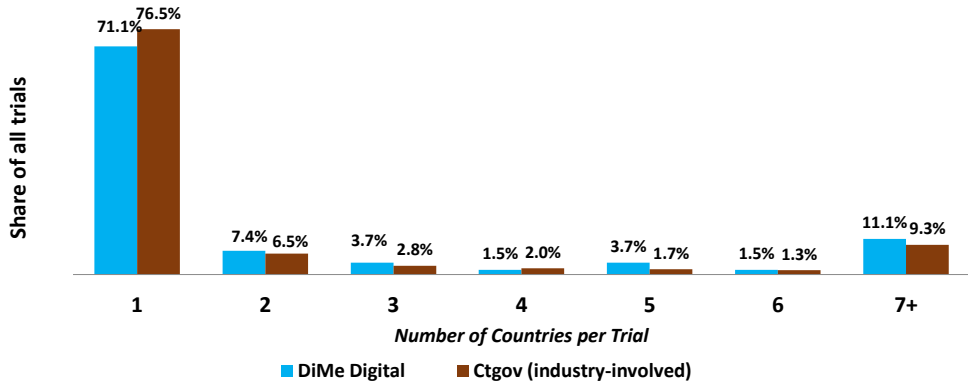
DiMe digital: n = 135 trials
ClinicalTrials.gov (industry-involved): n = 126,339 trials

Figure S3. Mean Number of Countries per Trial in ClinicalTrials.gov and DiMe Digital Endpoints Data

Countries per Trial

2.76 — DiMe Digital

2.56 — Clintrials (industry-involved)

DiMe digital: n = 135 trials
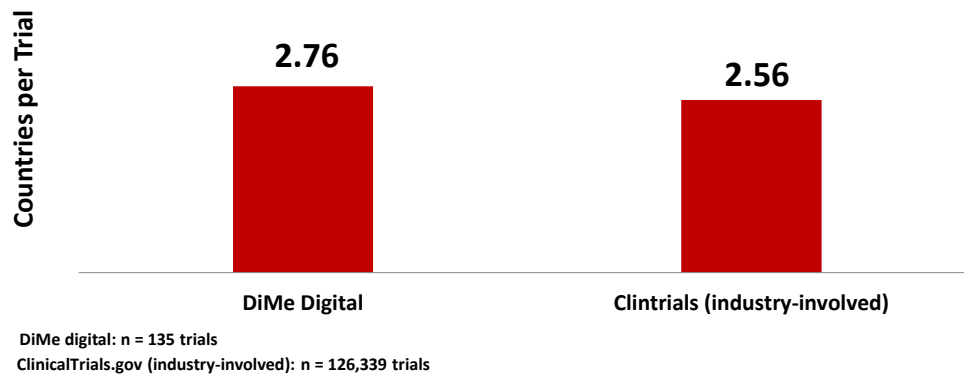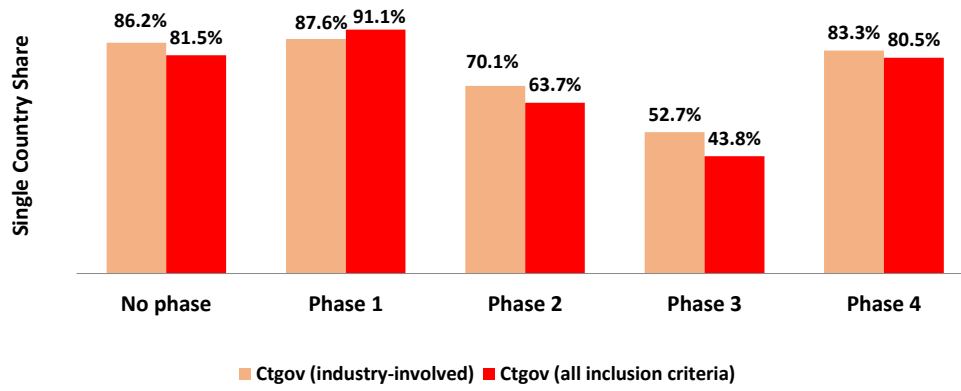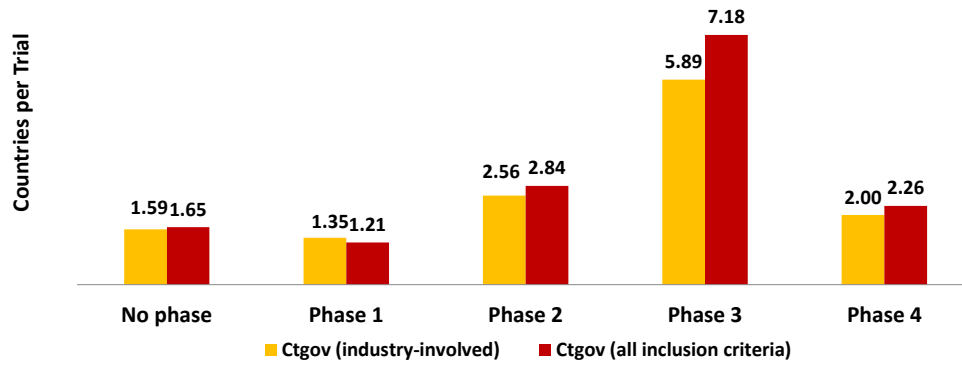ClinicalTrials.gov (industry-involved): n = 126,339 trials

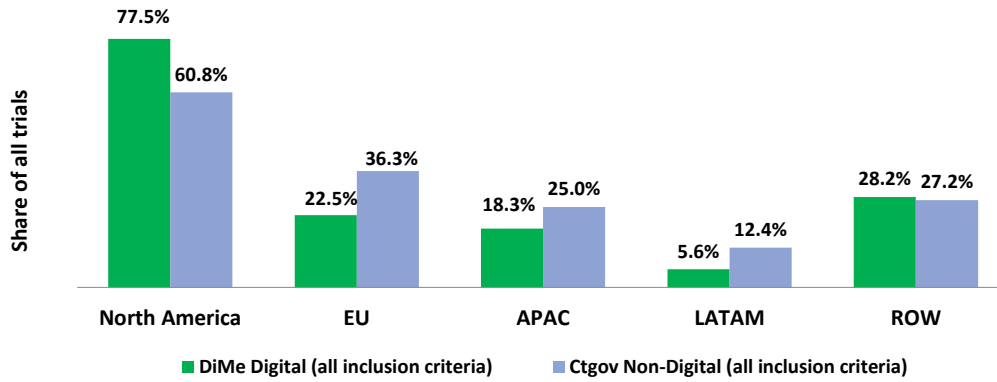## Figure S4. Single Country Share of Trials in ClinicalTrials.gov by Trial Phase

	No phase	Phase 1	Phase 2	Phase 3	Phase 4
Ctgov (industry-involved)	86.2%	87.6%	70.1%	52.7%	83.3%
Ctgov (all inclusion criteria)	81.5%	91.1%	63.7%	43.8%	80.5%

ClinicalTrials.gov (industry-involved): n = 126,339 trials
ClinicalTrials.gov (all inclusion criteria): n = 10,394 trials

Figure S5. Mean Number of Countries per Trial in ClinicalTrials.gov

Countries per Trial

	No phase	Phase 1	Phase 2	Phase 3	Phase 4
Ctgov (industry-involved)	1.59	1.35	2.56	5.89	2.00
Ctgov (all inclusion criteria)	1.65	1.21	2.84	7.18	2.26

■ Ctgov (industry-involved) ■ Ctgov (all inclusion criteria)

Clinicaltrials.gov (industry-involved): n = 126,339 trials
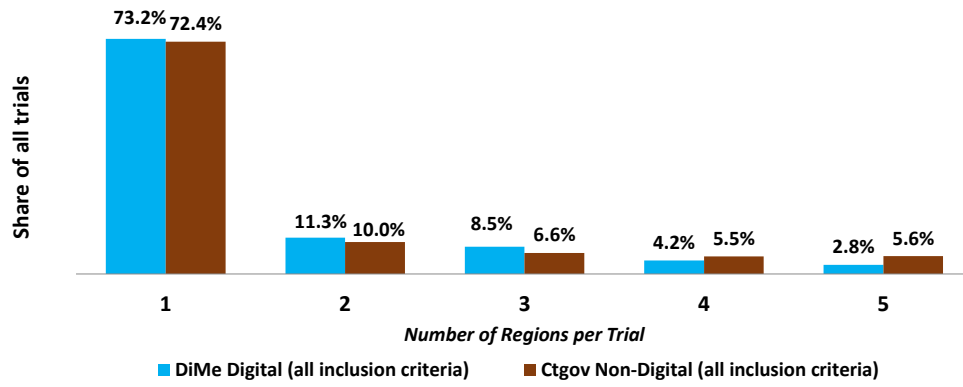**Clinicaltrials.gov (all inclusion criteria): n = 10,394 trials**

Figure S6. Geographic Distribution of Trials in DiMe Digital Endpoints and ClinicalTrials.gov Data by Region

Share of all trials

Region	DiMe Digital (all inclusion criteria)	Ctgov Non-Digital (all inclusion criteria)
North America	77.5%	60.8%
EU	22.5%	36.3%
APAC	18.3%	25.0%
LATAM	5.6%	12.4%
ROW	28.2%	27.2%

■ DiMe Digital (all inclusion criteria)   ■ Ctgov Non-Digital (all inclusion criteria)

DiMe digital (all inclusion criteria): n = 71 trials

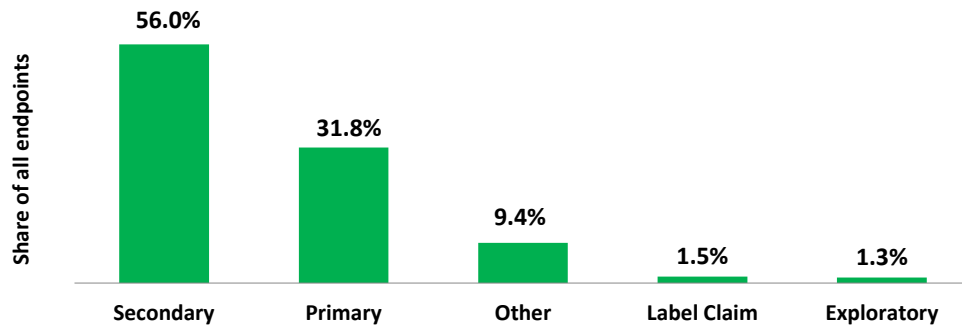ClinicalTrials.gov (all inclusion criteria): n = 10,399 trials

Percentages add to more than 100 because some trials are multi-regional

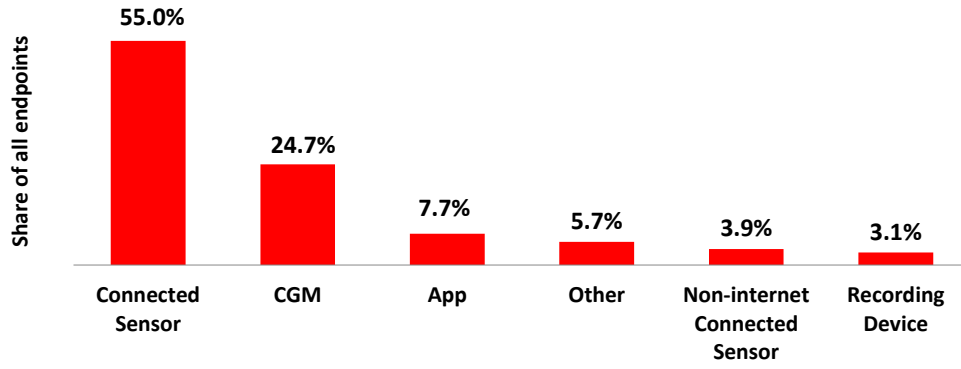**Figure S7. Distribution of Number of Regions per Trial for DiMe Digital Endpoints and ClinicalTrials.gov Data**

Share of all trials

| | 73.2% | 72.4% | 11.3% | 10.0% | 8.5% | 6.6% | 4.2% | 5.5% | 2.8% | 5.6% |

Number of Regions per Trial

■ **DiMe Digital (all inclusion criteria)** ■ **Ctgov Non-Digital (all inclusion criteria)**

DiMe digital (all inclusion criteria): n = 71 trials
ClinicalTrials.gov (all inclusion criteria): n = 10,399 trials

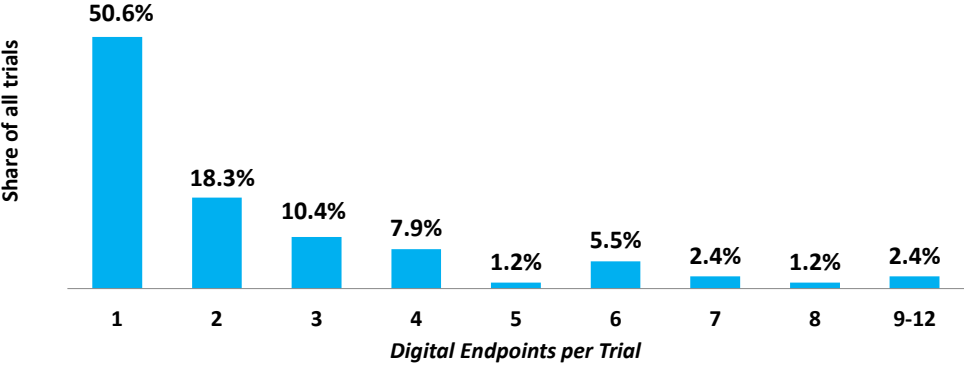## Figure S8. Distribution of Digital Endpoints by Trial Outcome Positioning

Share of all endpoints

Category	Value
Secondary	56.0%
Primary	31.8%
Other	9.4%
Label Claim	1.5%
Exploratory	1.3%

n = 363 digital endpoints

Figure S9. Distribution of Technology Types Used to Measure Digital Endpoints

Share of all endpoints

Connected Sensor	55.0%
CGM	24.7%
App	7.7%
Other	5.7%
Non-internet Connected Sensor	3.9%
Recording Device	3.1%

n = 389 digital endpoints

Figure S10. Number of Digital Endpoints per Trial

Share of all trials (y-axis)

- 1: 50.6%
- 2: 18.3%
- 3: 10.4%
- 4: 7.9%
- 5: 1.2%
- 6: 5.5%
- 7: 2.4%
- 8: 1.2%
- 9-12: 2.4%

Digital Endpoints per Trial

n = 164 trials

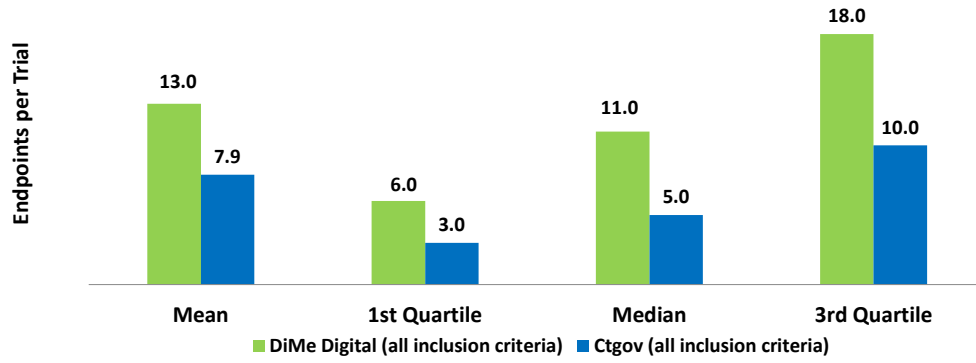**Figure S11. Number of Sites per Trial in ClinicalTrials.gov and DiMe Digital Endpoints Data**
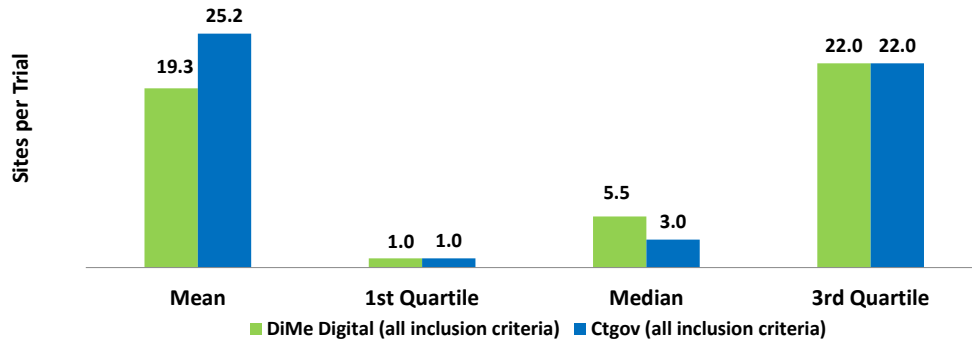
DiMe digital: n = 72 trials
ClinicalTrials.gov: n = 10,408 trials

Figure S12. Number of Sites per Trial in ClinicalTrials.gov and DiMe Digital Endpoints Data (extreme outliers excluded – IQR rule)
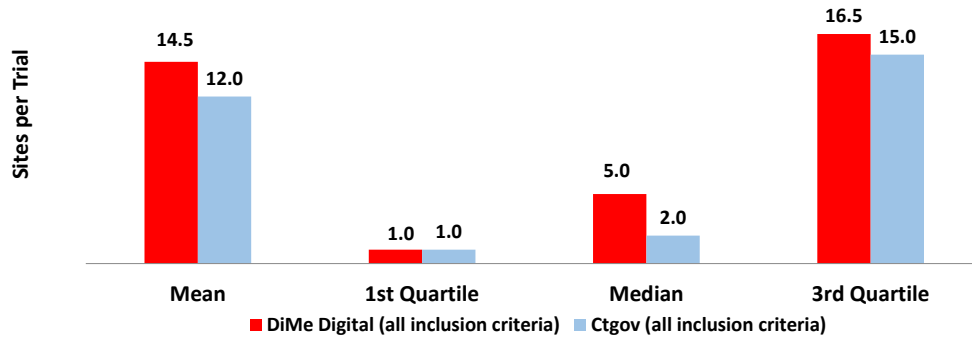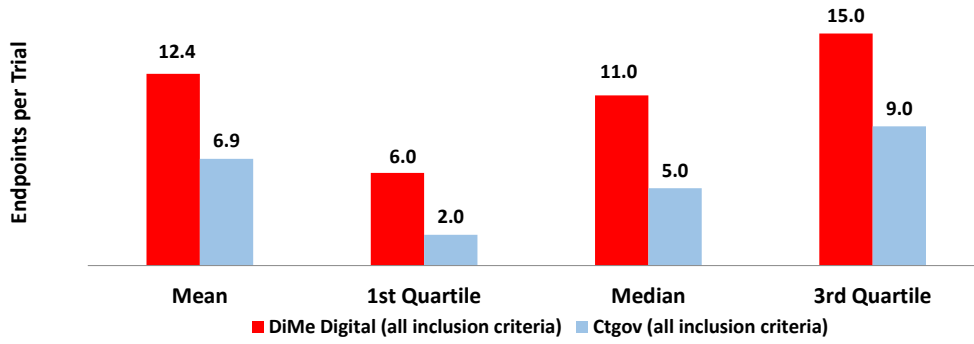

DiMe digital: n = 68 trials
ClinicalTrials.gov: n = 9,602 trials

Figure S13. Total Number of Endpoints per Trial in ClinicalTrials.gov and DiMe Digital Endpoints Data

DiMe digital: n = 79 trials
ClinicalTrials.gov: n = 11,363 trials

Figure S14. Total Number of Endpoints per Trial in ClinicalTrials.gov and DiMe Digital Endpoints Data (extreme outliers excluded – IQR rule)

DiMe digital: n = 78 trials
ClinicalTrials.gov: n = 11,104 trials

Table S1. Final Model Regression Coefficients for Trial Time and Size by Phase

	Dependent Variable			
	Log of phase 2 duration	Log of phase 3 duration	Phase 2 enrollment	Log of phase 3 enrollment
Explanatory variables				
Intercept	2.2402	2.53354	167.12977	5.48882
Digital	-0.27431	-0.24874	-15.23932	-0.12445
CNS	0.24135	0.27220	-21.5209	-0.12081
Cardio	0.07549	0.18121	-37.85677	-0.54550
Year	0.02228	0.01915	-2.98029	0.01075
Sites	0.00377	0.00135	---	---
Endpoints	---	0.00281	0.54203	0.01196
	N=1,192; F=16.2; p<0.0001	N=1,303; F=31.5; p<0.0001	N=1,244; F=9.7; p<0.0001	N=1,378; F=14.1; p<0.0001

Table S2. Mean Values for Continuous Independent Variables for Cycle Time and Trial Size Regressions for Phase 2 and Phase 3

	Cycle Time		
	Number of sites	Number of endpoints	Year*
Phase 2	18.5	9.0	13.8
Phase 3	73.9	10.4	12.6
	Trial Size		
	Number of Sites	Number of Endpoints	Year*
Phase 2	16.8	8.9	13.6
Phase 3	57.0	10.2	12.2

* 2005 = year 0

Figure S15. Sponsor Costs from Implementing, Developing, and Validating Digital Endpoints in Clinical Trials (2023 $)

$438,692	$1,000,000	$3,416,060	$15,061,198
Minimum	Median	Mean	Maximum
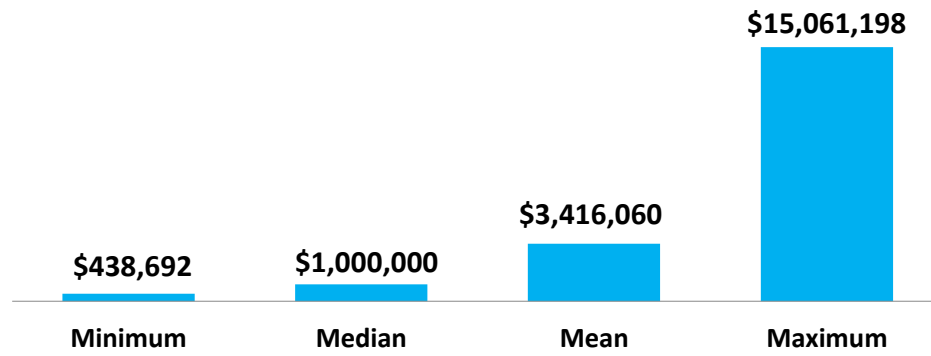
n = 11

Table S3. Key Parameters and Data Sources

Parameter	Data Source	Parameter	Data Source
Development and review times	DiMasi et al., *J Health Econ* 2016;47:20-33 and CSDD protocol database	Peak sales and years to peak	Cortellis pipeline database (consensus analyst forecasts)
Development costs	DiMasi et al., *J Health Econ* 2016;47:20-33 and CSDD protocol database	Effective tax rate	Public financial data for top 10 pharma firms
Phase success rates	BIO/Informa/QLS, Feb 2021	Digital endpoint implementation cost	CSDD/DiMe Sponsor and Developer Cost Survey
Cost of capital	DiMasi et al., *J Health Econ* 2016;47:20-33	Change in trial duration	ClinicalTrials.gov and DiMe databases
Approved supplemental indications	Drugs@FDA	Change in trial size	ClinicalTrials.gov and DiMe databases

Figure S16. Mean Number of FDA-approved Indications by Therapeutic Area and Approval Period
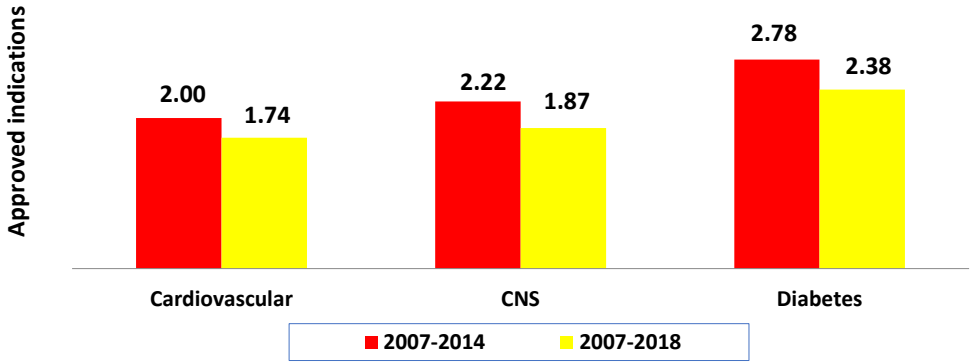
Table S4. Development Risk Parameter Values for eNPV Analysis (indication transition probabilities)

Transition	Cardiovascular	Endocrine	Neurology
Phase 2 to Phase 3	21.0%	26.6%	26.8%
Phase 3 to Regulatory Review	55.2%	66.2%	53.1%
Regulatory Review to Approval	82.5%	86.3%	86.7%
Phase 2 to Approval	9.6%	15.2%	12.3%
Phase 3 to Approval	45.5%	57.1%	46.0%

Table S5. Relative[*] Clinical Phase to Phase Durations and Phase R&D Costs

	Cardiovascular	Diabetes	CNS
Phase 2 to Phase 3 relative duration	90.4%	98.9%	102.0%
Phase 3 to regulatory review relative duration	110.5%	76.1%	95.0%
Phase 2 relative cost	94.9%	97.1%	163.1%
Phase 3 relative cost	46.8%	62.9%	119.7%

* Relative to overall averages for drug in general

Source for overall averages and relative durations and costs: DiMasi et al., *Journal of Health Economics* 2016;47:20-33 and Tufts CSDD Protocol Complexity Benchmark Database

III. SENSITIVITY ANALYSES

Figures S17 and S18 show ROI at varying assumed reductions in trial durations holding base case reductions in trial size constant for phase 2 and phase 3 trials and by therapeutic area. We also examined the sensitivity of ROI for varying assumptions about percentage reductions in trial sizes, holding base case reductions in phase duration constant for phase 2 and phase 3 trials and by therapeutic area (Figures S19 and S20). In this way, we can isolate the effects on financial value for the two types of benefit.

The results show generally higher ROIs for diabetes indications compared to cardiovascular and CNS indications. The exceptions are phase 2 reductions in trial sizes, holding phase duration constant, for high assumed percentage reductions in trial sizes (30% or more in relation to CNS trials). ROIs for phase 3 trials are at least twice the investment cost for trial size variation. For phase 2, with the exception of CNS trials, at very low reductions in phase duration or trial size (one month for phase duration reduction and 5% for trial size reduction) the ROIs become zero or negative. Finally, the ROIs are much higher in all cases, and uniformly positive, if median implementation cost is used in the modeling.

Figure S17. Phase 2 digital endpoint ROI by reduction in trial duration (at base case decrease in trial size and mean implementation cost)
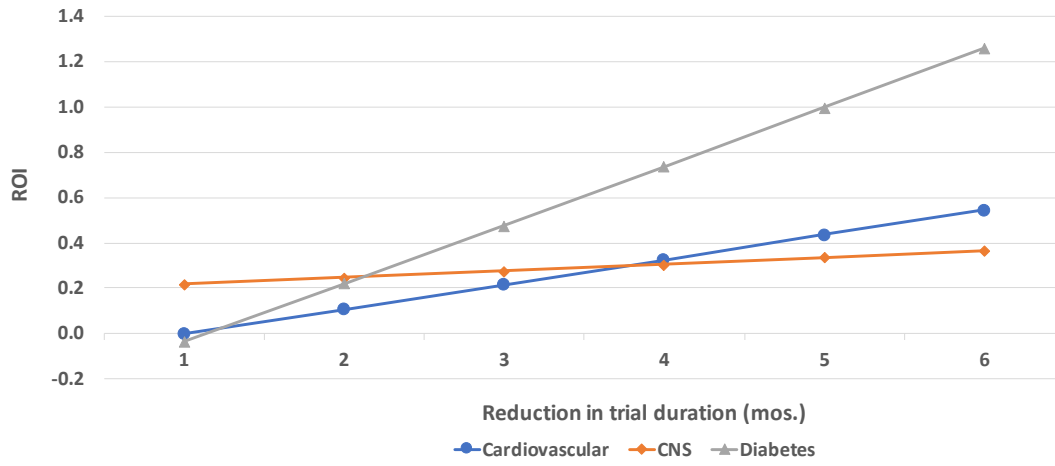
Figure S18. Phase 2 digital endpoint ROI by percentage reduction in trial size (at base case decrease in trial duration and mean implementation cost)
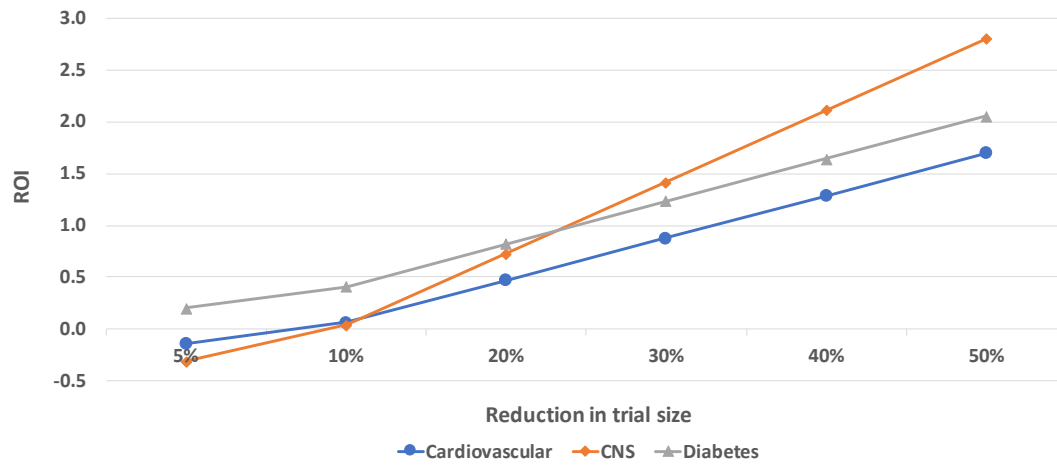
Figure S19. Phase 3 digital endpoint ROI by reduction in trial duration (at base case decrease in trial size and mean implementation cost)
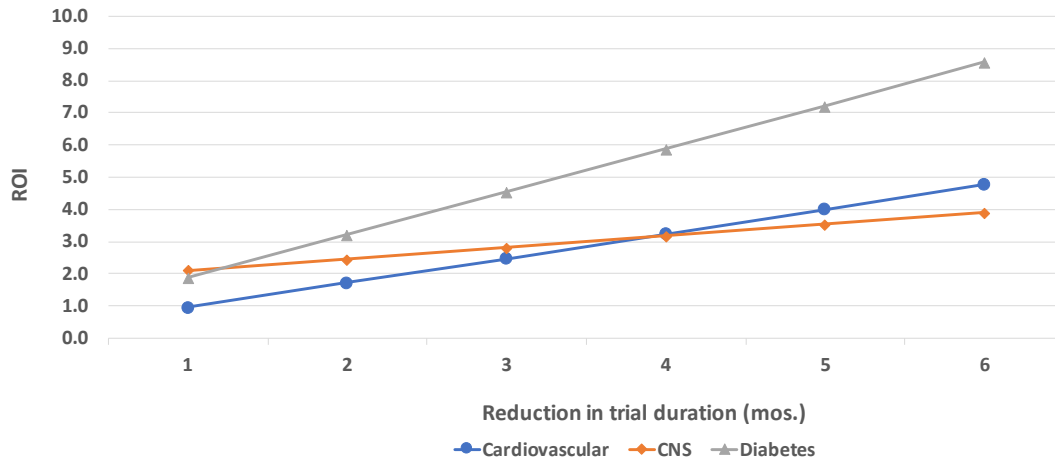
Figure S20. Phase 3 digital endpoint ROI by percentage reduction in trial size (at base case decrease in trial duration and mean implementation cost)
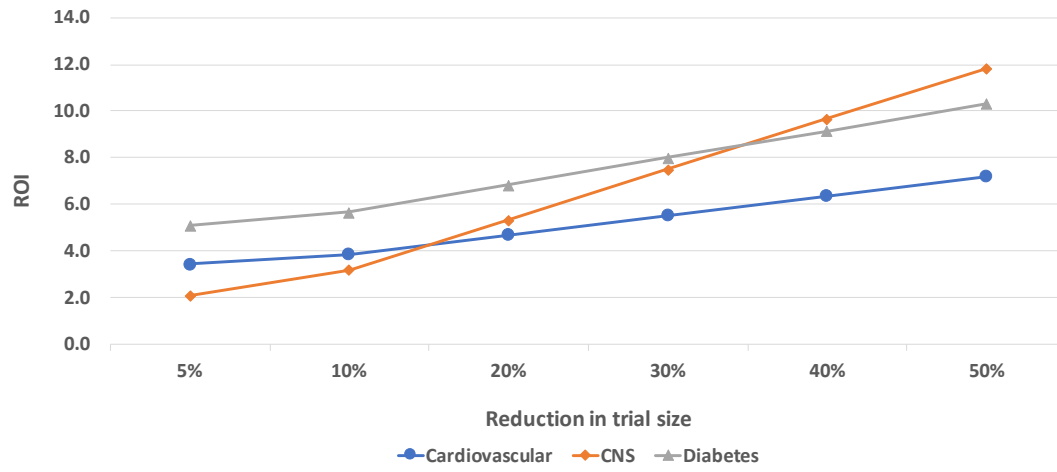
Table S6. eNPV Delta (thousands 2023 USD) by Therapeutic Area and Clinical Phase for Varying Assumptions About the Number of Pre-Approval Investigational Indications

Clinical Phase	Pre-Approval Indications	Therapeutic Area		
Phase 2		Cardiovascular	CNS	Diabetes
	1	$5,350	$5,832	$5,125
	2	$2,215	$2,087	$3,256
	3	$1,103	$721	$2,570
Phase 3				
	1	$28,525	$22,256	$44,623
	2	$33,279	$27,343	$48,404
	3	$34,413	$28,597	$49,374

Base case: Two pre-approval investigational indications

Table S7. Return on Investment (ROI) by Therapeutic Area and Clinical Phase for Varying Assumptions About the Number of Pre-Approval Investigational Indications

Clinical Phase	Pre-Approval Indications	Therapeutic Area		
Phase 2		*Cardiovascular*	*CNS*	*Diabetes*
	1	78.3%	85.4%	75.0%
	2	32.4%	30.5%	47.7%
	3	16.1%	10.6%	37.6%
Phase 3				
	1	4.2x	3.3x	6.5x
	2	4.9x	4.0x	7.1x
	3	5.1x	4.2x	7.3x

Base case: Two pre-approval investigational indications