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RESEARCH LETTER

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The cost of emulated target trials: Is real-world data cheaper than randomized studies?

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A recent study in JAMA examined the results of the RCT-DUPLICATE project.[1] Investigators found that among 32 randomized clinical trials (RCTs) submitted to the Food and Drug Administration (FDA), emulated trials could replicate the results of RCTs with statistical significance agreement in 75% of cases (56% full and 19% partial agreement). Additionally, 66% met estimate agreement, and 72% met standardized difference agreement.

One virtue of emulated trials is that they do not incur the financial costs of randomized experimentation. This is particularly relevant for policymakers interested in granting drug approvals based on routinely collected data (RCD) (typically called 'real-world evidence', although we believe this term should be abandoned since RCT evidence is also 'real-world'). All trials selected for the RCT-DUPLICATE project were designed for regulatory submissions.

However, in order to emulate a trial, investigators first have to examine a body of observational data in which a drug was prescribed for an indication. This requires hundreds, if not thousands, of individual doctors using the drug in some, but not all, patients with a certain condition. Although there is no administrative cost to this, there is a cost borne by public payers and the health system. Namely, the cost to pay for the drug among those who receive it outside of a trial.

Here, we seek to compare the cost of running a randomized trial at the outset of a therapy versus the cost of insurers, payers and persons paying for the drugs' use, with subsequent trial emulation study, outside of a protocolized trial. In the former case, administrative costs may be sizable (by administrative costs, we mean financial costs involved in monitoring, data collection and analysis, pharmacovigilance, administrative processes, etc.). Yet, in the latter case, the drug cost may be formidable, given that, as a general rule, far more people receive a drug in the real world than are required by the power calculation of a randomized trial.

Using data provided by the RCT-DUPLICATE authors, we sought to estimate the cost of the emulated trials, that is the cost of purchasing and administering the drug to the sample size used in the observational dataset. This cost is not borne by manufacturers, but by insurers and patients. We contrast this with hypothetical RCT costs, assuming the manufacturer obtains the drug at the price of chemical synthesis, and with varying administrative costs per patient ($10, 20, 30 or 40K). We conducted a simplified, comparative cost analysis of the 32 RCTs and respective emulated trials. We estimated overall costs per trial under several assumptions: (1) for the main analysis, the study drug in the RCT was priced at 5% of the average wholesale price (AWP), a value selected to align our estimated total RCT costs with similar estimations found in the literature (see Supplement); (2) drugs in emulated trials were priced at the AWP; (3) four hypothetical administrative costs per patient were considered for each RCT: $10, $20, $30 and $40K; and

Intervention (exposure)	n (intervention arm) RCT	n (intervention arm) Obs	Trial duration (months)	RCT estimated cost (assuming drug cost = 5% AWP) Hypothetical administrative cost 10K	20K	30K	40K	Emulated trial estimated cost (assuming drug cost = AWP and 0 admin cost)
Liraglutide	4668	84346	42,0	$143	$190	$236	$283	$34 752
Dapagliflozin	8582	24895	50,4	$108	$194	$280	$365	$1 280
Empagliflozin	4687	51875	37,2	$53	$100	$147	$194	$1 413
Canagliflozin	5795	76099	42,0	$67	$125	$183	$241	$2 292
Linagliptin	3494	50913	26,4	$38	$73	$108	$143	$847
Sitagliptin	7257	174739	36,0	$82	$154	$227	$299	$4 341
Saxagliptin	8280	91064	25,2	$89	$172	$254	$337	$1 336
Liraglutide + metformin	482	373	5,7	$6	$11	$15	$20	$14
Prasugrel	6813	21932	14,5	$71	$140	$208	$276	$212
Ticagrelor	9333	13980	12,0	$96	$190	$283	$376	$91
Prasugrel	2012	7300	12,0	$21	$41	$61	$81	$47
Apixaban	9120	110259	21,6	$98	$189	$281	$372	$1 700
Dabigatran	6067	39070	24,0	$62	$123	$184	$244	$223
Rivaroxaban	6958	51318	19,3	$74	$144	$213	$283	$645
Rivaroxaban	1731	12985	10,0	$18	$35	$53	$70	$94
Rivaroxaban	2419	15899	6,0	$25	$49	$73	$97	$69
Dabigatran	1279	2671	5,5	$13	$26	$38	$51	$3
Apixaban	2609	3570	6,0	$27	$53	$79	$105	$16
Rivaroxaban	1537	17438	1,1	$15	$31	$46	$62	$13
Telmisartan	2954	20024	56,0	$31	$60	$90	$120	$188
Telmisartan	8576	17626	56,0	$90	$176	$261	$347	$166
Zoledronic Acid	3875	9003	36,0	$39	$78	$116	$155	$3
Teriparatide	516	2164	24,0	$7	$12	$17	$22	$119
Dapagliflozin	2152	6070	28,8	$25	$46	$68	$89	$178
Sacubitril/Valsartan	4187	3033	27,0	$46	$88	$130	$172	$66
Mometasone furoate/ formoterol	191	1054	5,7	$2	$4	$6	$8	$1
Budesonide+ formoterol	5847	12088	5,7	$59	$117	$176	$234	$12
Fluticasone, umeclidinium, vilanterol	4145	4439	12,0	$43	$84	$125	$167	$24
Tiotropium	3707	4358	12,0	$38	$76	$113	$150	$32
Fluticasone propionate + salmeterol	658	49410	24,0	$7	$13	$20	$27	$377
Linagliptin	3023	24131	70,8	$37	$67	$97	$128	$1 076
Degarelix	275	568	12,0	$3	$6	$8	$11	$4
Average (n) **/ median** (trial duration, costs)	4033	31395	23	**$39**	**$77**	**$114**	**$152**	**$143**
Range / IQR	191-9333	373-174,739		$20-72	$39-141	$59-209	$78-278	$22-904
Median cost of medication relative to overall RCT cost				4%	2%	2%	1%	

Green: RCT cheaper than emulated trial; red: RCT more expensive than emulated trial.
IQR: interquartile range; RCT: randomized clinical trial; AWP: average wholesale price.

FIGURE 1 Estimated costs of the 32 randomized clinical trials (RCTs) and corresponding emulated trials analysed in the RCT-duplicate project (costs in million unit).

(4) administrative costs of emulated trials were deemed negligible. In addition, we estimated the median RCT overall cost considering different drug prices: 1%, 5%, 20%, 35%, 50% and 65% of the AWP. For more details on our methods, see Supporting Information.

On average, emulated trials included 7.5 times more patients in the intervention group than RCTs (31,395 and 4163 patients, respectively). In Figure 1, we compare estimated costs of RCTs and emulated trials. The median estimated cost of emulated trials was $143 million (IQR 22-904), while the median estimated cost of RCTs ranged between $39 million (IQR 20-72) and $152 million (IQR 78-278) assuming administrative costs of $10 and $40K, respectively. When administrative costs of $10, $20 or $30K were assumed, 23 (72%), 20 (63%) and 17 (53%) emulated trials were more expensive than the corresponding RCT, respectively (Figure 2). The median cost of medication in each RCT was <5% the overall trial cost.

In Figure 3, we represent varying RCT costs depending on the AWP of the study drug. Compared with the median emulated trial cost of $143 million, RCTs may become more expensive only when administrative costs are expected to exceed $40K, even if the study drug is priced at 65% of the AWP. For administrative costs below $40K, RCTs generally remain less costly.

Using data from a recent JAMA publication, we estimate the direct cost of conducting target trials. This includes the cost of purchasing the drug for 7.5 times as many people as in corresponding RCTs. Given the simplicity of our analysis and the assumptions made, our findings should be approached with caution and viewed as providing only a general overview. We find the median study cost to be $143 million—costs borne by insurers and the public. It is important to note that our main analysis of RCT costs assumed that study drugs are priced at 5% of the AWP, a value chosen arbitrarily due to the lack of data on typical costs. Our complementary analysis revealed that RCTs only surpass the cost of emulated trials when administrative costs reach $40K or more, even with study drug prices as high as 65% of the AWP.

Using varying assumptions about RCT costs, we find that under many scenarios, RCTs are cheaper, though this cost is borne by the industry and not payers. Although not the primary focus of our analysis, significant indirect costs may emerge after the study is completed. For example, a drug that is reimbursed based on RCD may later be found to be ineffective or to have unforeseen adverse effects.

One could argue that, because studies based on RCD are performed retrospectively, medications are a sunk cost. However, several RCD-based studies depend on medication use in areas where evidence is limited or nonexistent—for example in populations typically excluded from clinical trials—or depend on data resulting from off-label prescriptions,[2] since these are the reasons the studies are conducted in the first place. While these practices are, to some extent, expected in clinical practice and in situations where drugs are approved on preliminary evidence, they are arguably undesired if high standards of evidence quality are upheld. Unlike a scenario where most evidence comes from clinical trials, the gold standard for evaluating drug efficacy,[3] a regulatory framework encouraging RCD-based studies ultimately relies on lower quality data and methods, favouring faster drug marketing over rigorous evaluation. Thus, in our view, when the FDA prospectively establishes a framework for the use of RCD to support the approval of new indications for existing drugs or fulfil post-approval study requirements,[4] three implications arise: it risks neglecting its duty to minimize the use of drugs in areas of very limited evidence (potentially incentivizing them), it lowers the bar for evidence quality, and it overlooks the financial burden on society.

Several therapies are thought to work, but when studied in well-designed and rigorously conducted RCTs, the purported effect is no longer seen, and some may even be

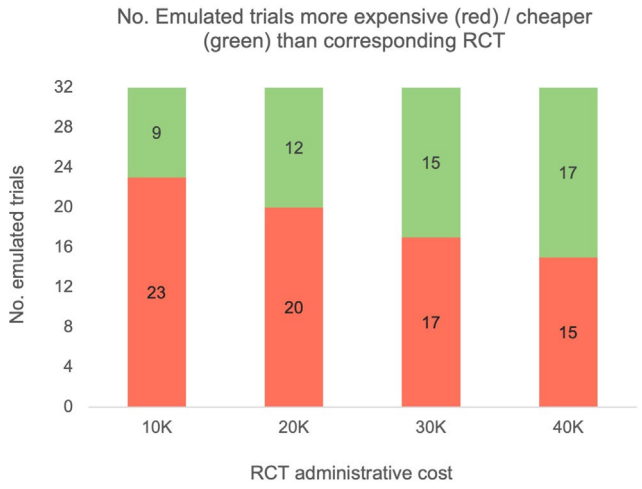

FIGURE 2 Comparative cost of emulated trials and corresponding randomized clinical trials (RCTs).

FIGURE 3 Estimated randomized clinical trial (RCT) costs with varying drug average wholesale prices (AWP) and administrative costs, colour coded for comparison with the median emulated trial cost of $143M.

Estimated RCT cost – median (IQR)

Hypothetical admin cost	Study drug cost (% of AWP) 1%	5%	20%	35%	50%	65%
10K	$38 (20-67)	$39 (20-72)	$46 (22-89)	$52 (24-104)	$57 (26-116)	$62 (28-131)
20K	$76 (39-125)	$77 (39-141)	$84 (41-152)	$90 (43-172)	$97 (45-188)	$103 (47-203)
30K	$114 (58-188)	$114 (59-209)	$117 (61-220)	$129 (63-236)	$135 (65-255)	$141 (67-271)
40K	$152 (78-251)	$152 (78-278)	$155 (80-288)	$164 (82-299)	$173 (84-320)	$179 (86-338)

Green: RCT cheaper than median emulated trial cost; yellow: RCT more expensive if considering the 3rd quartile value; red: RCT more expensive than median emulated trial cost.
IQR: interquartile range; RCT: randomized clinical trial; AWP: average wholesale price.

harmful.[5] This is why the bar for initial drug approval is set high and randomized trials are necessary. In the context of RCD programmes, the evidence bar is lowered for the sake of logistics and costs. However, we have shown that the assumption that costs are lower with emulated trials may not hold.

Our study likely overestimates RCT costs. Moore et al. estimated the costs of 225 pivotal trials and found the median cost to be $19 million,[6] which is half our estimate when administrative costs are at the lower end. Although the authors did not include medication costs, our findings suggest these represent a very small fraction of the overall RCT cost. Additionally, we did not consider any administrative cost for real-world studies. Important limitations of our study include the wide range of assumptions and the oversimplified cost analysis. Regrettably, there is very limited data and transparency on RCT costs.[7]

Our results provide useful information for regulators and policymakers when considering drug approvals based on prospective real-world studies. In addition to issues of causal inference, issues of societal cost must be considered.

AUTHOR CONTRIBUTIONS

MB contributed to the concept and design, acquisition, analysis and interpretation of data, drafting of the manuscript, statistical analysis. VP contributed to the concept and design, acquisition, analysis and interpretation of data, drafting of the manuscript, critical review of the manuscript for important intellectual content, supervision. MB and VP had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Dr. Barosa reports receiving grants from the Luso-American Development Foundation (FLAD) during the conduct of the study. Dr. Prasad reports receiving grants from Arnold Ventures Research funding during the conduct of the study; royalties from Johns Hopkins Press, Medscape and MedPage; consulting fees from UnitedHealthcare and OptumRx; subscription revenue from YouTube, Patreon and Substack outside the submitted work. No other disclosures were reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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