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Private Manufacturers' Thresholds to Invest in Comparative Effectiveness Trials

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Abstract

The recent rush of enthusiasm for public investment in comparative effectiveness research (CER) in the US has focussed attention on these public investments. However, little attention has been given to how changing public investment in CER may affect private manufacturers' incentives for CER, which has long been a major source of CER. In this work, based on a simple revenue maximizing economic framework, we generate predictions on thresholds to invest in CER for a private manufacturer that compares its own product to a competitor's product in head-to-head trials. Our analysis shows that private incentives to invest in CER are determined by how the results of CER may affect the price and quantity of the product sold and the duration over which resulting changes in revenue would accrue, given the time required to complete CER and the time from the completion of CER to the time of patent expiration. We highlight the result that private incentives may often be less than public incentives to invest in CER and may even be negative if the likelihood of adverse findings is sufficient. We find that these incentives imply a number of predictions about patterns of CER and how they will be affected by changes in public financing of CER and CER methods. For example, these incentives imply that incumbent patent holders may be less likely to invest in CER than entrants and that public investments in CER may crowd out similar private investments. In contrast, newer designs and methods for CER, such as Bayesian adaptive trials, which can reduce *ex post* risk of unfavourable results and shorten the time for the production of CER, may increase the expected benefits of CER and may tend to increase private investment in CER as long as the costs of such innovative designs are not excessive. Bayesian approaches to design also naturally highlight the dynamic aspects of CER, allowing less expensive initial studies to guide decisions about future investments and thereby encouraging greater initial investments in CER. However, whether the potential effects we highlight of public funding of CER and of Bayesian approaches to trial design actually produce changes in private investment in CER remains an empirical question.

Key points for decision makers

- Private manufacturers often have incentives to invest in comparative effectiveness research (CER) that will generate public knowledge about the relative effectiveness of competitor interventions. A non-strategic increase in public investments in CER may crowd out these private investments
- Incentives to private investments remain low for CER that requires longer follow-up. Public investments in these settings become more useful
- Novel designs for CER, such as Bayesian adaptive trials, and novel methods to analyse data from these trials can help in the efficient production of information for both private and public stakeholders. Additional emphasis on training and development of these methods will be worthwhile

1. Introduction

The investment in comparative effectiveness research (CER) by the 2009 American Recovery and Reinvestment Act has reinvigorated the interest and focus of many stakeholders in using this information for clinical and healthcare decision making. Despite sceptics, many parties believe that this renewed interest can help to improve the traditional approaches to CER, thereby generating richer information that will be easier to translate to clinical practice.[1] However, which clinical areas are in most need of such research remains ambiguous. Moreover, who will, or should, invest in such research, once a priority area is identified, remains unclear. The Institute of Medicine (IOM) recently developed a list of initial priorities for CER.[2] Even among those initial priorities there will be a need to prioritize topics, and discussions about future priorities are only beginning. The role of public versus private incentives to investing in CER, appropriate research designs to generate information precisely and efficiently, and practical ways to translate this information to practice will all figure in these discussions.

This work is intended to contribute to one specific aspect of those discussions by presenting an economic framework for understanding the incentives for public versus private investments. Generally, the incentives to invest in CER are driven by the expected value of information that it produces net of its expected costs.[3] The value of CER information, in turn, depends on the expected incremental benefits, costs and risks that CER has the potential to produce by changing current decisions. The decisions that CER may change may be at the patient level (e.g. choice among alternative therapies) or at the policy level (e.g. coverage policy). Therefore, the responsiveness of these patient-level and policy-level decisions to CER evidence become critical in understanding the value of research. With these ideas in mind, and building on our recent white paper originally developed for the IOM,[4] we will explore the conditions under which a private manufacturer stands to appropriate additional value once new information is generated. It is presumably under these conditions that private manufacturers will be willing to bear the costs of investing in CER. Despite a wealth of research literature discussing issues about private industry's incentives to innovate,[5-7] less has been written about incentives to conduct CER once such innovation is already accomplished.

Our primary goal is to generate predictions on thresholds to invest in CER for a private manufacturer that compares its own product to a competitor product in head-to-head trials, based on a simple revenue maximizing economic framework.[1]

1 Throughout the paper, we will refer to 'trials' as randomized controlled trials or other designs, investments in which are readily transparent to other stakeholders. Private manufacturers may engage in comparative observational studies to generate priors for comparative effects. However, they are more likely to keep such investments and the resulting information private, especially when there are unfavourable results in terms of effectiveness. However, current laws do prevent hiding of such information when there is evidence of harm.

We provide evidence based on manufacturers' observed investment behaviour to support these predictions.

Although comparative trials figure to be a large part of the CER agenda going forward, some have questioned whether traditional trial designs are well suited to answer such questions.[8,9] As currently conducted, randomized controlled trials (RCTs) are inefficient and have become more complex, time consuming and expensive.[9] It has been argued that Bayesian designs (such as adaptive clinical trials[9,10]) may be less time consuming and costly and more flexible to meet the needs of CER. Moreover, from the manufacturers' point of view, investment in CER runs the inherent risk of producing evidence that may either support or go against their business interests. Bayesian designs may be particularly well suited to reduce this risk of unfavourable results due to chance alone.

Accordingly, we study how manufacturers' thresholds to invest in CER are altered by Bayesian trial designs that can alter both the time and the cost to trial results and reduce the risk of errors in results. We will also study the role of public investments in light of the manufacturers' incentives to invest.

In the next section, we lay out some of the economic rationales for incentives to invest in comparative effectiveness. In section 3, we provide a more detailed theoretical discussion for studying the private manufacturer's incentive to invest in such research, followed by studying the effects of competition in the CER information market (section 4). In sections 5 and 6, we study the role that Bayesian trials may have in modifying the private manufacturer's incentives to invest in CER and the implications this has for public investment in this area. We support our discussions with intuitive formal models in the appendix in the Supplemental Digital Content (SDC), http://links.adisonline.com/PCZ/A154.

2. Economics of Comparative Effectiveness Information

We begin by summarizing the conceptual ideas behind the economics of CER that we have recently elaborated in a white paper originally prepared for the IOM Roundtable on Evidence-Based Medicine.[4] These ideas can be best illustrated using a stylized example. Broadly speaking, two outcomes are possible when a set of interventions (say A and B) are compared. First, either A or B can be found to be the better of the two alternatives based on some risk-benefit trade-off perspective. Second, A and B can be found to be identical in effectiveness and safety, or at least close enough that selection based solely on price is possible. Each of these two basic outcomes has different implications for the interests of patients and manufacturers. A third outcome is also possible, where A and B can be found to each sometimes be better than the other for defined subgroups. We will ignore issues of heterogeneity here and model our discussions as if they are addressing one such subgroup.[2]

Patients may benefit from the results of CER in both of the above cases. If A is better than B, or B better than A, patients and their physicians can know to choose the better of the two alternatives assuming cost is not a concern.[3] If A and B are found to be identical or sufficiently close in efficacy, the patient may benefit from knowing that they can choose the cheaper of the two. In a competitive market, this will tend to drive down the prices of both, although not to their respective marginal costs if both the products are on patent. When at least one of the products is generic, market entry will push down the price towards the marginal cost, unless the newer entrant relies on some other measure besides comparative effectiveness to retain demand for its product at a higher price.[4]

Manufacturers may benefit from CER when the intervention they provide is found to be superior

2 It is worth noting that certain types of adaptive trials, such as adaptive assignment of treatments within a trial, are well suited to study and estimate the extent of such heterogeneous treatment effects.

3 This is also facilitated by the coverage decision.

4 Newer entrants usually spend large amounts on detailing and advertisement, especially highlighting selected dimensions of outcomes where their products may be better than the generics.

by some set standards. Sometimes this may be apparent from the time any research is begun. If so, the incentive to perform CER may be high because the manufacturer may be able to increase the price and/or quantity of the intervention that it provides if the results of the study are in its favour. However, more often, there is some real uncertainty about whether a treatment will be superior. Consequently, even when the study may have appeared more likely to benefit the manufacturer, the study would certainly carry risk, and risk-averse firms or specialty groups, or individual decision makers within them, might well be reluctant to bear that risk. It is interesting to note that the adverse effects of such risk on the private incentives to perform research are opposite to those of the social benefits in the sense that research is most valuable from the patient's perspective when there is the greatest uncertainty about the relative benefits of the alternatives being considered. Finally, if the treatment was found to be uniformly identical to alternatives, manufacturers would likely be harmed by downward pressures on prices.[5] Therefore, the risks associated with comparative effectiveness information can lower the incentives for manufacturers to perform CER. However, in practice, manufacturers often engage in a portfolio of products and research, knowing that comparative effectiveness information on any single product can become public through other sources such as competition from other manufacturers or public investments. Such portfolios can make manufacturers less risk averse as that would seem to enable them to make investment decisions based on expected gains and losses, but if individual decision makers with the firm are rewarded based on the outcomes of their decisions, the overall decision-making process of a firm may nevertheless be a highly risk averse one.

3. An Economic Model for Private Manufacturers' Incentives

Consider a profit maximizing manufacturer trying to decide about investing in a comparative effectiveness study that compares the manufacturer's product, A, with its competitor's product, B. The incentives to invest in CER are driven by three parameters: (i) the expected revenue stream without its investment in CER (later we study the possibility that results from CER may be available from other sources); (ii) the time and money required for conducting CER; and (iii) the expected revenue stream resulting from investment in CER.[6] We assume that both products A and B are on patent. We also assume that following patent expiry, competitive forces drive down the equilibrium prices to the marginal cost of the product, which in many cases is close to zero.[7] A formal model describing this optimization from a manufacturer's point of view is given in the appendix in the SDC.

The revenue stream that would arise with investment in CER of length, say T_{CER}, would consist of the pre-CER (*status quo*) revenue stream until CER results are revealed followed by a counterfactual revenue stream that arises as a consequence of CER evidence. CER is expected to influence expected revenue in three ways: it changes the equilibrium quantity for A, it changes the equilibrium price for A, and it determines the time over which the manufacturer would collect these CER-influenced revenues. We will refer to the CER-influenced prices and quantities as the counterfactual prices and quantities. The manner in which CER information is able to change equilibrium price and quantity is discussed at length in Basu et al.[11] In private markets, CER information will shift (increase) demand for the more effective treatment at the expense of the less effective

5 This is especially true in competitive product markets where it is difficult for one manufacturer to negotiate with payers for a lower price and a larger share of the market.

6 Sometimes CER results may lead to new indications for a product, thereby expanding its market. We will ignore such complications for now.

7 Price erosion may be limited for biologics since the generic market expansion for biologics will be limited by regulatory and manufacturing hurdles as well as competition from the introduction of next-generation biotherapeutics.

treatment. Consequently, there will be an increase in the equilibrium price and quantity demanded for the more effective treatment. In a subsidized market, where payers provide a subsidy for treatment use, thereby separating supply (reimbursement rates) and demand (co-pays) prices, the effects of CER will be in the same direction as in private markets, but even more pronounced due to the multiplier effect of the subsidy.[8]

Given that the marginal cost of producing A remains insensitive to CER investments, the manufacturer of A will have an incentive to invest in CER only if its expected revenue stream with CER is higher than the one without CER investments. Thus, the manufacturer of A's incentives will hinge on the expectation of favourable results from CER and the anticipation of price and quantity changes conditional on a favourable CER outcome. The ambiguity in obtaining favourable results from CER can be expressed using a probabilistic approach for outcomes (this aspect of decision making is formalized in the appendix in the SDC). As we discussed earlier, the outcome of CER comparing two products, A versus B, can be any one of the following: A > B, B < A or A = B denoted by index $k = 1$, 2 or 3, respectively. Therefore, the expected counterfactual revenue stream post-CER will be a weighted average of conditional revenue streams under each of these outcomes, weighted by the *expected posterior* beliefs on the likelihood of these outcomes (denoted as w_k, $k = 1, 2, 3$). The expected posterior beliefs can be empirically derived using simulation exercises building off current (prior) beliefs about the outcome.[12,13] The decision criterion for the manufacturer to invest in CER is thus driven by contrasting the expected benefit from conducting CER, which is the difference between this weighted counterfactual revenue stream and the *status quo* revenue stream during the post-CER time periods, against the cost of conducting the CER.

A general prediction that comes out of such a criterion is that a manufacturer of an incumbent product in the market will have less incentive to invest in CER than the manufacturer of a newer product. For example, if the residual patent life of A is shorter than that of B, then the price of A will fall drastically as soon as A's patent expires, with or without CER information resulting in small differences between the counterfactual prices and the *status quo* prices for A. Moreover, any positive CER result for A will now be shared publicly by market entrants for the generic competitors for A, thereby making the counterfactual quantity similar to and even lower than the *status quo* quantity. Consequently, expected benefits from CER investments may well be quite small or negative for the manufacturer of an incumbent product, especially when there is a larger time gap until the market entry of its brand name competitor.

For example, a search on the clinicaltrials.gov registry revealed that since 2000 there have been 25 industry-sponsored phase IV trials comparing the efficacy of antipsychotic drugs among schizophrenia patients in head-to-head fashion with active comparators. Of those trials, 22 (88%) were sponsored by the manufacturer of the drug that entered the market later than its comparator.

4. Competition in Comparative Effectiveness Research (CER) Investments

In the above discussions, we have assumed that the manufacturer of A is the only entity deciding to invest in CER. However, market competition would suggest that, even if the manufacturer of A does not have an incentive to invest, its competitors may have such an incentive.[9] This is especially true because if the prior likelihood of success for A is small, it generally implies a high prior likelihood of success for B. Moreover, recent investments of public funds to carry out CER suggest that such CER information may become public irrespective of private industries' interests. Concurrent information about whether research on a

8 The multiplier effect arises mainly because the demand curve may become more inelastic when pushed outward, thereby increasing the difference between demand prices (co-pays) and supply prices (reimbursements).

9 We continue to assume a two-competitor market. Our general results extend to a market where there are multiple competitors.

particular comparison is being conducted by other parties is becoming more readily available through resources such as clinical trial registries, which make it more difficult to suppress potential adverse findings of clinical studies. Consequently, even if the manufacturer of A does not invest in CER, there is a chance that the manufacturer of A will see the CER-influenced equilibrium price and quantity for its product. The manufacturer's new expected *status quo* revenue stream will then be a weighted average of the counterfactual revenue stream and the original *status quo* revenue stream, weighted by the probability that CER will be conducted nevertheless (and assuming that T_{CER} will be the same whether or not it is conducted by alternative stakeholders). Compared with the decision criterion for investment in CER in section 3, the new incremental expected benefit to the manufacturer of A for conducting a CER study is reduced by a factor that is equal to the probability that someone else will conduct this study. It signifies that competition for CER investments among alternative stakeholders will reduce the incentive for private manufacturers to invest in CER. Consequently, public investment in CER may to some extent crowd out private investments. Such crowd out implications for public investments in CER have not been discussed in depth in the literature.

An interesting aspect of such decision making lies in anticipating proprietary information that the manufacturer of B may possess that is unobserved by the manufacturer of A and *vice versa*. For example, using this new decision criterion and the prior information available to it, the manufacturer of A can anticipate whether the manufacturer of B possesses the incentive to invest in CER. However, if the revealed behaviour of manufacturer B is to not invest, even when it seems to have the incentive, this may help the manufacturer of A to update or readjust its priors on comparative benefits.

Importantly, the probability to invest in CER by other stakeholders may actually vary by the length of CER itself. The longer it takes for a CER study to be completed, the lower the incentive for a private manufacturer to invest in the study due to its increased costs and lack of return in terms of expected changes in revenue. On the other hand, a high social value of the information may still preserve the incentive for public investments in such trials. Consequently, it can be expected that the probability to invest in CER by other stakeholders may increase with the required length of a CER trial.

For example, a search on the clinicaltrial.gov registry for head-to-head phase IV trials since 2005 that had at least one commercial product as a comparator revealed that in diseases like lung cancer, characterized by very short life expectancies, six out of eight (75%) were sponsored by industry. In contrast, among similar trials for prostate or breast cancer, for which CER usually demands a longer follow-up, only four out of 12 (33%) trials were found to be industry sponsored.

5. The Role of Bayesian Trials in Altering Manufacturers' Incentives

Bayesian trials, such as those employing adaptive designs, are being increasingly used in clinical research as they are ideally suited to adapting to information that accrues during a trial, potentially allowing for smaller, more informative trials that offer better treatments to patients.[8] For example, information accumulation on a comparative question may be deemed sufficient when the probability of any one outcome (A > B, B < A or A = B, in our stylized example) crosses a threshold (say 0.95) or the probability that none will reach that mark itself crosses some threshold (i.e. stopping due to futility). Given a prior probability distribution for these outcomes, as data from a randomized trial accumulate, an interim posterior probability distribution can be computed in an almost continuous fashion. This enables investigators to modify trials midcourse. Modifications include stopping the trial, adaptively assigning patients to therapies that are performing better or that will give more information about the scientific question of interest, adding and dropping treatment arms, and extending accrual beyond that originally targeted when the answer to the question posed is not satisfactorily known.[10]

In Bayesian approaches, incorporating prior probabilities of success or failure can provide

more reliable and valid *a priori* (i.e. before investment) estimates of w_k, and can therefore help reduce the *ex post* (i.e. after investment is made) risk of unfavourable results due to chance alone.[10] The validity of the estimates for w_k directly affects the expected value calculations in the last section and may guide investment decisions in CER within a firm. Incorporating prior evidence of success or failure for a drug relative to its competitor may either reinforce its manufacturer's incentive to invest by providing a larger expected posterior belief of success with a new comparative trial or protect it from the risk of investment where the expected posterior belief of success is found to be small. The reliability of estimates for w_k can affect investment decisions, especially when these decisions are made by an individual or a small group of individuals within the firms who may be risk averse.

To the extent that Bayesian trial designs can reduce the time to trial completion, they can affect the incentives for a manufacturer to invest in CER in three ways:

1. They will change the expected benefits for a manufacturer as the effects of evidence on equilibrium prices and quantities will occur earlier.
2. They can change the probability that CER information will be public through other sources. Since the feasibility of employing a Bayesian design changes the expected benefits to the manufacturer, it will also concurrently change the expected benefits to the competitors and public payers from investing in CER.
3. They may affect the cost of conducting CER. The effects of Bayesian trials on the costs of executing a trial remain ambiguous. For example, on one hand, a Bayesian adaptive trial would reduce costs by shortening the length of trial. On the other hand, such a design may require more intense use of resources, which may increase total costs of trial.

In fact, if the expected benefits from investment in CER using traditional designs were positive for the private manufacturer, then they will remain positive or increase under Bayesian designs. This is formally shown in the appendix in the SDC. Further, if changes in expected costs due to Bayesian designs are not positive then it implies that, with the reduction of time to CER completion brought about by such designs, expected net benefits of investment should always rise for a private manufacturer compared with following a traditional design for CER. This rise can also induce a private manufacturer to invest in a CER with a Bayesian design even when the expected net benefits were not positive under traditional designs.

However, we did not find a single industry-sponsored phase IV study on clinicaltrials.gov that employs Bayesian designs (we did find a few phase I–III studies with Bayesian designs). This signifies that the diffusion of such specialized designs has been slow, along with the methods required to analyse data from such designs. This is not unexpected from the pharmaceutical industry's perspective given that their core statisticians continue to be specialized in traditional RCT designs due to the demands of the US drug approval process. However, a shift in specialization for industry statisticians may be anticipated going forward given the interests in and changing demands for adaptive seamless phase II/III trials.[14]

6. Implications for Public Investment in CER

With the high potential social value of CER information and the limited public resources for conducting CER studies, it is prudent to prioritize studies so that such investments generate the most value. From a public perspective, investments in CER become inefficient if such investments would have otherwise been made by the private sector. As discussed, there is often a window of time during which the private sector has the most incentive to invest. Optimal investment strategies for public dollars would avoid crowding out private investments and benefit from recognizing when such a time-window of high private incentives occurs. In fact, initial public investments can foster

10 Such prior development can occur with investments in observation studies and Bayesian indirect treatment comparisons that are considerably less expensive than RCTs.

private participation in CER by helping to generate such windows of investment opportunities for private stakeholders.

When private incentives to invest are lacking, small-scale public investments can prove to be of great value as they may alter the expected posterior belief about the likelihood of outcomes to the extent that they induce immediate private investments. On one hand, compared with a direct public investment of a long-term CER, the time lost due to the sequential nature of public and private investments may cut into the overall social value of CER information. On the other hand, such a sequential approach may save resources by avoiding crowd out in investments. Moreover, Bayesian adaptive designs may also be a natural option for public investments in CER as these designs can not only generate information more rapidly but can also effectively allow revision of the posterior predictive distribution in real time to devise efficient stopping rules. That is, they can facilitate generation of only the necessary information that is sufficient to generate positive incentives for CER investments by private manufacturers.

In fact, if such information markets work well, then it is quite plausible to see public-private partnerships in generating CER information. Not only will such partnerships enable more efficient production of information, but they also can help alleviate some of the controversial issues about private manufacturers' conflict of interest in generating such information when they do so independently.

Obviously, prioritizing incentives for public investments based on social value presumes that such investments are always motivated by efficiency concerns. In reality, the political economy of CER is complicated and there may well be many other forces in play that would lead to investments with lower social value. Nevertheless, the growing interest in employing systematic tools such as value-of-information analysis to prioritize research investments within the National Institutes of Health (NIH) and the Agency for Healthcare Research and Quality (AHRQ) seems to indicate that efficiency concerns play a central role in these investments.[15]

7. Discussion

The recent rush of enthusiasm for public investment in CER in the US has focussed attention on these public investments. However, private investment in CER has long been the primary source of CER and little attention has been given to how changing public investment in CER and the increasing use of new methods for CER, such as Bayesian adaptive designs, may affect private incentives for CER. Our work highlights that private incentives to invest in CER may often be less than public incentives to invest in the same and may even be negative if the likelihood of adverse findings is sufficient. Our analysis also highlights that private incentives to invest in CER are determined by how the results of CER may affect the price and quantity of the product sold and the duration over which resulting changes in revenue would accrue given the time required to complete CER and the time from the completion of CER to the time of patent expiration.

We find that these incentives imply a number of predictions about patterns of CER and how they will be affected by changes in public financing of CER and CER methods. For example, these incentives imply that incumbent patent holders may be less likely to invest in CER than entrants, and that public investments in CER may crowd out similar private investments.[11]

In contrast, Bayesian approaches that can shorten the time for the production of CER may increase the expected benefits of CER, which may lead to an increase in private investment in CER as long as the costs of such trial designs are not excessive. Bayesian approaches to trial designs also naturally highlight the dynamic aspects of CER, allowing

11 It is possible that sometimes an incumbent may benefit from a well done Bayesian adaptive CER study that shows substantial previously unreported benefits for an older product that helps extend the 'effective' patent life of the product at very little cost to the innovator. However, such favourable outcomes at the middle or tail-end of a product life-cycle are usually hard to come by and such investments must ride on strong priors of benefits.

less expensive initial studies to guide decisions about future investments, and therefore encourage greater initial investments in CER. Targeted public subsidies for initial studies may also have similar effects when the case for initial public incentives is insufficient. These approaches may also be ideally suited for revealing nuanced subgroups over which comparative effectiveness estimates vary.

Theoretical analysis of incentives to invest in CER such as the one that we provide is important as pharmaceutical firms make decisions about investments in CER and as public policy is formed. However, whether the potential effects we highlight of public funding of CER and of Bayesian trial designs actually produce changes in private investment in CER is ultimately an empirical question. For example, it is possible that actual patterns of investment in CER are driven instead by cashflows into pharmaceutical firms or by scientific advances, such as the growth of personalized medicine, or social changes, such as health reform in the US. This would make it difficult to determine whether private CER has indeed been affected by the forces we discuss. In fact, empirical studies using contingent valuation techniques may help us understand factors that influence a manufacturer's willingness to invest in CER. Nevertheless, it seems likely that the forces we consider will not be ignored by public and private decision makers in the future and those decision makers who are aware of these forces will be more likely to realize favourable returns on their investments.

For such advantages to accrue, however, decision makers must be able to develop empirically meaningful assessments of questions such as how likely a given type of study is to yield a favourable result and the likelihood that relevant CER will be performed even if they themselves do not do it. How to analyse such decisions is not straightforward, but tools including economic analysis, value-of-information analysis, and analysis of political decision-making processes are likely to be relevant.[16-18] Our model, though simple and intuitive, misses the complexity of predicting future returns of CER due to the dependence of returns on the decision of others to invest in CER, adding the potential for game theoretic issues to influence investment. For example, companies may selectively choose to invest or not invest in CER based in part on how their investments might affect returns for competitors and concern that a competitor harmed by CER might retaliate by producing CER on the same or even an unrelated product. There is no evidence whatsoever that such behaviours are common, but these behaviours would be very difficult to prove directly. However, one can deduce, to a certain extent, the existence of these external influences given revealed behaviour is contrary to what the expected impact of investment on revenue would suggest. In fact, fear of retaliatory behaviour would imply that, in the era of transparency brought about by clinical trial registries, overall investment interest in CER by private firms would suffer. Qualitative studies understanding the preferences of decision makers on CER investments within a firm would be useful in gaining a better handle on these complicated issues.

8. Conclusions

In summary, our analyses reveal three key features in the private versus public incentives for investing in CER:

- Private manufacturers often have incentives to invest in CER that will generate public knowledge about the relative effectiveness of competitor interventions. A non-strategic increase in public investments in CER may crowd out these private investments.
- Incentives to private investments remain low for CER that requires longer follow-up. Public investments in these settings become more useful.
- Novel designs for CER, such as Bayesian adaptive trials, and novel methods to analyse data from these trials can help in the efficient production of information for both private and public stakeholders. Additional emphasis on training and development of these methods will be worthwhile.

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