PRELIMINARY AND INCOMPLETE DRAFT

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The Impact of Comparative Effectiveness Research on the Quality and Cost of Health Care [1]

by

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Abstract

Public subsidization of Comparative Effectiveness Research (CER) has received considerable attention as a tool to simultaneously raise quality and lower cost of health care. However, little conceptual and empirical understanding exists concerning the quantitative impact of CER. This paper analyses the impact of CER on health and medical care spending interpreting CER to shift the demand for some treatments at the expense of others. We trace out the spending and quality implications of such shifts in private- as well as subsidized health care markets. In contrast to current wisdom, our analysis implies that CER may well increase spending and lower quality of care when treatment effects are heterogeneous. We illustrate these economic effects for antipsychotics that are among the largest drug classes of the US Medicaid program and for which CER has been conducted. We find that if subsidies were tailored towards the more effective treatments in CATIE without respecting heterogeneity in treatment effects, a net loss of health valued annually from $1.2 to $4.2 billion dollars would be observed in the US population.

Section 1: Introduction

As both private and public payers attempt to improve efficiency of health care spending, comparative effectiveness research (CER) has been offered as a potential solution to improve quality and lower costs. The rationale for CER is to generate better evidence about what works and does not work in health care and to thereby improve the productivity of health care spending. Recent public subsidization of CER through the Obama stimulus bill has raised awareness and funding for CER.

Although CER is taken for granted to raise quality and lower costs, little is understood about how exactly this will take place. Indeed, despite the importance of comparative effectiveness research in the policy debate, there has been little explicit and quantitative analysis of the impact of CER on health or medical care spending. Given this lack of understanding of the consequences of CER, the purpose of this paper is to attempt to provide a framework to quantitatively evaluate the effects of CER. Such a framework is needed to estimate whether investments in CER are outweighed by their benefits in terms of impact on the quality and costs of care.

The paper may be outlined as follows. Section 2 specifies the economic context in which we analyze the impact of CER. We interpret the evidence generated by CER to raise the demand of some treatments at the expense of others. Section 3 considers the quality and costs implications of such demand shifts induced by CER in a private market. Section 4 analyzes these quality and costs impacts in a subsidized market where treatments that fare better under CER are subsidized more by public payers, e.g. through less formulary restrictions or lower co-pays. Section 5 discusses the impacts of such CER-responsive subsidies when there is heterogeneity in treatment effects. An important issue here is that subsidies may favor one treatment, deemed "the best", even though the best treatment varies across patients. Our overall finding from the conceptual analysis is that CER has indeterminate effects on costs and quality of care—under plausible conditions CER may even lower quality and raise costs. Among the factors that govern the health and spending impact of CER include the price-elasticity of supply of treatments as well as how evidence-elastic demand is.

Section 6 provides an empirical analysis for antipsychotic treatments for which we simulate the effects of reimbursement subsidies being responsive to CER. This drug class is among the top spending classes covered by Medicaid and there has been considerable interest in the comparative effectiveness issues surrounding them. This is partly due to the 1999 CATIE trial that found that second generation therapies were equally effective on average as first-generation therapies. Naturally, some have suggested that Medicaid should respond to subsidize only first generation treatments through restricting access to second generation treatments. However, our analysis finds that there would be a net loss in patient health valued annually at $4.2 billion if Medicaid followed such a responsive subsidy policy following this CER. This is because the CATIE trial data provides strong evidence on the heterogeneity in treatment

effects so that many patients that did not respond to first generation therapy would respond to second generation therapies.

Lastly, section 7 concludes by discussing the future research and the policy implications our analysis suggest.

Section 2: The Basic Framework

This section specifies the framework in which health and spending implications are analyzed and estimated. There are two aspects to CER – one is the generation of comparative information between two treatment alternatives. This is usually accomplished using randomized trials or other appropriate evaluation methodologies that produces an estimate for the treatment effects. Second is the potential response by the market or public payers to this information affecting the use or uptake of treatments in the population.

Consider two treatments with true treatment effects q=(q1,q2) which we interpret as product qualities. For example, these two treatments may be first-and second generation treatments for a given clinical condition. The beliefs over the unknown levels of quality for the two treatments are specified as F=F(q1,q2) before the CER and F'=F'(q1,q2) after the CER . Throughout, we denote by un-primed quantities the variables prior to CER and by primed quantities the corresponding levels after the CER. The demand functions for the two treatments are given by D1 and D2 and depend on the perceived qualities through F as well as prices. For example, demand functions may be governed by the expected quality levels given the evidence. We consider the impact that CER has not only on the evidence of quality of products but also on market prices and quantities. We let Y=(Y1, Y2) and P=(P1,P2) denote the equilibrium quantities and prices of the two treatments. The total spending S and health outcomes Q in this clinical area are determined by the use of both the first and second generation technologies and their average cost-effectiveness is determined by their ratio

$$S/Q = (Y1 \cdot P1 + Y2 \cdot P2) / (Y1 \cdot q1 + Y2 \cdot q2))$$

CER has two possible effects on market outcomes. First, it may generate evidence that changes quality beliefs and shifts demand and second may thereby affect equilibrium prices and quantities observed. The CER changes the average health outcome according to

$$\Delta Q = (Y1' - Y1) \cdot q1 + (Y2' - Y2) \cdot q2$$

Regardless of the perceived health benefits of the treatments, the true quality level determines the actual health impact. Thus, the true quality differences and quantity changes complement each other in determining the overall health impact of CER. CER impacts demand through learning and the changes in equilibrium quantities this implies. Naturally therefore, the evidence- and price elasticity of demand is central to the health impact of CER.

The CER changes overall spending on the two treatments according to

$$\Delta S=[Y1'\cdot P'1 + Y2'P'2]- [Y1\cdot P1 + Y2P2]$$

There are thus two ways in which CER may affect spending. One is to lead to substitution to cheaper treatments holding prices constant. The other is a change in equilibrium prices induced by the CER.

Although CER is typically concerned with only evaluating effectiveness of treatments, it naturally has consequences for the cost-effectiveness of treatments through affecting the health and spending patterns in equilibrium. More precisely, the impact of CER on cost-effectiveness is the ratio of the increased spending and health impact, $\Delta S/ \Delta Q$. Cost-effectiveness is higher if spending responds less than the levels of health and is lower if spending responds much more than health governed by price or quantity responses to the CER

Section 3: Impact of CER in a Private Market

Consider first the implications of CER in a private and competitive market. As illustrated in Figure 1 we assume that, without loss of generality, the demand for the superior (first) product shifts weakly outward and the demand for the inferior (second) product shifts weakly inward as a consequence of the CER; $D'1 \geq D1$ and $D'2 \leq D2$. Moreover, we assume that the evidence of the CER is valid in the sense that these demand shifts are consistent with true quality levels; $q1 \geq q2$. For illustrative purposes only, the Figure concerns the case when the two demands are equal prior to the CER and supply curves coincide.

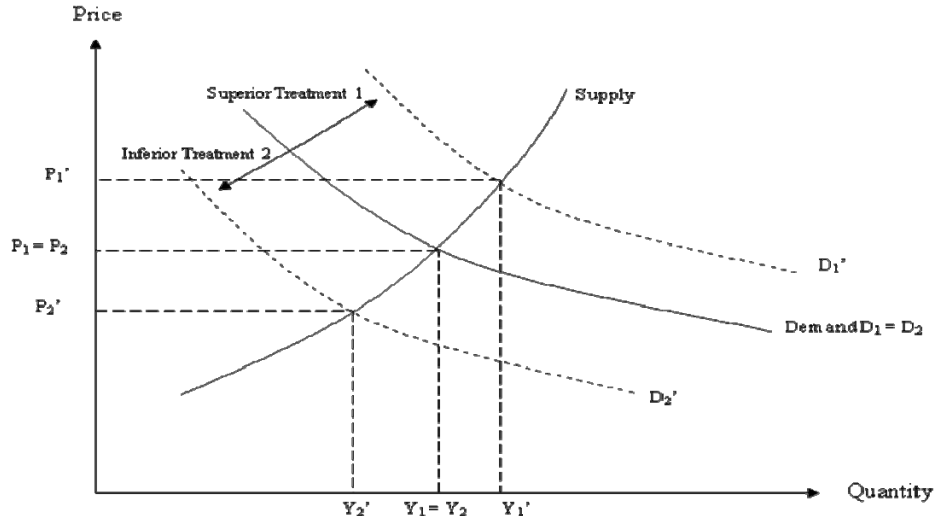

Figure 1: Demand shifts associated with CER

In a competitive market, the supply functions of the two products are not assumed to be affected by the CER but determined by the costs of production of the two treatments. An outward (inward) shift in demand holding supply constant raises (lowers) both the equilibrium quantity and price. In other words, for the superior treatment 1 its price and quantity rises as opposed to for the inferior treatment 2 they fall

$$P'1 \geq P1 \;\&\; P'2 \leq P2 \quad \text{and} \quad Y'1 \geq Y1 \;\&\; Y'2 \leq Y2$$

The magnitudes of these price- and quantity changes induced by CER are determined by the price-elasticity of supply. By standard arguments, when demand for the two products shifts in response to the evidence generated by the CER, the equilibrium quantities and prices that result will "trace out" the supply curve as in the Figure above. Thus, the impact of CER on health and spending are not merely driven by how sensitive demand is to the evidence generated by the CER but more importantly how responsive supply is to price.

Now consider the health and spending implications of these market responses to CER. As both quantity and price rise (fall) for the superior (inferior) treatment, it follows directly that spending on the superior (inferior) treatment rises (falls). The impact on overall spending, ΔS, is thus indeterminate as it may rise or fall dependent on whether the positive spending effect of the superior treatment dominates the negative spending effect of the inferior treatment. However, the overall health effect is clearly positive, $\Delta Q \geq 0$, as long as the evidence of the CER is valid. This is because quantity is raised for the superior treatment and lowered for the inferior second treatment. The magnitude of the health effect induced by CER is determined by the price-elasticities of supply. For example, consider when demand and supply for a treatment is linear $D(p)=a(F)-bp$ and $S(p)=c+dp$ where the demand is shifted by the treatment beliefs. The equilibrium quantity that equates demand and supply is then given by

$$Y=(a(F)d+cb)/(b+d)$$

This implies the change in quantity

$$\Delta Y=[(a(F')-a(F)][d/(b+d)]$$

If a change in the beliefs F shifts the demand through raising (lowering) the intercept a(F) for the first (second) treatment then the impact on health, $\Delta Q=\Delta Y1q1+ \Delta Y2q2$, is governed to a large extent on how sensitive supply is to price, d. For example, it is generally true that in the standard long-run case of a infinitely elastic industry supply, corresponding to free entry, then there are no price-effects from CER. For example, this may be the case for markets for generic drugs or the market for procedures that are not patentable. In this case, ΔY converges to $a(F)-a(F')$ above as d goes to infinity so that the impact on health and spending is driven only through quantity effects induced by how sensitive demand is to the evidence generated by the CER.

Section 4: Impact of CER in Subsidized Market

In most countries, health care markets are subsidized thereby separating supply-and demand prices. For example, the US government through the Medicare and Medicaid program pays manufacturers and providers at prices above the co-pays of those eligible for the programs. In a market subsidized at rate s, let the equilibrium quantity, supply- and demand price for a treatment be denoted by Y (s), $P_S(s)$ and $P_D(s)$ as depicted in Figure 2.

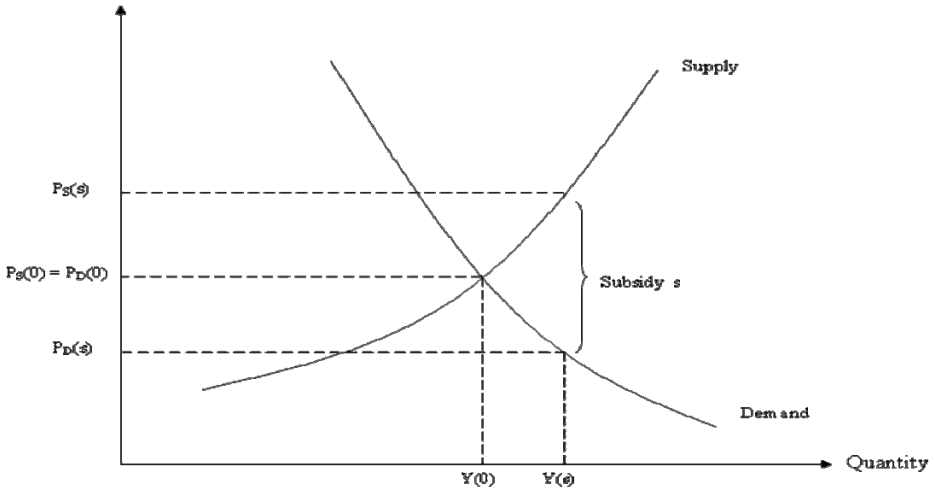

Figure 2: Quantity, Demand Price, and Supply Price as Function of Subsidy

As illustrated in Figure 2, for a given market it is well known if the subsidy s increases then the supply price rises, the demand price falls, and the equilibrium quantity rises ; $dP_S/ds \geq 0$, $dP_D/ds \leq 0$, $dY/ds \geq 0$.

In a subsidized market, CER will impact health and spending not only through the demand shifts discussed earlier but also through any changes in subsidy levels set by governments as a consequence of the CER. For example, governments may reimburse more heavily those treatments that did well in CER. We denote by s=(s1,s2) the subsidy levels for the two treatments prior to the CER and s'=(s'1,s'2) the corresponding subsidies after the CER. We term the subsidy policy as *responsive* when CER leads governments to subsidize the first superior treatments relatively more compared to the second inferior treatment

$$s'1 \geq s1 \quad \& \quad s'2 \leq s2$$

We denote by ΔQ (s,s') and ΔS(s,s') the corresponding impact on overall health and spending of the treatment class for a given subsidy policy. In Figure 2, we can trace out the impact on prices and quantities under a responsive subsidy policy. For the superior first treatment, demand shifts outward as before but in addition the subsidy-wedge between the demand- and supply price increases. For the

inferior second treatment, the demand shifts inward as before, but in addition the subsidy- wedge decreases. It follows that a responsive subsidy policy has a reinforcing *multiplier-effect* on prices and quantities compared to the private market effects. The subsidies act in the same direction as the changes induced by the shifts in demand implied by the CER.

More precisely, if Y1(F,s) and Y2(F,s) denote the equilibrium quantities under a given demand and subsidy structure then a responsive subsidy policy implies that not only does demand itself change quantities, but that subsidy changes those quantities further in the same direction

$$Y1(F',s') \geq Y1(F',s) \geq Y1(F,s) \quad \& \quad Y2(F',s') \leq Y2(F',s) \leq Y2(F,s)$$

This multiplier effect implies that the impact of CER on health is magnified under responsive subsidy policy compared to an unresponsive policy and in turn compared to no subsidies that coincides with the private market case

$$\Delta Q(s,s') \geq \Delta Q(s,s) \geq \Delta Q(0,0)$$

In a subsidized market, the total spending effects are governed by supply prices as that covers both consumer and government spending on the treatment. However, as before, there is an indeterminate effects on the spending levels, as spending on the superior first treatment rises and spending on the inferior treatment falls, although both at greater magnitudes due to the multiplier effect induced by a responsive subsidy policy.

Section 5: Impact of CER under Heterogeneous Treatment Effects

This section extends the previous analysis of health- and spending impacts of CER by considering heterogeneity in treatment effects or quality across patients. As opposed to the previous sections, responsive subsidy policy may adversely affect health in this case.

We consider expectations about treatment effects that are heterogeneous, F(q, h), where the parameter h may vary across patients distributed according to G(h). The demand function for the entire patient population is the patients aggregated across these types

$$D_k = \int D_k(h) dG(h)$$

where $D_k(h)$ is the demand for treatment k for the patients of type h. The demand functions D' after the CER is determined similarly by $D'_k = \int D'_k(h) dG(h)$

When a CER subsidy policy is responsive it favors a given treatment after the CER has been conducted. When subsidies are *product-specific* but treatment effects are *patient-specific* then subsidies may favor one treatment, deemed "the best", even though the best treatment varies across patients. Contrary to the case of homogeneous effects where CER improved health and responsive subsidies had a multiplier

effect on that improvement, this may imply that health is adversely affected. To illustrate, consider Figure 3 in which a given point in the figure corresponds to the qualities q for patients of a given type h and the distribution of points in the Figure corresponds to the distribution F(q) across all subgroups . The patients below (above) the 45-degree line are those benefitting more from the first (second) treatment. As revealed in the Figure, say the first treatment had a higher mean treatment effect than the second treatment and therefore was deemed "the best" by the CER.

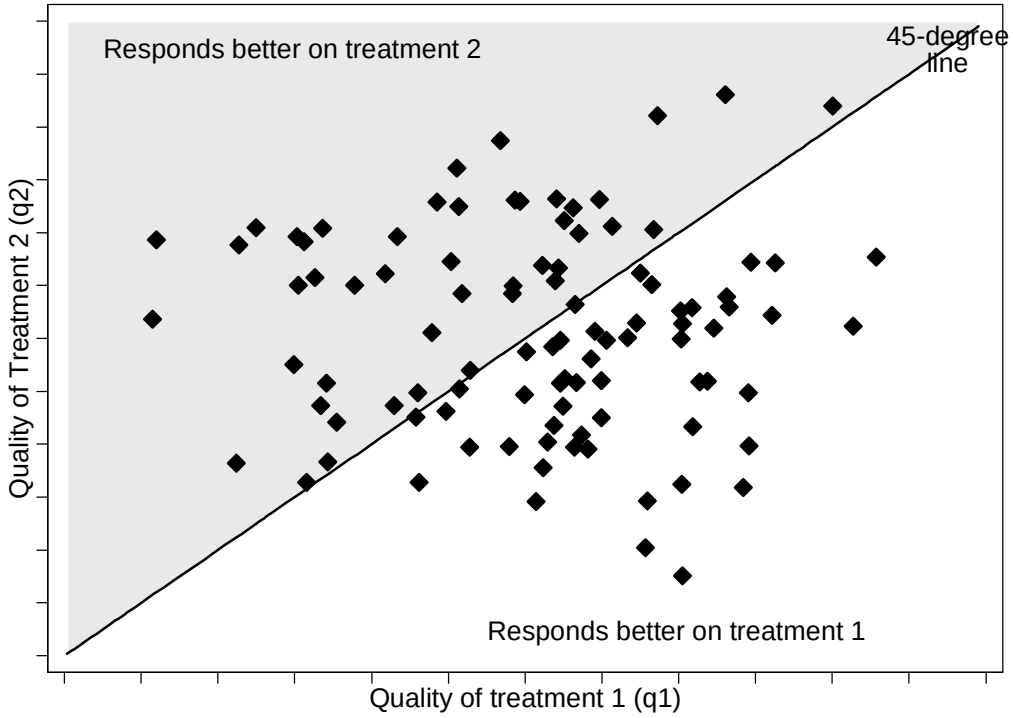

Figure 3: Distribution of Treatment Responses

Now consider when a responsive subsidy policy therefore favored the first treatment because it had a higher mean treatment effect than the second treatment. To illustrate, consider the extreme case when the second treatment was not reimbursed at all, s'2=0, and the patients of the program were too poor to be able to afford it as a consequence, Y2'=0. Then the patients above the 45-degree line would suffer a loss in quality corresponding to the vertical distance from their point down to the 45 degree line because the best treatment for them was not the one deemed best by the CER. The relative size of the negative health impact of some patients compared to the previously discussed positive impact of the rest of the population now makes the overall health impact effect indeterminate.

More generally, the average quality before and after the CER are given by

$$Q=Y1\cdot E1 + Y2\cdot E2$$

$$Q' = Y'1E'1 + Y2'E'2$$

where the expectations Ek and E'k, k=1,2 are the average quality levels conditional on selecting the treatment before and after the CER. The impact on health ΔQ is therefore partly determined by the effects among people who change their treatment choices due to the responsive policy, as is also the case under homogenous treatment effects. However, in the heterogeneous case, this impact comprises of the effect on those whose new choices lead to better outcomes and the effect on those whose new choices lead to inferior outcomes. The degree of heterogeneity and the extent of self-selection before the responsive policy would determine the overall effect of these two groups.

A responsive subsidy policy may alter quantity towards the first treatment that is superior on average but, due to heterogeneity, the overall effect on those selecting into that treatment may very well be negative. For example, if due to a responsive subsidies the demand for the first treatment absorbs the demand for the second treatment, then Y'1=Y1+Y2. This implies that the impact on health is determined by the effects of those who selected the second treatment prior to the CER

$$\Delta Q = Y2(E'2 - E2)$$

If those who picked the second treatment prior to the CER did this because it dominated the first treatment for them, then this health impact is negative. However, if those who were on the second treatment prior to the CER were incorrect in their choice, then the impact is positive[2].

Because of the potential negative impact on health from responsive subsidies, CER may have indeterminate effect on incremental cost-effectiveness, CE=Δ S/Δ Q. This is because the cost per unit of quality may fall or rise dependent on the patient heterogeneity in the population. For example, in Figure 3 above if responsive subsidies induces everyone to choose the first treatment then clearly average quality of care is lowered, thereby lowering cost-effectiveness under constant prices.

Section 6: Empirical Analysis of Responsive Subsidies for Antipsychotics

In this section we conduct an illustrative empirical analysis of the potential impact of CER responsive subsidies. We consider the recent CER that has been conducted for antipsychotics in the US and the proposed changes in subsidies that has been discussed surrounding this evidence. We compare a factual pre-CER world in which current market conditions and subsidies prevail with a counter-factual post-CER world in which some of the proposed responses in subsidies are simulated.

[2] See Meltzer et al (2003) for evidence of such self-selection among diabetes patients. See also Basu(2009) for a discussion of these effects.

Antipsychotic drugs represent the primary treatments for patients with schizophrenia. Beginning from 1990, a second generation of antipsychotic drugs, also known as the atypicals, was introduced. These drugs are believed to cause less movement disorders as side effects compared to the first generation antipsychotics (also known as typical or neuroleptics). More recently, some of the second generation antipsychotics are linked to increased metabolic side-effects such as weight gain and diabetes. Antipsychotics is a very important drug class to consider because it is the largest class in one of the major US public subsidy programs, Medicaid. Also, in 1999, the National Institute of Mental Health (NIMH)-funded the $42.6 million Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study to compare the effectiveness of one first-generation antipsychotic, perphenazine, and all second-generation antipsychotics available in the US. One of the basic findings that were reported, and contested, by the CATIE trial was that more expensive second-generation antipsychotics (treatment 2 in our analysis) were equally effective as the less expensive first-generation treatment (treatment 1 in our analysis). Several CATIE investigators, including the authors of the CATIE study, have stated that that study was not designed to directly answer questions of policy regarding access to antipsychotic drugs, while others have suggested that the CATIE results establish that it is wasteful to use public funds to pay for second-generation antipsychotics, a perspective that has been adopted by some influential media outlets, and some pharmacy benefit managers (Rosenheck, 2007; NY Times, 2005; Soumerai and Law, 2007). This has led to considerable policy debate on whether the effectiveness evidence generated by the CATIE trial should be used as basis for limiting reimbursement for second-line antipsychotics, that is, whether subsidies should be responsive to the CER.

More specifically, the pre-CER world we consider prior to the CER (CATIE) is the typical case today with both generation antipsychotics are covered under the Medicaid program. Since the second generation drugs are costlier, this resembles a greater subsidy on the second generation drugs compared to first generation drugs (i.e. $s2 \geq s1$). Demand for these drugs are partly determined by the demand prices faced by the patients, which were close to zero, i.e. $P_D(s) = 0$, so that overall spending closely coincide with the supply prices P_S and has involved substantial spending by Medicaid for this drug class.[3] Demand is also affected by heterogeneity in treatment effects as with unrestricted coverage physicians were able to try out alternative drugs and often settle on a drug that appears to produce better quality for an individual patient.

We use the share of drug-specific scripts (total from both Medicaid and commercial) estimated from IMS data to derive the equilibrium market quantities Y before the CER. We represent the quality levels,

[3] Total Medicaid expenditures on antipsychotic medication increased from $484 million in 1995 to $1.3 billion in 1998 (Lewin Group, 2000). In 2004, the annual health care costs for patients with schizophrenia is estimated to be about US $28 billion, of which nearly one-third can be attributed to pharmacy costs (Gilmer et al., 2004). More recent estimates suggest that expenditures on antipsychotic medications have crossed $10 billion this year and account for a third to a half of all mental health expenditures (NIMH, 2006).

q for the drug as the intention to treat effects estimated from the CATIE data as described below. These intention-to-treat effects represent the average quality levels for a given initial drug assignments after incorporating the effect of trial-and-error selection into the best treatment. To estimate the effects of a CER-responsive subsidy policy, we compare this pre-CATIE scenario with two hypothetical (counter-factual) post- CER scenarios. In the first scenario, in response to the CATIE results the responsive subsidy policy entails the second generation drug not being covered; s'2=0. Given the low income of the Medicaid population, this is assumed to eliminate demand in this population so that the post-CER quantity satisfies Y'2=0. In the second scenario, the responsive subsidy policy the second generation drugs are less subsidized than before , s'2 < s2, but only one of the second generation drugs is covered , thereby allowing Y'2 to be positive.

6.1 Methods

We focus on 3 second-generation antipsychotic drugs, risperidone, olanzapine, quetiapine as well as 1 first generation drug perphenazine. These comprise nearly 70% of the market of antipsychotic prescriptions written in the United States.

Since many of these drugs influence both the symptoms and the side-effect profile in patients, we focus on the effect of these drugs on quality-adjusted life year that integrates these effects into a single metric. We will use the Positive and Negative Syndrome Scale (PANSS) scores, which measure severity of psychotic symptoms among patients with schizophrenia, to compute a severity index (Mohr et al., 2004) and then assign quality of life weights to each severity category. Similarly, we will assign quality of life weight to each of the popular side-effects, akathisia, akinesia and weight gain. Overall quality of life for a patient at any given time is computed by taking the minimum of the symptom-based QOL and side-effects based QOL. The key outcome on which comparisons are made is the average monthly change in QOL.

Pre-CATIE scenario: We assume that the drug-specific shares of scripts estimated from the 2005 IMS data represent equilibrium shares of use both at the extensive margin (across patients at the initial assignment) and at the intensive margin (within each initial assignment over a one year period). Therefore, we use these shares to split the 1.5 million patients with schizophrenia to obtain the number of patients initiating with each of these drug. Also, the total number of scripts (Yk) for each drug over a one year period is calculated by multiplying the number of patients initiated on a drug times twelve 30-

day scripts.[4] The health effect Ek of corresponding drug initiations under this scenario are calculated based on the intention-to-treat estimates on monthly changes in QOL.

We apply mixed effects linear models to individual-level longitudinal quality of life data from CATIE and estimate the intention-to-treat effects of the initial assignment of alternative drugs. Specifically, we look at look at the coefficients on treatment-time interaction to compare the average rate of change in QALYs under alterative first line treatment.

To calculate the total costs under this policy, we use the intention-to-treat effects on total drugs and services costs that were reported by Rosenheck et al (2005) in their Supplemental Table C (reproduced here in Table 1) and multiply them with the number of patients initiating each drug.

Post-CATIE scenario with responsive subsidies, Scenario #1: In this scenario, the typical antipsychotic (perphenazine) is the only drug subsidized and the atypicals are not reimbursed. That is, s'1 is set so that the consumer price is zero and s'2 =0. We will assume that all patients are initiated with perphenazine, a proportion of these patients (estimated using CATIE data) will find perphenazine to be efficacious and tolerable and therefore continue on it. The remaining will discontinue perphenazine (median time to discontinuation estimated using CATIE data) but will not be able to switch to other drugs due to lack of subsidies (i.e. Y'2=0). We run separate mixed effects models to estimate the effect of the initially assigned drug on monthly changes in quality of life over the duration of the trial for those who continued on their initial assignment and till the time of discontinuation for those who discontinued the initially assigned drug. Under this scenario, we use the QOL effects for continuers and discontinuers for the perphenazine assignment (Table 2).

Among the discontinuers, we assume, conservatively, that 11% of them will have a relapse (Weiden and Olfson, 1995) and the remaining will not experience any more gain in their quality of life in that year. Patient who relapse, will on average experience two hospitalization worth $14,000 each and a loss in quality of life of 0.45 per patient (Lenert et al. 2004).

Costs for the compliant group are calculated based on the estimates on total drugs and services reported by Rosenheck et al (2005) in their Supplemental Table D, where treatment crossovers were excluded. The same monthly costs are applied to the noncompliant group during the first 6 month when they were on perphenazine. After discontinuation, additional costs of hospitalization due to relapse are added to these estimates. The *post-CER scenario #1* is illustrated in Figure 4.

[4] All patients do not continue on their initially assigned drug but can switch to alternative drugs as they have access to all the alternatives. However, in equilibrium, the estimated share of scripts from IMS data will reflect these swtitchings.

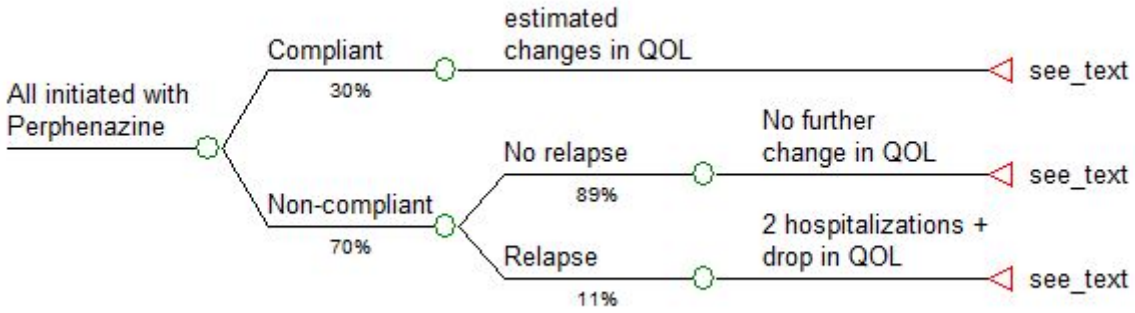

Figure 4: Patterns of utilization under the post-CATIE scenario # 1 with a responsive subsidy policy.

Post-CATIE scenario with responsive subsidies, Scenario #2: In this second scenario, the typical antipsychotic (perphenazine) and only one atypical antipsychotic are subsidized but the other atypicals are not reimbursed. That is, s'2 for one atypical and s'1 are set so that the consumer prices are zero for each while s'2 =0 for all other atypicals. We will consider olanzapine to be the atypical reimbursed and assume that all patients who had chosen an atypical to initiate their treatment under the pre-CER policy would now choose to initiate treatment with olanzapine as it is the only atypical covered.

Similar to Scenario #1 above, we will assume that among all patients who initiate with olanzapine, a proportion (estimated using CATIE data) will find olanzapine to be efficacious and tolerable and therefore continue on it. The remaining will discontinue olanzapine (median time to discontinuation estimated using CATIE data) but will not be able to switch to other drugs due to lack of subsidies for the other atypicals, and the clinical infeasibility to switch to a typical (Jobson, 2009). We use the QOL effects for continuers and discontinuers for the olanzapine assignment (Table 2) to calculate the total effect of this assignment. Among the discontinuers, we assume, conservatively, that 11% of them will have a relapse (Weiden and Olfson, 1995)and the remaining will not experience any more gain in their quality of life in that year. Patient who relapse, will on average experience two hospitalization worth $14,000 each and a loss in quality of life of 0.45 per patient (Lenert et al. 2004).

Patients initiating with perphenazine will follow the same route as in scenario #1, with a difference in that among the discontinuers of perphenazine, a proportion can switch to olanzapine and prevent relapse. Since we do not directly have an estimate for the magnitude of such an effect from the CATIE data, we will assume that the relapse rate among discontinuers of perphenazine reduces from 11% to 5%.

Costs for the compliant groups under each drug initiation are calculated based on the estimates on total drugs and services reported by Rosenheck et al (2005) in their Supplemental Table D, where treatment crossovers were excluded. The same monthly costs are applied to the noncompliant group during the first 6 month when they were on perphenazine or olanzapine. After discontinuation, additional costs of hospitalization due to relapse are added to these estimates. The *post-CER scenario #2* is illustrated in Figure 5.

Each patient who initiates and continue wth olanzapine counts for twelve 30-day scripts. Each patient who discontinues olanzapine is assumed to discontinue at 9 months[5] and count for nine 30-day scripts. In order to be conservative, we ignore the number of scripts sold to patients who switch to olanzapine after discontinuing from perphenazine. We will defer the discussion of price responses for olanzapine that is expected as its equilibrium quantity soars to the next section.

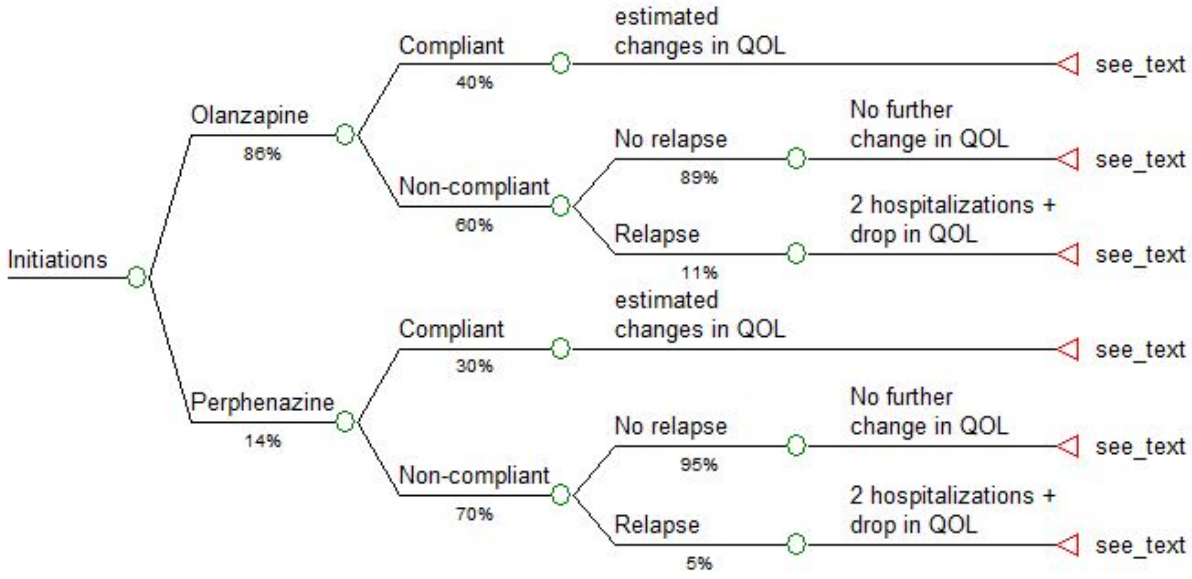

Figure 5: Patterns of utilization under the post-CATIE scenario # 2 with a responsive subsidy policy.

We compare the expected incremental costs and benefits, in terms of Quality adjusted life years (QALYs),) between the pre- and post CER scenarios.

[5] Median time to discontinuation for the quetiapine groups estimated using CATIE data (Lieberman et al., 2005).

6.2 Results

Table 1 reports the intention-to treat effects of initial assignment on the mean changes in quality of life per month based on CATIE data. In line with the results presented by CATIE investigators, we find that these intention-to-treat effects are significant for each of the initially assigned drug but not significantly different from each other. These effects are used to calculate total QALYs and costs under the pre-CER policy. Table 2 presents results on the effects of the initially assigned drug among those who continued on that drug throughout the length of the trial and those who discontinued. For those who continued with their initial assignments, results are found to be similar to the intention-to-treat effects. However, among those who discontinued their initial assignment, the effects of the initial drug till the time to discontinuation were significantly different from each other. The QALYs effects of each drug, in general, are smaller for those who discontinue than those who continue except for olanzapine. For olanzapine, the average effect on quality of life among those who discontinue are slightly higher, mainly because discontinuation is based predominantly based on weight gain in this cohort, which does not translate to a major decrement in quality of life. Tables 1 and 2 also reports the total monthly cost estimates by initial assignment as reported by Rosenheck et al (2005) based on CATIE data.

Tables 3 and 4 reports the total quality adjusted life years and the annual costs associated under the pre- and post CER scenarios for the US. All estimates are based on a population of 1.5 million patients with schizophrenia.

Pre-CATIE Scenario: The number of patients initiating with each drug are given in Table 3. The number of 30-day scripts (Yk) for each drug sold in an year are estimated to be 6.4 millions for quetiapine, 5.6 millions for risperidone, 3.5 millions for olanzapine and 2.5 millions for perphenazine. Based on the intention-to-treat effects of initial assignment, the total QALYS generated in a year adds up to 52,391 (Table 3) while the total costs add up to $26.9 billion dollars (Table 4).

Post- CATIE Scenario with responsive subsidies, Scenario#1: When perphenazine is the only subsidized drug and all of 1.5 million schizophrenic patients are started on perphenazine, only 30% of them continue with perphenazine (Lieberman et al, 2005). These patients generate a total of 15,660 QALYs and $5.2 billions in total annual costs. Among those who discontinue perphenazine (assumed to be at the 6 month mark (Lieberman et al, 2005) but does not relapse add a total of 15,120 QALYs and $13.6 billions. Among those who discontinue perphenazine and relapse suffer a *loss* of 51,975 QALYs and adds $4.9 billions to total annual costs. Consequently, this post- CER scenario would produce a *loss* of 21,195 QALYs at total annual costs of $23.7 billions, mainly due to the severe effect on the quality of life of those who relapse due to the unavailability of drugs. The number of 30-day scripts (Y'k) for perphenazine sold in a year soars to 11.7 million, while for the atypicals Y'k-s drop to zero.

The incremental loss in QALYs (ΔQ) observed due to the CATIE-responsive subsidies in Scenario #1 compared to pre-CATIE scenario amounts to 73,586 QALYs. This CATIE-responsive subsidy policy will generate an annual saving of $3.2 billion dollars (ΔS) compared to the pre-CATIE scenario despite the extra costs incurred due to the additional relapse related hospitalizations. This is in line with Duggan's (2005) analysis that rise in expenditures on second generating antipsychotic does not produce cost offsets. However, the real story lies in the impact on health or effectiveness. The savings in costs with such a CATIE-responsive subsidy are only worth the money if the societal willingness to pay for an additional QALY falls below $44,000. At a threshold of $100,000 per QALY, the CATIE-responsive policy will result in an annual loss of $4.2 billion dollars in value.

Post- CATIE Scenario with responsive subsidies, Scenario#2: When perphenazine and olanzapine are the only two drugs that are subsidized, 14% of the 1.5 million patients with schizophrenia are expected to initiate with perphenazine and the rest with olanzapine. Patients initiating with olanzapine will generate a net of 3,833 QALYs and those initiating on perphenazine will generate a net of 880 QALYs, totaling to 4,713 QALYs (Table 3) for this scenario at a cost of $23.3 billions (Table 4).

The number of 30-day scripts (Y'k) for olanzapine in a year is expected to rise to 13.2 million.

The incremental loss in QALYs (ΔQ) observed due to the CATIE-responsive subsidies in Scenario #2 compared to pre-CATIE scenario amounts to 47,678 QALYs, which is much lower than the incremental loss expected with Scenario #1. This CATIE-responsive subsidy policy will generate an annual saving of $3.6 billion dollars (ΔS) compared to the pre-CATIE scenario. Since this saving is larger than the expected saving with Scenario #1, Scenario #2 clearly dominates Scenario #1. The savings in costs with this CATIE-responsive subsidy are only worth the money if the societal willingness to pay for an additional QALY falls below $75,500. At a threshold of $100,000 per QALY, this CATIE-responsive policy will result in an annual loss of $1.2 billion dollars in value.

More generally, the debate about whether second generation treatments should be reimbursed by Medicaid is somewhat misguided as it relies on the wrong evidence to argue that higher-priced second generation treatments are equally effective but less cost-effective than lower-priced first generation treatments. However, this concerns the evidence *after* the CER but prices *before* the CER, that is, F and p' in our framework. Rather, what should matter is the evidence and prices both *after* the CER, F' and p' in our framework. The important point here is that the prices after the CER will adjust dependent on whatever the Medicaid responsive subsidy rules are. Thus, endogenous pricing is central to any conclusion of appropriate Medicaid reimbursement after the CER. Even if, hypothetically, threshold was less than $44K/QALY and the estimates from scenario #1 were considered to be precise, which would have favored the CATIE-responsive subsidy policy, prices of atypical could have adjusted in response to the new evidence. Any estimates of cost-savings from not reimbursing second generation treatments

assuming that p'=p are unlikely to be consistent with actual pricing behavior after the CER. Those cost-savings may be an upper bound and should contrasted to cost-savings that occur under a given reimbursement rule in place. The endogenous nature of prices given government subsidy rules is central to determine the welfare effects of reimbursement of first vs second generation antipsychotics[6]. In fact, a credible threat of instituting CER-responsive subsidies might provide the government with the leverage to adjust the prices down in this case. However, in the case of CATIE, the estimates are far from being precise to make such a threat credible (Meltzer et al, 2009).

Section 7: Concluding Remarks

Given the growth in public subsidization of CER to raise quality and lower cost, little conceptual and empirical understanding exists concerning the quantitative impact of CER. This paper analyzed the impact of CER on quality and costs interpreting CER to shift the demand from some treatments at the expense of others. We traced out the spending and quality implications of such shifts in private- as well as subsidized health care markets. In contrast to commonly held views, our analysis implies that CER may well increase quality of care but also spending when treatment effects are homogenous; in contrast, CER may increase spending and lower quality of care under plausible circumstances where treatment effects are heterogeneous .. We illustrated these economic effects for antipsychotics that are among the largest drug classes of the US Medicaid program and for which CER has been conducted. We found that if subsidies were tailored towards the more effective treatments in CATIE, a loss of health valued annually at $4.2 billion dollars would be observed in the US population.

Concerns about the implications of CER-responsive subsidy policies in the face of heterogeneous treatment effects cut across many other clinical scenarios. Indeed, it is difficult to think of a single drug class where the drug that is best for one patient is always best for every other patient. The literature is voluminous on the many other classes to which our analysis may generalize including, for example, the use of antipsychotics drugs in Alzheimer's disease (Schneider et al., 2006), use of antihypertensive drugs (Matchar et al., 2008) and the treatments for clinically localized prostate cancer (Wilt, 2008).

The analysis suggests several future issues to consider. First, our analysis of the impact of CER-responsive subsidies suggests that a better understanding need to be obtained on how CER should be stratified towards obtaining the right treatments for the right subpopulations rather than focused on the best treatment for all patients. There may not be a "one size fits all" for the entire patient population so having reimbursement based on such a policy induces inefficiencies. In particular, our analysis suggests that the data generated by CER should not only consider aggregate measures of response but more

[6] See Jena and Philipson (2009) for a more general analysis of endogenous pricing in response to government reimbursement policy.

individualized measures. In particular, traditional RCTs that focus on intention-to-treat effects are not useful when there is sequencing of treatments over time with a first line therapy, second line therapy and so on. This is because RCTs generate *marginal* distributions of treatment responses. What would be more valuable to know would be *conditional* distributions of treatment responses that estimate the treatment responses of the second stage conditional on failure of the first-stage treatment. If there is dependence in treatment responses, as suggested by the data we considered for the CATIE trial, learning about the joint distribution is of great value (Basu, 2009).

Second, future analysis should consider the impact of market power on the analysis. The basic quantity and price implications of CER will likely carry over to some non-competitive market conditions as well. For example, standard monopoly analysis would imply that an outward (inward) shift in demand raises (lowers) price and quantity, just as in the competitive case discussed. Under the case when both treatments have market-power, many differentiated oligopoly models may also imply the quantity and price implications discussed in response to the demand shifts discussed to be induced by CER.

Third, evaluating the effects of CER is a special case of the general issue of assessing the value of randomized clinical trials for understanding real treatment choices in a real health care setting. This is so because a RCT investigates effects under different prices and information than what is present after the RCT. Using the discussed framework for a more general examination of the value of RCTs for assessing patient welfare in real world markets is an important area of future research.

As better understanding develops along these lines, we hope that improved evaluation can take place regarding the value of CER itself. As it stands right now, there are no methods to quantitatively assess the impact on quality and cost of care from CER. We hope that quantitative frameworks similar to the ones discussed here will help to bridge that gap, making precise assessments of the value of public subsidies for CER feasible.

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Table 1: Intention-to-treat effectiveness and cost estimates from CATIE data used for pre-CER policy

Initial Assignment	Effect of initial assignment on average monthly changes in QOL+	Effect of initial assignment on average monthly total costs (drugs and services)
Quetiapine	0.0030 (0.0006)*	$1657
Risperidone	0.0028 (0.0005)*	$1529
Olanzapine	0.0030 (0.0005)*	$1428
Perphenazine (typical)	0.0028 (0.0006)*	$1139

Table 2: Estimated treatment effectiveness and costs stratified by continuers and discontinuers of initial treatment assignment, used for post-CER responsive policy.

Initial Assignment	Effect of initial assignment on average monthly changes in QOL	Effect of initial assignment on average monthly total costs (drugs and services)
	AMONG THOSE WHO CONTINUED ON INITIAL ASSIGNMENT	
Quetiapine	0.0027 (0.0008)*	$1657
Risperidone	0.0031 (0.0007)*	$1529
Olanzapine	0.0030 (0.0009)*	$1428
Perphenazine (typical)	0.0029 (0.0009)*	$1139
	AMONG THOSE WHO DISCONTINUED ON INITIAL ASSIGNMENT	
Quetiapine	0.0019 (0.001)	-
Risperidone	-0.0020 (0.001)	-
Olanzapine	0.0038 (0.001)*	-
Perphenazine (typical)	0.0024 (0.001)	-

Note: Joint test for treatment-time interaction for QOL effect among continuers not significant (p= 0.94); Joint test for treatment-time interaction for QOL effect among discontinuers significant (p= 0.015)

* p-value < 0.05

Table 3: Effects of alternative policies on quality adjusted life years for the population with schizophrenia

Initial Assignment	# of patients	Discontinue on initial Assignment		Relapse (conditional on discontinuation)	TOTAL QALYS
		YES/NO	%		
BEFORE CATIE					
Quetiapine	535,570 (36%)	Multiplied with			19,280
Risperidone	464,085 (31%)				15,593
Olanzapine	294,139 (19%)	intention-to-treat effects			10,589
Perphenazine (typical)	206,206 (14%)	from Table 1			6,929
				TOTAL	**52,391**
AFTER CATIE – RESPONSIVE SUBSIDIES, SCENARIO #1					
Perphenazine (typical)	1,500,000 (100%)	NO	30%	-	15,660
		YES	70%	NO (89%)	15,120*
				YES (11%)	-51,975**
				TOTAL	**-21,195**
AFTER CATIE – RESPONSIVE SUBSIDIES, SCENARIO #2					
olanzapine	1,293,794 (86%)	NO	40%	-	18,630
		YES	60%	NO (89%)	23,628+
				YES (11%)	-38,425**
Perphenazine (typical)	206,206 (14%)	NO	30%	-	2,153
		YES	70%	NO (95%)	1,975*
				YES (5%)	-3,248++
				TOTAL	**4,713**

*Discontinued at 6 months (Lieberman et al, 2005) with zero change in QOL thereafter.
+ Discontinued at 9 months (Lieberman et al, 2005) with zero change in QOL thereafter
**11% experience a relapse after discontinuation which results in a 0.45 loss in quality of life
++5% experience a relapse (as some of them switch to olanzapine) after discontinuation which results in a 0.45 loss in quality of life
(based on utility change for Mild to Extreme psychotic state reported by Lenert et al. 2004)

Table 4: Effects of CER-responsive subsidies on total annual costs (drug and services) for the population with schizophrenia

Initial Assignment	# of patients	Discontinue on initial Assignment YES/NO	%	Relapse (conditional on discontinuation)	TOTAL COSTS (in billions)
BEFORE CATIE					
Quetiapine	535,570 (36%)	Multiplied with			10.6
Risperidone	464,085 (31%)				8.5
Olanzapine	294,139 (19%)	intention-to-treat effects			5.0
Perphenazine (typical)	206,206 (14%)	from Table 1			2.8
				TOTAL	**26.9**
AFTER CATIE –RESPONSIVE SUBSIDIES					
Perphenazine (typical)	1,500,000 (100%)	NO	30%	-	5.2
		YES	70%	NO (89%)	13.6*
				YES (11%)	4.9**
				TOTAL	**23.7**
AFTER CATIE – RESPONSIVE SUBSIDIES, SCENARIO #2					
olanzapine	1,293,794 (86%)	NO	40%	-	8.9
		YES	60%	NO (89%)	8.9*
				YES (11%)	3.5**
Perphenazine (typical)	206,206 (14%)	NO	30%	-	0.85
		YES	70%	NO (95%)	0.94*
				YES (5%)	0.25++
				TOTAL	**23.3**

*Average monthly costs for those who discontinued initial assignment are estimated by equating intention-to-treat estimates to the weighted average of those who continued and those who discontinued initial assignments.

**11% (++ = 5%) experience a relapse after discontinuation which results in two additional hospitalizations at $14000 each.