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A Probability Approach to Pharmaceutical Demand and Price Setting: Does the Identity of the Third-Party Payer Matter for Prescribing Doctors?

Abstract

TNF-alpha inhibitors represent one of the most important areas of biopharmaceuticals by sales, with three blockbusters accounting for 8 per cent of total pharmaceutical sale in Norway. Novelty of the paper is to examine, with the use of a unique natural policy experiment in Norway, to what extent the price responsiveness of prescription choices is affected when the identity of the third-party payer changes. The three dominating drugs in this market, Enbrel, Remicade, and Humira, are substitutes, but have had different and varying funding schemes - hospitals and the national insurance plan. A stochastic structural model for the three drugs, covering demand and price setting, is estimated in a joint maximum likelihood approach. We find that doctors are more responsive when the costs are covered by the hospitals compared to when costs are covered by national insurance.

JEL-Code: C350, D430, I180, L110.

Keywords: pharmaceuticals, discrete choice model, funding-schemes.

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1. Introduction

The agency problem faced by insurance companies and governments, and its consequences for health care financing has been subjected to extensive theoretical and empirical research². The moral hazard problem in health care arises due to third-party funding and doctors' superior information about diagnosis and preferred treatment choices. Pharmaceutical expenses – both on individual prescription drugs and on more specialized drugs used by hospitals – are often covered by medical insurance. Extensive insurance explains why pharmaceuticals markets often are characterized by price inelastic demand, and, subsequently, why many countries exert various means to control these expenses.

In an insurance-based health care system there are at least two candidates for being the third-party payer. When prescribing a drug on behalf of an insured patient, the cost may be covered by traditional insurance plans – private or public – on a fee-for-service basis - or by the hospital with which the doctor and patient are affiliated. The agency problem differs between a global hospital funding scheme and a fee-for-service approach adopted by traditional insurance plans. Treatment costs covered by the national insurance plan do not represent a direct cost for the doctor and the hospital. To the extent that treatment costs still affect the choice of drug under a pure national insurance plan funding can be explained by doctors' understanding and adherence to national guidelines for cost-effective treatment choices. However, when treatment costs are covered by the hospital, the opportunity costs becomes more “tangible” to the doctors. Increased treatment costs on one patient reduce available resources for other activities at the affiliated hospital. For this reason, treatment choices may be under a tighter control or monitoring when costs are covered by the local hospital instead of a national, and tax funded, insurance plan.

With use of a unique natural policy experiment in Norway, we are able to investigate to what extent the price responsiveness of prescription choices is affected when the identity of the third-party payer changes. Our case in point is the Norwegian market for Tumor Necrosis Factor (TNF) alpha inhibitors. To date TNF-alpha inhibitors represent the most important way to treat arthritis and other autoimmune diseases

² See McGuire (2000) for a review

(Feldmann and Maini, 2003). Treatment choices with TNF-alpha inhibitors in Norway are made by hospital doctors, and all patients receiving treatment are insured against the cost, but, importantly for our study, the funding source has differed, both between the three available drugs and over time.

When the market for TNF-inhibitors opened in Norway in 2000, the first entrant Enbrel was fully covered by the obligatory national insurance plan. The treatment with Enbrel is initiated by the hospital doctor, but the cost was automatically covered by the national insurance plan. The second entrant Remicade did not obtain the same type of coverage. Instead the treatment cost had to be fully covered by the doctor's affiliated hospital. Importantly, the hospitals' budget did not include earmarked grants for these patients. Cost of treatment with Remicade, therefore, competed with other expenses within the hospital. This sharp asymmetry in funding scheme reflects a quality attribute of the two drugs. Enbrel is administrated by the patients themselves (pump injections), while Remicade requires several hours infusion at hospitals. In fall 2002 the government modified the plan for Remicade. Choosing Remicade after fall 2002, the government required a copayment of 20 per cent from the doctor's affiliated hospital. Enbrel maintained its full insurance plan coverage. The third entrant Humira is also administrated by pump injections by patients, and received the same funding plan as Enbrel when the drug entered in January 2003.

The important policy change exploited in our study, however, took place in 2006. Then the asymmetry of financing between Enbrel and Humira, and Remicade was entirely removed by returning the entire funding responsibility to the hospitals for all three drugs. Since then all costs of treatment with TNF-alpha inhibitors have to be covered by the doctors' affiliated hospital. By creating large and exogenous variations in hospital and insurance plan treatment costs, these funding switches becomes the crucial source of identification in our empirical model.

We specify a discrete choice model in which the doctor's choice among the available of TNF-alpha inhibitors depends on the prices. Furthermore, the price response is allowed to vary with the identity of the third-party payer. The discrete choice model results in three market share equations which are estimated on aggregate data. The results show that doctors' choice of TNF-alpha inhibitor is responsive to price differences, and

that this price response becomes stronger when hospitals cover the costs. However, the 95 per cent confidence intervals clearly overlap. Moreover, when the squared residuals are regressed against prices we obtain significant results which imply that homoscedasticity is rejected. The explanation for this could be that there are unobserved factors say, quality aspects, which are absorbed in the random terms and correlate with the prices. The quality of the three considered drugs varies, with the two most expensive ones offering more efficient treatment. To deal with this problem we have estimated two alternative models. First, we have instrumented the Norwegian prices by using German prices as instruments prices. Now, homoscedasticity is **not** rejected. Again we find that doctors are more responsive when the costs are covered by the hospitals compared to when costs are covered by national insurance, but also now the 95 per cent confidence intervals related to the crucial parameters overlap. It is interesting to note that the numerical value of the own-price elasticities increases, in particular for the two most expensive ones. Apparently, when prices are instrumented otherwise disturbing unobserved quality aspects are taken somewhat into account. Doctors pay attention to price, but also to quality of the drugs, even when the opportunity cost increases.

But we can do even better and control for quality aspects as well as for a variety of unobserved heterogeneity. We have thus modeled the market equilibrium for the three drugs, which means that price setting that follows from a non-cooperative Nash equilibrium is added to the market share equations. We allow for correlation across unobserved elements in the market share equations and price setting equations. This equilibrium model is estimated in a joint maximum likelihood approach. As in the instrument approach the results show that homoscedasticity is **not** rejected. We find that doctors are more responsive when the costs are covered by the hospitals compared to when costs are covered by national insurance, and now the 95 per cent confidence intervals related to the crucial parameters nearly not overlap. The 90 per cent confidence intervals do not overlap. Moreover, the numerical values of the own-price elasticities increase substantially. The reason why is that when endogeneity (correlation between prices and error terms in the demand equations) are ignored the price coefficients are biased downward in magnitude. Since higher prices are associated with desirable attributes, doctors prescribe the higher priced drugs Enbrel and Humira *more* than they

would if the higher prices did not reflect any desirable - and here unobserved- quality attributes, see Train (2009) ch.13. We have also extended the equilibrium model to account for autocorrelation. The estimates of the two crucial parameters capturing the price responses under the different funding schemes remain the same in magnitude and they are both clearly significant from zero, but from a statistical point of view they are now closer.

The remainder of the paper is organized as follows. In Section 2 we relate our paper to the existing literature. Section 3 briefly describes the market for TNF-alpha inhibitors. In Section 4 we describe the data used in the analysis. Section 5 presents the econometric model and the results. Section 6 concludes.

2. Related literature

Our research relates to two strands of the health economics literature. One is the literature on pharmaceutical demand in general and in particular previous attempts to estimate price elasticities. The other is the literature studying the effect of reimbursement schemes on spending. Note, however, that these two areas of research are interlinked since many of the studies of price responses in pharmaceutical demand exploit variations in reimbursement schemes and patient charges.

Ellison et al. (1997) estimate a demand model for a class of anti-infective drugs called cephalosporins. Their data contains four different chemical substances, and three of these substances experienced significant generic entry in the sample period. The model, therefore, allows studying both therapeutic and generic substitution. Looking at substitution between different substances, they find evidence of low (and often insignificant) price responses in demand. One of the drugs comes out with a significant own-price elasticity of -0.3. As expected, substitution between brand names and generics reveals much higher price responses. Besides being a different type of drug, treating patients with other types of diseases, cephalosporin drugs differ from our TNF-alpha inhibitors by having a relatively low level of hospital consumption.

Another study related is Berndt et al. (2003). They do not study the effect of insurance on prescription choices, but estimate a demand model for a growing market with competing brand names available. They use data for H2-antagonist antiulcer, and their data

starts at the entry of the first patent Tagament. Similar to our study, therefore, they investigate the pharmaceutical demand in a market with several competing brand-name (patented) drugs. They develop a rich model that includes a dynamic component of diffusion. Their market share model allows the drug choice to depend on prices, in addition to marketing. Doctors' are found to respond to prices, but similar to the findings of Ellison et al. (1997), price responses appear to be relatively low. They find own-price elasticities in the range of about -0.3 and -0.6.

There is a larger literature studying the demand responses to changes in co-payment by patients. A seminal contribution was made by Leibowitz et al. (1985), who used data from the Rand Health Insurance experiment to study the relationship between the degree of cost sharing with patients and prescription drug utilization. They found that patients with a more generous insurance scheme buy more prescription drugs. Another early contribution, using monthly time-series from the National Health Service (NHS) in England, is O'Brien (1989). He found co-payment elasticities in the range of about -0.3 and -0.6. A more recent contribution along this line of research is made by Contoyannis et al. (2005). Using micro data (individual patients) from Quebec, they estimate the elasticity of expenditure for prescription drugs with respect to patients' marginal prices (cost sharing). These were found to be relatively low - in the interval -0.12 to -0.16.

Iizuka (2007) is a recent contribution to the literature on agency problems in prescription drug market. In the Japanese market, doctors make profit from selling prescribed drugs. Using data with both prices and doctors' own mark-up, he estimates a nested logit demand model for the hypertension market, including 40 brands in 5 different therapeutic classes. Iizuka finds that prescription decisions are influenced by the size of mark-up, but that doctors care more about patient welfare than their own profit. Hence, if the retail price of a brand increases, the doctor becomes less likely to prescribe that drug.

Other papers studying the importance of doctor and prices in prescription choices are Coscelli (2000) and Lundin (2000). The main contribution of Lundin is to show how the level of patients' co-payment influences doctors choices (between generics and brand-name). He finds that doctors' are more responsive to patients' co-payment than the cost of the insurance provider.

Lundin (2000) relates to our analysis by showing that doctors' responses to prices are influenced by the funding source. In Lundin's analysis the two funding sources are the patients themselves or the insurance provider. In our paper, we are instead able to investigate different types of third-party funders – hospitals and national insurance plans. Hellerstein (1998) provides evidence of the importance of insurance plans for the agency problem in prescription choices. She finds that doctors with a higher fraction HMO-patients (Health Maintenance Organization) relative to patients who are enrolled in traditional insurance plans, more often prescribe generics instead of the brand-name drug. Since her data did not contain prices, however, she is not able to capture the effect on doctors' price responsiveness.

3. The market for TNF-alpha inhibitors

The biotechnological revolution that emerged in the last decades of the 20th century was expected to yield significant benefits to the pharmaceutical sector through improvements in drug discovery and development (Lawrence, 2006; Lawrence 2007; Walsh 2003). The biopharmaceutical market is now characterized by competition among few firms that act at a global level, and biotech drugs claim an increasing share of novel treatments approved by the regulatory authorities (Kneller, 2005). The number of biotech blockbusters, i.e. drugs on the market that have sales over 1 billion USD per year, is rapidly increasing. Recombinant therapeutic proteins represent the main business sector of biotechnological drugs, followed by monoclonal antibodies. Several proteins and antibodies are used in the treatment of arthritis and other autoimmune diseases, and the most important subgroup is described as tumor necroses factor (TNF) alfa inhibitors. There are three biotechnological drugs acting as TNF alpha inhibitor in the treatment of rheumatoid arthritis (RA).

The first is Enbrel (etanercept), a recombinant protein of human origin: it was approved by the Food and Drug Administration (FDA) in 1998 for the reduction of signs and symptoms of moderate to severe RA, and in Europe by European Medicin Agency (EMA) in 1999; it is administered twice a week by subcutaneous injection. At the time of introduction, it was indicated for use by patients who had an inadequate response to one of the other disease-modifying anti-rheumatic drugs (DMARD) (Moreland et al., 1997), and in combination with Rheumatex (methotrexate): clinical trials proved that the addition of etanercept to methotrexate therapy resulted in rapid and sustained

improvement (Weinblatt et al., 1999). Enbrel gained approval also for the treatment of juvenile RA and psoriatic arthritis, and further studies demonstrated its effectiveness as compared with methotrexate in patients with early active RA (Bathon et al., 2000), making it a first-line treatment for RA and a leading brand within the new class of DMARDs. Enbrel was developed by Immunex, a biotechnology company that in 2001 was acquired by Amgen. The product is marketed jointly with Wyeth Takeda.

The second TNF-based RA product on the market is Remicade (infliximab), a chimeric (human and mouse) monoclonal antibody that proved to be safe and effective with persistently active RA not responding to methotrexate therapy (Lipsky et al., 2000). It is marketed by Centocor together with Schering Plough and the Japanese company Mitsubishi Tanabe Pharma. In Europe EMEA granted marketing authorization in March 2000. It is administered every four to eight weeks via an intravenous infusion that may take several hours to complete and requires qualified personnel monitoring of adverse reactions: this is considered as a disadvantage in comparison with Enbrel. Nevertheless, Remicade progressively increased its sales gaining high market shares. Price of Remicade is lower than Enbrel.

The third TNF alpha inhibitor in the market is Humira (adalimumab), a fully human monoclonal antibody approved by FDA in December 2002 and by EMEA in September 2003, and marketed by Abbott in the form of subcutaneous injection every two weeks, setting the drug price in parity with Enbrel. Its attracting dosing profile was considered a key success factor, but relatively short after its launch, the growth of sales slowed and it seemed not to threaten significantly the market position of its two competitors.

Market penetration in terms of sales value has been highly successful in Norway. Sale of Enbrel, Remicade and Humira accounted for 8 per cent of total pharmaceutical sale in Norway in 2008.³

4. Data

The dataset consists of monthly wholesale value and quantity sold, expressed in defined daily doses (DDD), for each of the three drugs Enbrel, Remicade and Humira. The data set covers the months from January 2000 to March 2008, indicated as running from $t=1$ to $t=99$ in Figures 1 and 2 below. The price per DDD is constructed from combining the value and

³ Norwegian Association of Pharmaceutical Manufacturers. Facts and Figures (2009).

quantity information. Figure 1 shows the monthly wholesale value of sale.

The market opened early 2000, with the entry of both Enbrel and Remicade. Enbrel had a far stronger growth during the first year, and became soon the leading drug. In 2001-2002 Enbrel experienced problems of supplying the global market. Worldwide capacity shortage forced the producer to reduce the sale of Enbrel in Norway. This explains the drastic reduction in sale value for Enbrel, and its volatility shown in Figure 1.

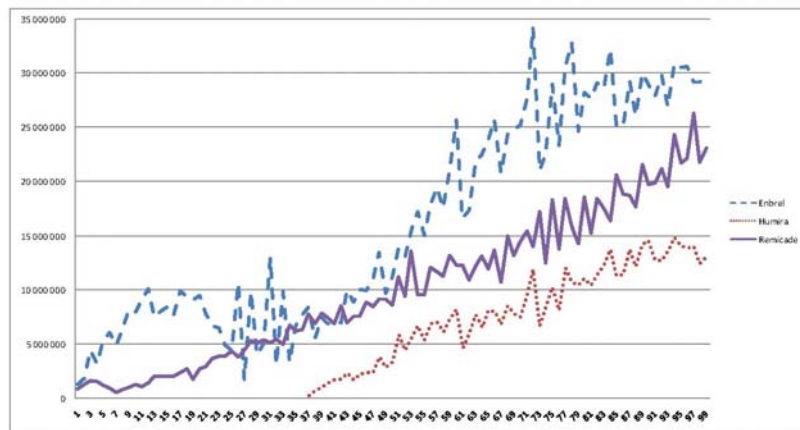


Figure 1: Monthly wholesale value of sale; 1000 NOK. As of October 2011 1 Euro~NOK 7.8

In the fall 2003, the third drug, Humira, entered. Although Humira experienced a steady growth in the fast growing market, it never succeeded in capturing a larger market share. Figure 2 shows the development of market shares.

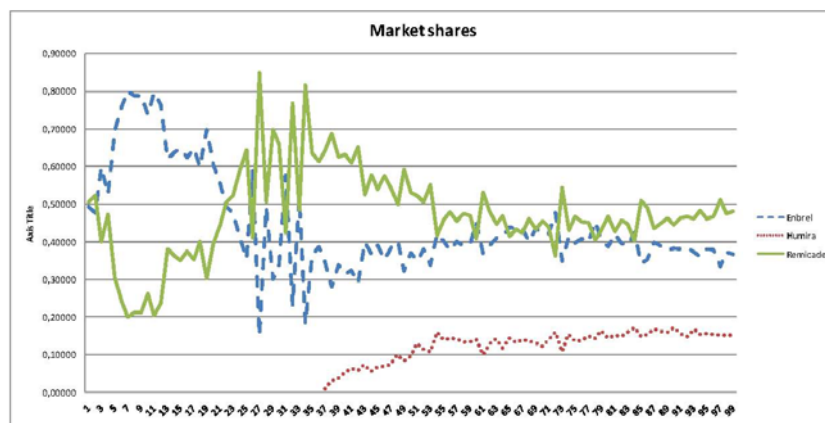


Figure 2: Market shares for the three drugs (DDD).

Within the first year, Enbrel reached a market share of 80 percent. The market share dropped rapidly, most triggered by the abovementioned shortage of production capacity. Since Remicade was the only alternative TNF-inhibitor in this period, it experiences an equivalent rise in its market share. Humira reached a market share close to 9 percent after a few months.

The price of Enbrel has always been very high relative to Remicade. Except for the first couple of months, the wholesale price of Enbrel per DDD stayed between 350 and 400 NOK until late fall 2001. Then the price dropped to a level closer to 300 NOK per DDD. Remicade started out with a price of 200 per NOK, but came down to a level between 160 and 170 NOK per DDD after a few months. Humira entered with a price much above the price of Enbrel. Although Humira has kept its position as the price leader, the price gap (compared with Enbrel) has been narrowed during the sample period. Figure 3 shows the development of wholesale prices. As mentioned in the introduction. Enbrel, Humira and Remicade had different and varying funding schemes over time.

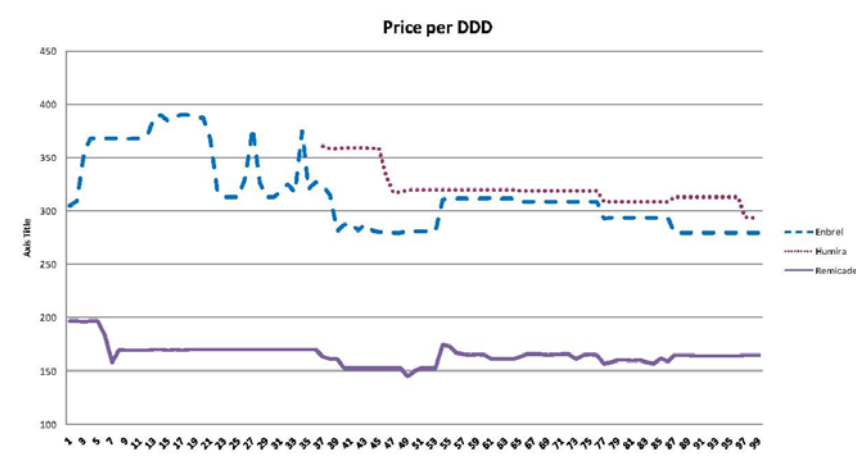


Figure 3. Wholesale prices, NOK per DDD.

We have chosen to restrict the sample period in our empirical analysis to t=38-99 for several reasons. First, there are reasons to expect demand behavior – and in particular price responses – to be different in the early stage of a new pharmaceutical market compared with the more matured market. In the early stage, doctors are unfamiliar with the particular technology of treatment (TNF-alpha inhibitors) – both its efficiency and its possible side-effects. In a more mature market, doctors have gained experience with the drug, and will be

better able to make treatment choices for the individual patients.⁴ Gaining experience with TNF-inhibitors, the doctors will be better able to take treatment costs into account when choosing between the available alternatives. Second, capacity shortage for the manufacture of Enbrel during the first years distorts demand. As seen in this Section, Enbrel experienced a sharp decline in sale 2001-2002 that was due to a global capacity problem of the manufacture. After a period of decline, sale and market shares were very unstable, until problems were resolved some months before the entry of Humira.

Summary statistics for the sample used in estimating our models are provided in Table 1. In that table, in addition to the drug prices as reported in the original data set, we also include the German prices (expressed in NOK). The reason why is that these prices are used in the instrument approach alluded to above.

Table 1. Summary statistics (62 obs)

Variable	Mean	Std. Dev.	Min	Max
<i>Enbrel:</i>				
DDD	73413.7300	28228.5300	17534.0000	111829.0000
market share	0.3860	0.0379	0.2802	0.4764
price	0.2942	0.0136	0.2794	0.3146
sales	21572.0700	8128.4650	5515.4780	34216.2800
a_h1	0.3548	0.4824	0.0000	1.0000
a_i1	0.6452	0.4824	0.0000	1.0000
<i>Humira:</i>				
DDD	26143.3400	13833.7300	2014.0000	47531.0000
market share	0.1278	0.0362	0.0322	0.1720
price	0.3206	0.0163	0.2935	0.3591
sales	8206.7740	4197.8050	722.3141	14838.1300
a_h2	0.3548	0.4824	0.0000	1.0000
a_i2	0.6452	0.4824	0.0000	1.0000
<i>Remicade:</i>				
DDD	88812.0800	30046.7300	43019.0000	159655.0000
market share	0.4862	0.0651	0.3639	0.6876
price	0.1608	0.0056	0.1446	0.1743
sales	14341.7000	5026.1530	6901.8260	26308.0300
a_h3	0.4839	0.3859	0.2000	1.0000
a_i3	0.5161	0.3859	0.0000	0.8000
<i>German IMS prices expressed in NOK:</i>				
p1_instr_Enbrel	0.3940	0.0143	0.3510	0.4321

⁴ See Berndt et al. (2003).

p2_instr_Humira	0.4281	0.0310	0.3886	0.5470
p3_instr_Remicade	0.1796	0.0081	0.1557	0.1949

5. Econometric models and results

The decision-making unit on the demand side is the physician, who acts as the patient's agent (Arrow, 1963). In making decisions, however, the physician needs to take into account the situation of each individual patient. In the formal model of demand, therefore, consumers are represented by physician-patient couples, $i=1,..,N_t$. The model is derived from a random utility model (see Train, 2009 for an overview of such models) in which consumers chooses among the available drugs, $j=1,..,J$, to maximize utility. The number of drugs is three. To this end they are numbered: Enbrel no1, Humira no2 and Remicade no3. The number of periods is 62.

Utility for the decision-making unit is given by

$$(1) U_{ijt} = -v_{jt}p_{jt} + a_{jt} + \varepsilon_{ijt}, \quad j=1,2,3 \quad t=1,2,\dots,62$$

where a_{jt} is an indicator of perceived treatment quality of drug j at time t . This is a common quality-indicator that applies to all patients that can benefit from TNF-alpha therapy. Like in Berry et al (1995) we will assume that a_{jt} depends on observed as well as unobserved attributes, which will be specified below. The unobserved part may reflect quality attributes of the three drugs that could be priced out in the market and hence the unobserved parts may correlate with prices. This creates estimation problems that will be addressed below. p_{jt} is the price variable associated with drug j at time t and v_{jt} are coefficients that capture the impact of the costs of treatment on utility. Note that we have specified the price part of the utility function so that a negative impact of price on utility requires v_{jt} to be positive. The random variable ε_{ijt} is extreme value.

The costs of treatment with TNF-alpha inhibitors are covered by a third-party. There are two third-party payers. One is the National Insurance Plan (NIS) (termed "I"), and the other is the hospital with which the prescribing doctor is affiliated (termed "H"). The funding split between the insurance plan and the hospital varies over time and across drugs: At a given time t the drug costs are fully paid by the hospital, fully covered by the insurance plan, or split between the two with 80 percent covered by insurance and 20 percent by hospitals.

Thus, v_{jt} is given by:

$$(2) \quad v_{jt} = \alpha_{ijt}\beta_I + \alpha_{Hjt}\beta_H; j=1,2,3$$

where

$$(3) \quad \begin{aligned} \alpha_{ijt} &= \{1, 0.8, 0\} \\ \alpha_{Hjt} &= \{0, 0.2, 1\} \end{aligned}$$

The β -s are coefficients and represent the doctor's responses to drug costs under the different funding plans.

The main objective of our paper is to investigate to what extent doctors' responses to drug costs is sensitive to the identity of the third-party payer – the social insurance plan or the hospital. When the market for TNF- α inhibitors opened in 2000, Enbrel was fully covered by NIS (i.e. $\alpha_{I1t}=1$), whereas Remicade was covered by the hospitals ($\alpha_{H3t}=1$). In the fall 2002, the funding of Remicade changed. Hospital was to pay 20 per cent, whereas NIS paid the remaining 80 per cent ($\alpha_{I3t}=0.8$, $\alpha_{H3t}=0.2$). When entering in 2003, Humira was given the same funding plan as Enbrel, i.e. fully coverage by NIS ($\alpha_{I2t}=1$). In June 2006, the government then gave the full funding responsibility to the hospitals for all three drugs ($\alpha_{Hjt}=1$ for all j).

Because hospitals face budget constraints, the hospital's opportunity costs of drug treatment are strictly positive. Reduced treatment costs may benefit other activities and patients at the same hospital. With coverage by the national insurance plan, the direct opportunity cost of the hospital will be zero. Choosing a drug that is fully paid by the insurance plan has no impact on the resources available for other activities at the hospital. Doctors have guidelines that require cost consciousness in their choices of treatment. Therefore, we expect doctors to be price responsive also in the case of insurance plan coverage. However, in the case where the hospital pays the treatment costs, we expect doctors to become more concerned about these costs. This might be due to the personal incentives of doctors' to economize on costs in order to be able to spend extra resources on other patients, or just due to the fact that the hospital management has stronger incentives to monitor the individual doctor's treatment choices when these involves hospitals own budgets.

Our hypothesis thus is that (remember that positive coefficients imply a negative impact on utility):

$$\begin{aligned} H_0 &: b_H = b_L \\ H_1 &: 0 < b_L < b_H \end{aligned}$$

Because ε_{ijt} is assumed to be independently, identically extreme value distributed across individuals and products, the probability that the decision-making unit i will choose drug j at time t is given by:

$$(4) \quad \varphi_{ijt} = \varphi_{jt} = \Pr\left(U_{ijt} = \text{Max}_{k=1,3} U_{ikt}\right) = \frac{\exp(-v_{jt}p_{jt} + a_{jt})}{\sum_{k=1}^3 \exp(-v_{kt}p_{kt} + a_{kt})}; \quad j=1,2,3$$

We choose Enbrel to be the reference product, here denoted product 1, and if we assume there is no outside good whose utility can be normalized to zero, these probabilities can be written⁵:

$$(5) \quad \begin{aligned} \varphi_{jt} &= \frac{\exp(a_{jt} - a_{1t} - (v_{jt}p_{jt} - v_{1t}p_{1t}))}{1 + \sum_{k=2}^3 \exp(a_{kt} - a_{1t} - (v_{kt}p_{kt} - v_{1t}p_{1t}))} \quad j=2,3; \quad t=1,2,\dots,62 \\ \varphi_{1t} &= \frac{1}{1 + \sum_{k=2}^3 \exp(a_{kt} - a_{1t} - (v_{kt}p_{kt} - v_{1t}p_{1t}))} \end{aligned}$$

The observed parallel to the average of agents' probabilities that product j is chosen, is the market share of the product, m_{jt} . Because we only exploit aggregate data, our observed variables will be the market shares. The coefficient a_{jt} is assumed to depend on three parts: a deterministic drug-specific constant, α_j , a time trend, β_{jt} , and a stochastic variable e_{jt} . The deterministic drug-specific constants reflects some unobserved drug-specific elements, while the two others may reflect some factors related to doctors' perception of quality which may change over time and some of this is also unobserved.

This gives us the following log-odd ratios:

⁵ Unfortunately, we are not able to construct an outside option to treatment with one of the three therapies. This would require a record of all patients with these diagnoses – including those without medical treatment. Our model, therefore, assumes that variations in prices covered by hospitals or the insurance schemes only affects the allocation of patients on different therapies (drugs), and not the total number of patients treated.

$$(6) \quad \log \frac{m_{2t}}{m_{1t}} = \alpha_2 - (v_{2t}p_{2t} - v_{1t}p_{1t}) + \beta_2 t + e_{2t}$$

$$(7) \quad \log \frac{m_{3t}}{m_{1t}} = \alpha_3 - (v_{3t}p_{2t} - v_{1t}p_{1t}) + \beta_3 t + e_{3t}$$

First, we estimate the coefficients $\{\alpha_2, \alpha_3, \beta_1, \beta_H, \beta_2, \beta_3\}$ in the demand model using a 3SLS command in STATA. The results are given in Table 2.

Table 2. The demand model

Coefficients	Estimates	t-values
β_I	2.652	2.90
β_H	4.513	3.93
β_2 (Humira)	0.014	11.30
β_3 (Remicade)	-0.011	-4.77
α_2 (Humira)	-2.066	-20.49
α_3 (Remicade)	0.587	3.03
Number of observations	62	
R^2 (Humira)	0.7476	
R^2 (Remicade)	0.2351	

The point estimates imply that $\beta_I < \beta_H$, but the 95 per cent confidence intervals overlap: Lower limit for β_I is 0.8581 and upper limit is 4.4450, and for β_H the lower limit is 2.2627 and the upper limit is 6.7633. As mentioned above, the problem with this estimation is that the error terms in the market share equations may be correlated with the prices. There are several reasons for this and one is that prices are set by the drug providers so that unobserved quality aspects are priced out. When regressing the predicted squared residuals against prices we get significant results which clearly indicate that homoscedasticity is rejected. Berry et al (1995) recommend that the constants in the equations above should vary and represent the unobserved quality attributes that may be correlated with price. Next, these coefficients should be regressed against prices, or calibrated. The problem with that approach is the high number of constants; here equal to the number of observations. We have therefore chosen to apply two alternative approaches to deal with the endogeneity problems. First, we replace the prices in the

market share equations with instruments. Second, we model the price setting of drugs and estimate market shares and price setting equations simultaneously.

Alternative 1. An instrument approach

Prices, inclusive of the regulatory schemes, are regressed against the equivalent prices of the very same drugs in Germany. Prices for these three internationally sold drugs may be set so that a correlation across countries may occur, however, the regulatory schemes are different, and most likely also the treatment practises. In Germany, in contrast to Norway, the funding schemes is the national insurance throughout the whole period.

Alternative 2. A probability approach to drug demand and price setting.

In this alternative we assume that each drug provider sets the price on its drug so that expected profit is maximized, given the market share equations for the three drugs and the prices set by the other two providers. In this approach we also account for a possible correlation among the error terms in the model. This means that in addition to control for possible correlation between error terms and prices in the market share equations, we also control for a variety of unobserved heterogeneity.

Alternative 1. Instrument approach

Let p_{jt} be the price, inclusive of the regulatory schemes, in Norway of drug j at time t , $j=1$ (Enbrel), 2 (Humira), 3 (Remicade). Let q_{jt} be the equivalent price of the same drug j , in Germany. Then we do the regressions given in (8) and use the predicted values, together with the average of 40 per cent percent of the variation in the predicted residual from the regressions, in the market share equations instead of the Norwegian prices. To add the average of 40 per cent of the variation in the predicted residuals captures some of the unobserved factors implied by using instruments. The result is given in Table 3 below.

$$(8) \quad p_{jt} = a_j + \lambda_j q_{jt} + \delta_{jt}; \quad j=1,2,3$$

Comparing Table 2 and 3 we observe that the β -coefficients are scaled up, while the other coefficients are more or less the same. Again, the point estimates imply that $\beta_I < \beta_H$, but the 95 per cent confidence intervals clearly overlap: lower limit for β_I is 0.7927 and upper limit is 8.3731, and for β_H the lower limit is 2.2980 and the upper limit is 9.8680. In

contrast to the demand model, instrumenting the prices imply that there is no significant relationship between predicted squared residuals and prices. Thus homoscedasticity is **not** rejected.

Table 3. The demand model estimated with instruments for the prices

Coefficients	Estimates	t-values
β_I	4.582	2.37
β_H	6.083	3.15
β_2 (Humira)	0.016	12.26
β_3 (Remicade)	-0.011	-4.91
α_2 (Humira)	-2.131	-21.25
α_3 (Remicade)	0.323	1.03
Number of observations	62	
R^2 (Humira)	0.6988	
R^2 (Remicade)	0.3408	

Alternative 2. A probability approach to drug demand and price setting.

The market share equations for all three drugs can be written as:

$$(9) \quad m_{1t} = \frac{1}{1 + \sum_{j=2}^3 \exp(\alpha_j - (v_{jt}p_{jt} - v_{1t}p_{1t}) + \beta_j t + e_{jt})}$$

$$(10) \quad m_{2t} = \frac{\exp(\alpha_2 - (v_{2t}p_{2t} - v_{1t}p_{1t}) + \beta_2 t + e_{2t})}{1 + \sum_{j=2}^3 \exp(\alpha_j - (v_{jt}p_{jt} - v_{1t}p_{1t}) + \beta_j t + e_{jt})}$$

$$(11) \quad m_{3t} = \frac{\exp(\alpha_3 - (v_{3t}p_{3t} - v_{1t}p_{1t}) + \beta_3 t + e_{3t})}{1 + \sum_{j=2}^3 \exp(\alpha_j - (v_{jt}p_{jt} - v_{1t}p_{1t}) + \beta_j t + e_{jt})}$$

Note that we have:

$$(12) \quad \frac{\partial m_{jt}}{\partial p_{jt}} = -v_{jt}m_{jt}(1 - m_{jt}); \quad j=1,2,3$$

Expected profits of the seller of drugs are:

$$(13) \quad \pi_{jt} = (p_{jt} - C_{jt})N_t m_{jt}$$

Here C_{jt} are unobserved unit costs. In estimating the model we will assume that $C_{jt}=c_{jt}+\eta_{jt}$, where c_{jt} will be estimated below and η_{jt} is an unobserved part of the unit cost and/or unobserved factors in the profit maximization process. N_t is the number of potential customers.

Maximizing expected profit with respect to price yield the following first order conditions:

$$(14) \quad p_{jt} = C_{jt} + \frac{1}{v_{jt}(1-m_{jt})}; \quad j=1,2,3.$$

The econometric model we estimate is given by the following set of equations:

$$(15) \quad \log \frac{m_{2t}}{m_{1t}} = \alpha_2 - (v_{2t}p_{2t} - v_{1t}p_{1t}) + \beta_2 t + e_{2t}$$

$$(16) \quad \log \frac{m_{3t}}{m_{1t}} = \alpha_3 - (v_{3t}p_{3t} - v_{1t}p_{1t}) + \beta_3 t + e_{3t}$$

$$(17) \quad p_{1t} = C_{1t} + \frac{1}{v_{1t}(1-m_{1t})} + \eta_{1t}$$

$$(18) \quad p_{2t} = C_{2t} + \frac{1}{v_{2t}(1-m_{2t})} + \eta_{2t}$$

$$(19) \quad p_{3t} = C_{3t} + \frac{1}{v_{3t}(1-m_{3t})} + \eta_{3t}$$

where

$$(20) \quad v_{jt} = \alpha_{ijt}\beta_1 + \alpha_{Hjt}\beta_H; \quad i=1,2,3$$

We will allow for correlation across the random variables. The correlation structure is the following:

$$(21) \quad e_{2t} = \rho_2 \eta_{2t} + \mu_{2t}$$

$$(22) \quad e_{3t} = \rho_3 \eta_{3t} + \mu_{3t}$$

$$(23) \quad \eta_{1t} = \rho_{12} \eta_{2t} + \rho_{13} \eta_{3t} + \mu_{1t}$$

where

μ_{it} is normally distributed $N(0, \sigma_i)$.

From (17) and (20) we get:

$$(24) \quad e_{2t} = \rho_2 \left(p_{2t} - C_{2t} - \frac{1}{v_{2t}(1-m_{2t})} \right) + \mu_{2t}$$

From (18) and (21) we get

$$(25) \quad \varepsilon_{3t} = \rho_3 \left(p_{3t} - C_{3t} - \frac{1}{v_{3t}(1-m_{3t})} \right) + \mu_{3t}$$

And finally we have

$$(26) \quad \eta_{1t} = \rho_{12} \left(p_{2t} - C_{2t} - \frac{1}{v_{2t}(1-m_{2t})} \right) + \rho_{13} \left(p_{3t} - C_{3t} - \frac{1}{v_{3t}(1-m_{3t})} \right) + \mu_{1t}$$

The endogenous variables in our model is the market shares and the prices. In order to derive the distribution of these variables, given the distribution of the error terms in the equations above, we have to obtain the probability law of the observed random variables, $\{m_{1t}, m_{2t}, m_{3t}, p_{1t}, p_{2t}, p_{3t}\}$. Basically this means that we multiply into the likelihood of the sample the numerical value the Jacobian of transformation⁶. The Jacobi determinant gives the derivatives of of the error terms in each of the 6 equations above with respect to the 6 observed random variables present in the equations. If the Jacobi determinant explicitly depends on the unknown coefficients that we estimate, then it matters for the estimation to include the absolute value of the Jacobian determinant. This is the case here. The likelihood that we maximize with respect to the unknown coefficients is given in (26). In estimating the model the three c-s are assumed to be constant over time. The model is estimated in GAUSS.

⁶ See Haavelmo (1944), p 87.

$$\begin{aligned}
(27) \quad L = & \prod_{t=1}^{62} f \left(\frac{\log(m_{2t}) - \log(m_{1t}) - \alpha_2 + (v_{2t}p_{2t} - v_{1t}p_{1t}) - \beta_2 t - \rho_2 \left(p_{2t} - c_{2t} - \frac{1}{v_{2t}(1-m_{2t})} \right)}{\sigma_2} \right) \\
& \times f \left(\frac{\log(m_{3t}) - \log(m_{1t}) - \alpha_3 + (v_{3t}p_{3t} - v_{1t}p_{1t}) - \beta_3 t - \rho_3 \left(p_{3t} - c_{3t} - \frac{1}{v_{3t}(1-m_{3t})} \right)}{\sigma_3} \right) \\
& \times f \left(\frac{p_{1t} - c_{1t} - \frac{1}{v_{1t}(1-m_{1t})} - \rho_{12} \left(p_{2t} - c_{2t} - \frac{1}{v_{2t}(1-m_{2t})} \right) - \rho_{13} \left(p_{3t} - c_{3t} - \frac{1}{v_{3t}(1-m_{3t})} \right)}{\sigma_1} \right) \\
& \times f \left(\frac{p_{2t} - c_{2t} - \frac{1}{v_{2t}(1-m_{2t})}}{\sigma_{\eta^2}} \right) \\
& \times f \left(\frac{p_{3t} - c_{3t} - \frac{1}{v_{3t}(1-m_{3t})}}{\sigma_{\eta^3}} \right) \\
& \times |J_t|
\end{aligned}$$

where $f(\cdot)$ is the unit normal probability density and $|J_t|$ is the absolute value of the determinant of the Jacobian given by

$$(28) \quad |J_t| = \begin{vmatrix} \frac{m_{1t} + m_{2t}}{m_{1t}m_{2t}} & \frac{1}{m_{1t}} & -v_{1t} & v_{2t} & 0 \\ \frac{1}{m_{1t}} & \frac{m_{1t} + m_{3t}}{m_{1t}m_{3t}} & -v_{1t} & 0 & v_{3t} \\ \frac{1}{v_{1t}(1-m_{1t})^2} & -\frac{1}{v_{1t}(1-m_{1t})^2} & 1 & 0 & 0 \\ -\frac{1}{v_{2t}(1-m_{2t})^2} & 0 & 0 & 1 & 0 \\ 0 & -\frac{1}{v_{3t}(1-m_{3t})^2} & 0 & 0 & 1 \end{vmatrix}$$

The estimates are given in Table 4.

Table 4. Joint estimates of market shares and price setting

Coefficients	Estimates	t-values
β_I	11.645	37.02
β_H	13.022	30.57
β_2 (Humira)	1.161	6.46
β_3 (Remicade)	-0.032	-0.08
α_2 (Humira)	-1.635	-13.05
α_3 (Remicade)	-1.340	-4.705
c_1	0.159	36.76
c_2	0.226	66.36
c_3	0	0
σ_1	0.010	11.01
σ_2	0.187	11.01
σ_3	0.176	4.02
$\sigma_{\eta 2}$	0.017	10.93
$\sigma_{\eta 3}$	0.032	10.56
ρ_2	3.718	1.93
ρ_3	-4.901	-1.69
ρ_{12}	-0.177	-1.36
ρ_{13}	-0.078	-1.025
Log Likelihood	1055.700	
No of observations	62	

Like in the case with instrumenting the prices, the predicted values of the squared residuals in the market share equations do not vary significantly with prices and thus homoscedasticity is **not** rejected. The 95 per cent confidence intervals for the β_I and β_H do overlap just a little: lower limit for β_I is 11.018 and the upper limit is 12.2785, and for β_H the lower limit is 12.1640 and the upper limit is 13.8808. A 90 per cent interval do not overlap: lower limit for β_I is 11.1276 and the upper limit is 12.1624, and for β_H the lower limit is 12.3214 and the upper limit is 13.7266. Based on this model there are some clear evidences that doctors are more responsive when the hospitals cover the expenses compared to when national insurance is taking up the bill.

However, one cannot exclude the possibility of autocorrelation. To deal with this we have changed the model so that we allow for autocorrelation in the error terms in the model above. To simplify notation let $Y_{2t} = \frac{\log m_{2t}}{\log m_{1t}}$, $Y_{3t} = \frac{\log m_{3t}}{\log m_{1t}}$, and let r_j , $j=2,3,4,5,6$ be the coefficients that capture the possible correlation over time between the error terms

in the eqs (15)-(19) above. For instance $e_{2t}=r_2 e_{2t-1}+ e^*_{2t}$, where * indicate the new error terms that we get after assuming a first order autoregressive scheme. The equivalent to eqs. (15)-(19) is then

$$(15^*) \quad Y_{2t}=r_2 Y_{2t-1} - (v_{2t}p_{2t} - v_{1t}p_{1t})+r_2(v_{2t-1}p_{2t-1} - v_{1t-1}p_{1t-1}) + \beta_2(1-r_2)t + r_2\beta_2 + (1-r_2)\alpha_2 + e^*_{2t}$$

$$(16^*) \quad Y_{3t} = r_3 Y_{3t-1} - (v_{3t}p_{3t} - v_{1t}p_{1t})+r_3(v_{3t-1}p_{3t-1} - v_{1t-1}p_{1t-1}) + \beta_3(1-r_3)t + r_3\beta_3 + (1-r_3)\alpha_3 + e^*_{3t}$$

$$(17^*) \quad p_{1t} = r_4 p_{1t-1} + (1-r_4)c_1 + \frac{1}{v_{1t}(1-m_{1t})} - r_4 \frac{1}{v_{1t-1}(1-m_{1t-1})} + \eta^*_{1t}$$

$$(18^*) \quad p_{2t} = r_5 p_{2t-1} + (1-r_5)c_2 + \frac{1}{v_{2t}(1-m_{2t})} - r_5 \frac{1}{v_{2t-1}(1-m_{2t-1})} + \eta^*_{2t}$$

$$(19^*) \quad p_{3t} = r_6 p_{3t-1} + (1-r_6)c_3 + \frac{1}{v_{3t}(1-m_{3t})} - r_6 \frac{1}{v_{3t-1}(1-m_{3t-1})} + \eta^*_{3t}$$

where as before

$$(20) \quad v_{jt} = \alpha_{ijt}\beta_1 + \alpha_{Hjt}\beta_H; \quad i=1,2,3$$

The likelihood now becomes

$$(27) \quad L = \prod_{t=1}^{\infty} f \left(\frac{Y_{2t} - r_2 Y_{2t-1} + (v_{2t} p_{2t} - v_{1t} p_{1t}) - r_2 (v_{2t-1} p_{2t-1} - v_{1t-1} p_{1t-1}) - \beta_2 (1-r_2)t - r_2 \beta_2 - (1-r_2) \alpha_2 - \rho_2 \left(p_{2t} - r_5 p_{2t-1} - (1-r_5) c_2 - \frac{1}{v_{2t}(1-m_{2t})} + r_5 \frac{1}{v_{2t-1}(1-m_{2t-1})} \right)}{\sigma_2} \right) \\
\times f \left(\frac{Y_{3t} - r_3 Y_{3t-1} + (v_{3t} p_{3t} - v_{1t} p_{1t}) - r_3 (v_{3t-1} p_{3t-1} - v_{1t-1} p_{1t-1}) - \beta_3 (1-r_3)t - r_3 \beta_3 - (1-r_3) \alpha_3 - \rho_3 \left(p_{3t} - r_6 p_{3t-1} - (1-r_6) c_3 - \frac{1}{v_{3t}(1-m_{3t})} + r_6 \frac{1}{v_{3t-1}(1-m_{3t-1})} \right)}{\sigma_3} \right) \\
\times f \left(\frac{p_{1t} - r_4 p_{1t-1} - (1-r_4) c_1 - \frac{1}{v_{1t}(1-m_{1t})} + r_4 \frac{1}{v_{1t-1}(1-m_{1t-1})} - \rho_{12} \left(p_{2t} - r_5 p_{2t-1} - (1-r_5) c_2 - \frac{1}{v_{2t}(1-m_{2t})} + r_5 \frac{1}{v_{2t-1}(1-m_{2t-1})} \right) - \rho_{13} \left(p_{3t} - r_6 p_{3t-1} - (1-r_6) c_3 - \frac{1}{v_{3t}(1-m_{3t})} + r_6 \frac{1}{v_{3t-1}(1-m_{3t-1})} \right)}{\sigma_1} \right) \\
\times f \left(\frac{p_{2t} - r_5 p_{2t-1} - (1-r_5) c_2 - \frac{1}{v_{2t}(1-m_{2t})} + r_5 \frac{1}{v_{2t-1}(1-m_{2t-1})}}{\sigma_{n2}} \right) \\
\times f \left(\frac{p_{3t} - r_6 p_{3t-1} - (1-r_6) c_3 - \frac{1}{v_{3t}(1-m_{3t})} + r_6 \frac{1}{v_{3t-1}(1-m_{3t-1})}}{\sigma_{n3}} \right) \\
\times |J_t|$$

where $f(\cdot)$ is the unit normal probability density and $|J_t|$ is the absolute value of the same determinant of the Jacobian as before. The estimates are given in Table 5 below.

Comparing Tables 4 and 5 we observe that the crucial coefficients β_I and β_H are estimated to have the same magnitude, but when we account for autocorrelation the t-values become smaller. The latter means that now the 95 percent confidence interval clearly overlap. Still, the estimates imply $\beta_I < \beta_H$, but the evidence that doctors are more responsive when the hospitals cover the expenses is less clear.

When autocorrelation is accounted for the trend effects in market shares (β_2 and β_3) both are insignificant. The drug specific constants (α_2 and α_3) are estimated to be

negative (relative to Enbrel). Now both are significant and the numerical values becomes higher, in particular for Remicade. These results indicate that given the price, Enbrel is a favored drug in particular compared to Remicade. This accord with the fact that Enbrel yields a more efficient treatment, and with less side effects, than Remicade.

All unit costs are now significant and almost of the same magnitude as in the previous case, in particular for Enbrel and Humira. To account for autocorrelation, have no clear impact on the estimates of the variances of the error terms. However, the correlation between the unobserved factors in the market share of Remicade and its price setting is now estimated to be significantly less than zero. Also the correlation between the unobserved factors in the pricesetting of Enbrel and Remicade is estimated to be significantly negative. The first means that if there is negative shock in the price of Remicade, then its market share increases, *cet.par*. The latter estimate implies that a negative price shock for Remicade has a positive impact on the prices of Enbrel. However, it should be noticed that due to the observed part in the pricesetting equation for Enbrel a lower price of Remicade implies also a negative price response for Enbrel. This is due to the monopolistic competition among the three producers. The negative correlation between the unobserved factors in the pricesetting of Enbrel and Remicade modifies this price response and is obviously due to unobserved quality characteristic across the two drugs. The better quality of Enbrel makes it possible to reduce the price less as a response to a negative shift in the price of Remicade. This lesser response is here captured by the probabilistic structure of the pricesetting part in the model.

The estimates of the autoregressive coefficients are all positive, between 0 and 1 and clearly significant.

Table 5. Joint estimates of market shares and price setting, accounting for autocorrelation.

Coefficients	Estimates	t-values
β_I	12.842	7.75
β_H	13.368	7.86
β_2 (Humira)	0.556	1.68
β_3 (Remicade)	0.836	0.95
α_2 (Humira)	-2.400	-2.51
α_3 (Remicade)	-8.868	-0.91

c ₁	0.167	10.27
c ₂	0.223	17.47
c ₃	0.111	2.69
σ ₁	0.007	10.74
σ ₂	0.129	9.51
σ ₃	0.104	8.03
σ _{η2}	0.005	10.51
σ _{η3}	0.018	6.83
ρ ₂	3.649	0.88
ρ ₃	-10.040	-7.94
ρ ₁₂	-0.048	-0.25
ρ ₁₃	-0.299	-5.26
r ₂	0.691	7.60
r ₃	0.890	17.18
r ₄	0.664	6.36
r ₅	0.878	24.34
r ₆	0.662	2.87
Log Likelihood	1225.700	
No of observations	61	

To further compare the results of the three models we show mean own-price elasticities and how they develop over time. These elasticities are the elasticities of expected demand with respect to the prices p_{jt} . The elasticities are calculated by applying the following expression:

$$(29) \quad E_{jt} = \frac{p_{jt}}{m_{jt}} \frac{\partial \hat{m}_{jt}}{\partial p_{jt}} = -v_{jt} p_{jt} (1 - \hat{m}_{jt}); \quad j=1,2,3$$

Here the market shares are the predicted shares using the whole structural parts in the different models. In Table 6 we give the means over the periods in the sample.

Table 6. Mean price elasticities

	The market share model	Instrument approach	Demand and price setting approach	As the previous one, with autocorr.
Enbrel	-0.59	-0.92	-2.19	-2.34
Humira	-0.92	-1.42	-3.39	-3.63
Remicade	-0.29	-0.44	-1.02	-1.09

We clearly see that when unobserved quality and hence, endogeneity, is controlled for, the numerical value of the price elasticities increases, in particular in this case when a simultaneous demand and price setting model is applied. To account for autocorrelation has a negligible impact on the elasticities. The marked dips in the elasticities (increase in numerical value), when the new policy reform was implemented with all drugs being covered by the hospitals, become less marked when endogeneity is controlled for. This is particularly the case in the demand and price setting approach.

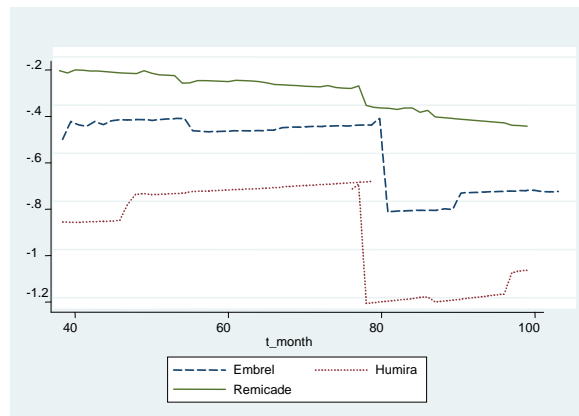


Figure 4. The development of elasticities in the market share model.

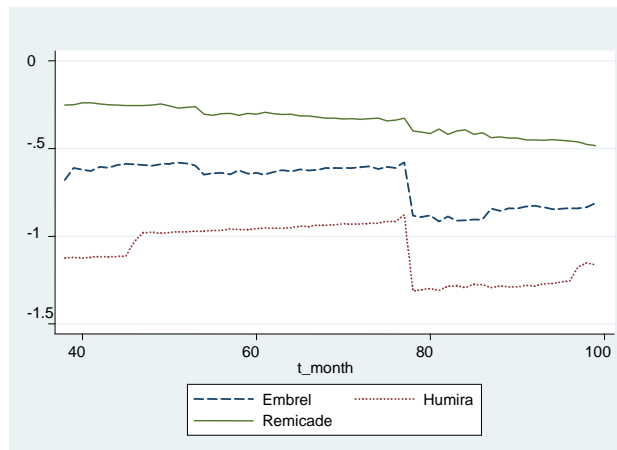


Figure 5. The development of elasticities in the instrument approach.

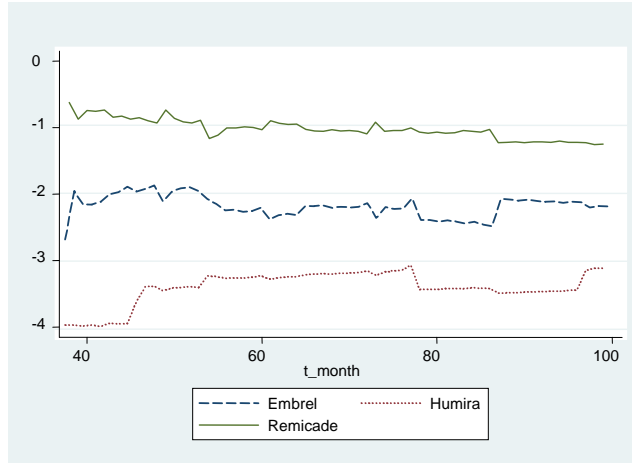


Figure 6. The development of elasticities in the demand and price setting approach.

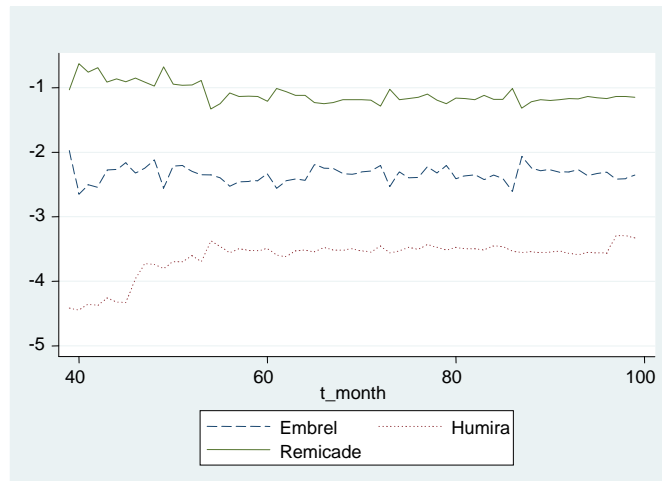


Figure 7. The development of elasticities in the demand and price setting approach, accounting for autocorrelation

6. Conclusions

In this paper we have used a discrete choice model in which the doctor's choice among TNF-alpha inhibitors depends on the prices. Price response is allowed to vary with the identity of the third-party payer, national insurance and hospitals. The estimate of the resulting market share model indicates that homoscedasticity is rejected, which may be due to neglected unobserved quality aspects of the drugs which are priced out in the market. The traditional way of dealing with this problem is to instrument the prices, which we have done and obtained better results. But we can do even better and control

for quality aspects as well as for a variety of unobserved heterogeneity. To do so we have modeled the market equilibrium for the three drugs, which means that price setting that follows from a non-cooperative Nash - equilibrium is added to the market share equations. We include correlation between market share equations and price setting equations. We also account for autocorrelation by estimating an AR1 model. This equilibrium model is estimated in a joint maximum likelihood approach. As in the instrument approach, the results show that homoscedasticity is not rejected. We find that doctors are significantly more responsive when the costs are covered by the hospitals compared to when costs are covered by national insurance. When accounting for autocorrelation the significance of this result becomes weaker. Moreover, the numerical values of the own-price elasticities increase substantially when a market share model, with and without instruments, is replaced by a market equilibrium model.

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