Mémoire n° 105
Juillet 2007

THE FORCED ADOPTION OF A FAST-TRACK APPRAISAL PROCESS FOR A BREAST CANCER TREATMENT IN UK

Eugen GRECU

Ce mémoire a été réalisé dans le cadre du DESS en économie et politique du médicament- Master in Pharmaceutical Economics and Policy (MPEP)

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INSTITUT D'ECONOMIE ET DE MANAGEMENT DE LA SANTE
UNIVERSITE DE LAUSANNE

MEMOIRE DE DESS EN ECONOMIE ET POLITIQUE DU MEDICAMENT

JUILLET 2007

EUGEN GRECU
DIPLOME EN MEDECINE DE L'UNIVERSITE DE IASI, ROUMANIE

REMERCIEMENTS

Au Prof. Gianfranco Domenighetti, PD, Professeur Titulaire a l'Université de Lugano, Directeur du Service de Santé Publique à l'Administration Sanitaire du Tessin, Professeur invité de l'Université de Lausanne qui a dirigé ce travail de mémoire.

A Stephane Guerard, MS in Management, Doctorant à l'IEMS, en tant qu'expert.

CONTENT

1. Introduction

Trastuzumab (Herceptin ® , Roche) is approved in UK for the treatment of the metastatic breast cancer since 2001. As of 2005, concomitantly with the publication of 3 studies that showed it produces a 50% reduction of the recurrence rates of breast cancer, trastuzumab started to be prescribed in the early adjuvant treatment of this disease. Until June 2006, trastuzumab did not have both: 1) regulatory approval and 2) NICE recommendation for the use in early stages of breast cancer. During this period until June 2006, the trastuzumab use in those patients was not reimbursed and because the cost of trastuzumab is equal with the yearly UK average income, most of patients could not self fund their treatment.

Before the publication of the final NICE guidance, the new data of trastuzumab in early breast cancer raised enormous patient and professional interest and expectations. A great volume of public and professional pressure was generated to transcend a system by which Primary Care Trusts can reimburse a treatment only after a formal guidance was issued.

This paper draw on a case study depicting and analyzing the process by which regulatory approval and NICE recommendations were achieved in a record time and how trastuzumab became a standard treatment on early adjuvant breast cancer. According to the data we gathered in this work we were witnessing one of the fastest processes of adoption of a health care technology since the creation of NICE, in 1999. This study addresses the following research question: How and why does the adoption pattern of trastuzumab differ from the rational decision-making model of the reimbursement process in UK?

2. Theoretical Background.

A number of adoption models are described in the literature.
The rational model explained by Rogers [1] (Rogers et all, 2005) and Abrahamson [2] proposes that the adoption of an innovation depends mainly on the strength of the scientific evidence backing it. This objective evidence comprises arguments of technical efficiency and is accepted in a smooth manner by passive stakeholders - the diffusion of the innovation is depicted as a smooth, rational process. It is the relative advantage of the innovation compared to the currently existing technologies that drives the pace of the process. The passive nature of the actors and the incontestability of the evidence are the major characteristics of those models.

Abrahamson [2] describes an institutional model where the adopting institutions have a deciding, coercitive role on its components. The innovation is accepted through imitation of external organizations which launch the "fashions" or through the imitation of other internal units of the same organization that already adopted it – "the fads". The process of adoption is passive and linear.

The political model is promoted by Denis and colleagues (Denis et. Al, 2002).[3] They argued that the diffusion of an innovation is a nonlinear process and showed that the scientific evidence has only a limited influence on the final outcome. Maguire (2002) shows the extreme fluidity of the political model and arguments that in the adoption process both the adoption system and the innovation undergo changes.[4]

Gelijns et al. (2005) show that it is the blend of scientific evidence and politics that make the final result and the institutions that are responsible for adopting the innovations have to master the synthesis between science and politics. [5]

The trastuzumab adoption case appears to be one of "over adoption" that is when the scientific evidence lags behind the speed and actual achievement of adoption. [3] Despite the lack of a full appraisal process and of regulatory clearance for its use in early breast cancer, physicians prescribed the drug and patients were fighting publicly for its free availability from the moment of publication in June 2005 of the preliminary results of 3 combined trials showing trastuzumab's activity in this disease area.

The final outcome – the NICE guidance - occurred as a result of a negotiation between the various stakeholders involved in the adoption process and we had a special interest in understanding their actions and motivations along this process. We found that, compared to a classical adoption model, the number and the influence of the key players changed during the process.

3. Methodology

For our longitudinal case study, occurring between June 2005 and June 2006, in a chronological order, we selected and studied for each and one of the actors involved in the trastuzumab adoption process, their most important actions, decisions, public statements that were of relevance for the final decision of NICE to recommend the use of trastuzumab in the treatment of early stage breast cancer. As major sources of information we used articles published in the medical and the lay press in the period and also news bulletins from major news organizations such as BBC.

It was by understanding the chronological order of those actions that we clarified the changes occured in the trastuzumab adoption process vs. the previous adoption and diffusion cases. Finally, after analyzing our findings we launched our proposed responses for the study question.

4. BREAST CANCER

The breast cancer is the most common malignancy in women. Worldwide, there are 1 million new cases every year. The incidence and mortality rates for breast cancer in UK are among the highest in the world. Overall, breast cancer accounts for 18% of all female cancers and there are 62.6 death per 100,000 population every year [6] (figure 1).

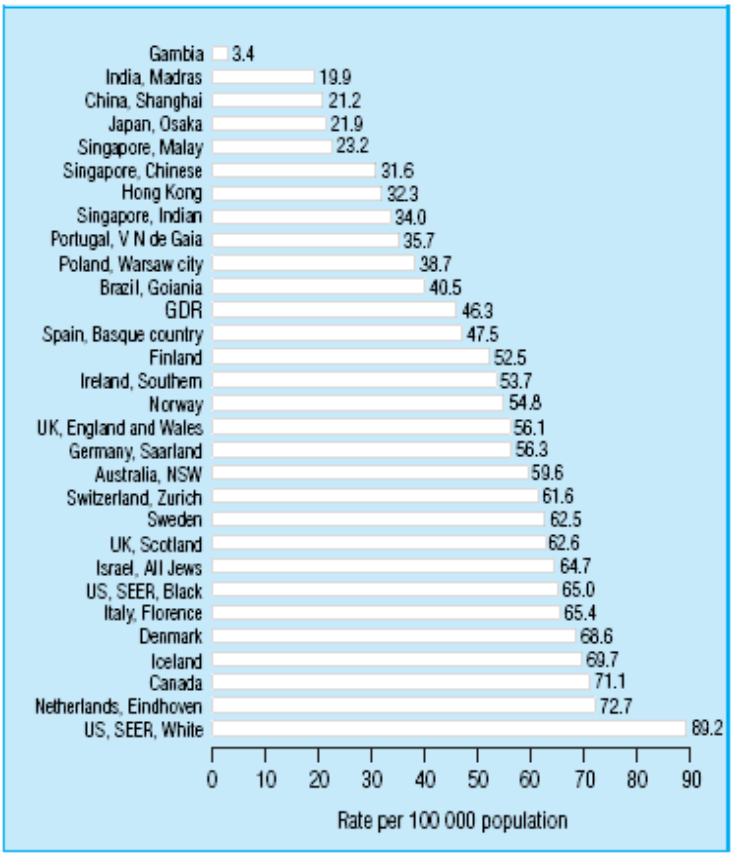


Fig.1 Standardized mortality for breast cancer in different countries (copyright BMJ 2000; 321: 624)

The past decade has seen an impressive decrease (of approximately 15%) in the breast cancer mortality rates in UK, despite a raising incidence of this disease.[7] Experts consider that the wide diffusion of the adjuvant (post surgical) systemic therapy is the main responsible for this positive trend. [7-10]

Polichemotherapy, endocrine therapy and trastuzumab are part of today's drug armamentarium in the treatment of early breast cancer. [7-10]They all reduce tumor recurrence and mortality yearly rates [7-10]. However, between various drugs exists significant differences in terms of clinical efficacy and side effects profile. In that perspective, major differences exist between the older therapies – chemotherapy and tamoxifens and the newer ones - aromatase inhibitors and trastuzumab. [7 -10] The efficacy gains are reflected in reduced risk of disease recurrence and overall prolongation of patient lives, whereas the side effect profile gains are mostly translated in improved quality of patient lives. All those benefits are considered fundamentals by physicians and their patients and explain the great expectations and interest for the new generation of drug therapies.

The access to the new drug treatments varies greatly across countries. US, Switzerland, Austria and France seem to be the countries with the most rapid adoption and diffusion rates of the newest breast cancer drug treatments such as trastuzumab, whereas UK together with Norway and countries from Central Europe display adoption rates bellow the average. [11] Within the same country, geographical variations of drug diffusion are reported as well. In UK, a study found a variation of up to 12-fold in the rate of prescribing for chemotherapy drugs appraised by NICE at that time. [12]

In the last period, the free access to the new cancer therapies became a major subject of medical, political, economical, and societal debate in UK. The future of the national drug research and development, the political aspects regarding the quality of the governance of the national health service (NHS), the role and the extent of the society in supporting particular needy individuals are among the fundamental points of this debate. [13, 14, 15]

It is in this dynamic context that we studied the adoption and diffusion of trastuzumab in the treatment of early breast cancer. That event had structural consequences for the future shape of the adoption and diffusion process of a medical innovation in UK. The institutions in charge with the adoption, the process of adoption and the innovation itself underwent significant changes by the end of this story.

This case study exhibits the evolution and contribution of a number of key players who had an important role in the final outcome - the guidance of NICE for reimbursement of trastuzumab prescribed in the treatment of the early stage breast cancer patients.

5. The Innovation: Trastuzumab (Herceptin®)

Trastuzumab is a recombinant monoclonal antibody (Herceptin, Roche) that was approved by the European Agency for the Evaluation of Medicinal Products (EMEA) in August 2000 for the treatment of patients with metastatic breast cancer whose tumors over express the human epidermal growth factor receptor 2 (HER2), which is normally involved in the regulation of cell proliferation. [16]

Over expression (abnormal increase in numbers) of the HER2 receptor occurs in 25-30% of the patients with primary breast cancer and is a prognostic factor for poor survival rates. [17]
In June 2006, EMEA approved trastuzumab for the treatment of patients with HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
According to the license granted by EMEA, Herceptin should only be used in patients whose tumors have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. [16]

The license was granted on the basis of 3 large randomized clinical trials which found hazard ratios for breast cancer recurrence of 0.48 when trastuzumab combined with chemotherapy was compared with chemotherapy alone, and 0.54 when the trastuzumab treatment was compared with a control intervention, meaning that trastuzumab contributed to reducing the risk of disease come back

by percentages between 48 and 54%. [18-20] At one year, the disease free survival rates were 85.8% with trastuzumab vs. 77.4% in the control arm, hence an absolute benefit of almost 8%.

Reported survival benefits were between 0 and 4.8% at four years.[18-20]
The recent publication of the results of 2 years follow up of the HERA trial (trastuzumab after adjuvant chemotherapy vs. chemotherapy alone) showed a survival benefit of 2.7% vs. the control group.[71] With all these, because trastuzumab was found to halve the breast cancer recurrence rates, the results of the trials were considered "not evolutionary but revolutionary."[21]

The number needed to treat (NNT) found in one of the 3 trials were 19, meaning that 19 patients need a treatment in order to prevent one recurrence.[23] In an analysis performed at the level of the Norfolk and Norwich University Hospital it was shown that for funding the treatment of 75 patients eligible for trastuzumab it was needed an amount of money that could fund otherwise the adjuvant treatment of 355 patients and the palliative treatment of another 30 patients with various cancers. For the overall population size of the trust, the analysis was showing that 3 extra patients would be cured with trastuzumab vs. 16 in case of the other combined treatments. [24]

A significant finding was the increased risk of cardiac toxicity, incidence of which ranged from 0.5% to 4.1% in the 3 clinical trials.[22] That triggers the need of regular cardiac monitoring hence increased treatment costs. Additional costs should be considered for the treatment of those adverse cardiac events that result in patient morbidity and reduced quality of life. [23]

The trastuzumab yearly average cost per person varies between £24,000 and £28,000. [24]

More costs should be considered, knowing that patients are to be tested for the HER2 receptor overexpression. From the 35,000 women with early breast cancer in UK, 20,000 would be suitable for testing for HER2 receptor. Approximately 20% would be eligible for treatment with trastuzumab. Nation wise, that would raise the cost of treatment at over £100m if the treatment with trastuzumab will be given to all eligible patients. [25]

At the time of publication of the new trastuzumab data, in UK more than a quarter of women were never tested for HER2 overexpression and only half were tested at the time of the initial diagnosis. [23]

5. The rational process and its guardian: NICE

NICE (National Institute for Health and Clinical Excellence) produces national guidance on health technologies, public health and clinical practice. The guidance issued by NICE is required to be implemented by the NHS organizations in England and Wales within 3 months of issue. [26]

NICE appraises the clinical and cost effectiveness of health technologies referred to it by the Department of Health. The process is complex, involves many interested parties (stakeholders) and usually takes around two years to complete. [27]

The critics of the NICE appraisal process say that this delay can allow patterns of treatment of uncertain cost effectiveness to be established. The eventual licensing of other treatments during the appraisal period may render the guidance outdated (NICE. Draft Scope - Macular degeneration (age-related). [28]

Following is a brief description of NICE the appraisal process,
(Adapted from: Developing NICE Technology Appraisals.
http://www.nice.org.uk/page.aspx?o=114218) [29]:

1. **Selection of the provisional appraisal topics.**
   The Department of Health (DH) produces a list of provisional appraisal topics.
2. **Identification of the consultees and commentators.**
   This includes: national organisations, groups representing patients and carers, bodies representing health professionals, manufacturers and research groups.
3. **Preparation of the scope**.
   NICE works with the DH to develop a scope. This document establishes what the appraisal will cover and the questions that need to be asked. Consultees and commentators comment on the draft scope.
4. **Referral of the appraisal topic.**
   The Department of Health refers technology appraisal topics to NICE.
5. **Preparation of the assessment report.**
   An independent academic centre reviews published evidence on the technology and prepares an assessment report. Consultees and commentators comment on the report.
6. **Preparation of the Evaluation report.**
   This includes the assessment report and comments the comments received.
7. **Production of the Appraisal consultation document (ACD).**
   An independent appraisal committee considers the evaluation report. It hears evidence from nominated clinical experts, patients and carers and than generates the ACD. The ACD is made available online for comment from health professionals and public.
8. **Final appraisal determination (FAD).**
   The independent appraisal committee considers the comments on the ACD, then makes its final recommendations in the FAD. The FAD is submitted to NICE for approval. In this phase consultees can appeal against the final recommendations in the FAD.
9. **Final Guidance.**
   If there are no appeals, or an appeal is not upheld, the final recommendations are issued as NICE guidance.

In September – November 2005, because of the great time lengths taken for appraising life saving drugs, and under the enormous pressure from the public and government generated by the trastuzumab case, NICE decided to short cut its own assessment timelines and developed and had approved "the single technology appraisal" process (STA). [30]

Trastuzumab was the first lifesaving drug to benefit from an appraisal period of about 4 months: in February 2006 the evidence was submitted by the manufacturers and in June 2006 NICE published the draft guidance. Few years before, the appraisal process for the adoption of trastuzumab in metastatic breast cancer lasted for 14 months, after EMEA approved the license. (A full chronology of the trastuzumab adoption process is described in ANNEX A).

Overview of the STA process

(Adapted from: Guide to the Single Technology Appraisal Process. September 2006. Appendix B. Available at: http://www.nice.org.uk/page.aspx?o=STAprocessguide) [31]

The STA process, from referral to the publication of guidance, consists of three distinct phases:
Phase1: NICE will notify the manufacturer/sponsor of the STA and request an evidence submission. Delay: min 8 weeks.
Phase 2: the Evidence Review Group's work (a minimum of 8 weeks), appraisal of the evidence and preparation of the recommendations.

Phase 3: a Final Appraisal Determination (FAD) document is issued containing the recommendations. Delay: between 7 and 15 weeks. Following release of a FAD, consultees have 15 working days to appeal.

In case no appeals are received, it will take between 32 weeks and 39 weeks to produce the guidance. (pls. see Annex B for the description of the STA timelines).

As described above, in the STA process, the evidence is submitted only by manufacturer of the drug, followed by an independent assessment by the institute and the issuing of the draft guidance. At this stage an appeal against the decision can be formulated by the interested organizations.[32]

There are three grounds on which stakeholders may appeal against a draft guidance: 1) process (due process), 2) perversity (given evidence), and 3) powers (exceeding its powers). A panel composed of 5 non executive NICE members, industry and patient representatives will hear the appeal. On the ground related to the due process an appellant may appeal if it believes the appraisal process was not a fair one, i.e. if not all data sets submitted were taken in consideration.
On the ground related to the given evidence one may appeal if it considers the decision in conflict or simply wrong in the light of the submitted evidence.
On the ground related to exceeded powers, the appeal may be founded on the consideration that NICE went over the attributions stated in its Statutory Instruments or simply that it acted unlawfully under the current legal frame (NICE: Appraisal Process: Guidance for Appellants). [33]

NICE does not have a threshold at which cost effectiveness becomes acceptable but most of the assessments done until now indicate that for incremental cost effectiveness ratios above £20,000 / QALY the case supporting the respective technology has to be increasingly strong. [26, 34]
Beyond this cost effectiveness analysis, the appraisals do not explicitly consider the affordability of the technologies within the NHS and NICE does not provide extrafunding or does not advise on additional source of funding for the adoption of the new technology. [35]

In a review article on the health service reform in UK, Maynard and Street found that NICE is confronted with four main issues: 1) technologies are approved on marginal cost effectiveness generating increased NHS spending for small health gains of the population, 2) there is failure in removal of the old, redundant technologies, 3) there is uneven implementation of the guidances across the country and 4) NICE lacks negotiation power over prices. On those grounds the authors conclude that NICE cannot fulfill its rationing function. [13]

7. Main players on the trastuzumab adoption scene:

7.1. Politicians

Setting public health as a priority on the political agenda is a key of government's and individual politician's success nowadays. In this context, members of the UK parliament frequently embrace popular cases such as supporting cancer patients.

A statistic of the House of Commons question book showed 84 questions on trastuzumab by April 2006. [36]

The Secretary of State for Health, Patricia Hewitt had frequent and decisive public interventions during the trastuzumab debate:

1. "I have asked for a fast track appraisal of the use of Herceptin in parallel with the licensing process" [37] (October 2005)

2. "Herceptin has the potential to save many women's lives and I want to see it in widespread use on the NHS".[38] (October 2005)
3. "Today I am asking Prof Mike Richards to ensure that the facilities are put in place to enable women who require it to be tested."[38](October 2005)
4. "I want the license for Herceptin to be granted as quickly as possible, without compromising people's safety, and to be available within weeks of the licence being given".[38] (October 2005)
5. "I share the huge frustration of many women about the delays in getting Herceptin licensed. I am determined to take action and this represents a major step forward in our fight against cancer."[38] (October 2005)
6. All women with early stage breast cancer would be tested for suitability for treatment with trastuzumab. "Testing now should mean women could receive the drug as soon as the licence is extended, probably next year"[39] (October 2005)
7. Primary health care trusts "should not refuse to fund Herceptin (trastuzumab) solely on the grounds of its cost"[40] (November 2005)
8. "PCTs should not rule out treatments on principle but consider individual circonstances"[40] (November 2005)

In a visit to Manchester in November 2005, asked about the trastuzumab funding by the Primary Care Trusts, prime minister Toni Blair said: "primary care trusts should go ahead and allow people to use it (trastuzumab)". [41]

The government interference over Herceptin appraisal by NICE received strong criticism. In a public intervention Iain Chalmers, founder of Cochrane Library, raised doubts over the capability of the government to see over the individual cases, thus compromising NICE's work.[42]

7.2. Media

All throughout the period in study, media was a permanent supporter of the patients in need for trastuzumab treatment. It generously offered the public platform to show the fight of individual patients in need of treatment, to quote statements coming from various advocacy groups and it was a permanent critic of the lengthy formal drug approval processes. In the period, there were reports from patients who were called by media outlets and were offered support in terms of pressing for obtaining funding for trastuzumab in exchange of rendering public their own personal stories.[43]

By carrying with perseverance a number of exemplar patient cases together with stories about "the wonder drug" prepared in the so called press releases, the media succeeded to maintain continuous public attention and pressure on authorities. [37] During the period January 2005 – December 2006, The Sun had 94 articles and press releases mentioning trastuzumab (Herceptin ®), in most cases centered on patients individual stories. [44]

The attitude of media towards the trastuzumab case was called "hyperbolic" and some authors have criticized the intense public pressures under which NICE had to deliberate on the file as a case of "rationing by media".[35]

In the trastuzumab case the media showed the validity and the great influencing power of the "rule of rescue", which is defined as a perceived duty to save endangered individual life wherever possible (NICE citizen council report – Rule of Rescue).[45]

This intense media campaign generated high emotional reactions on the breast cancer patients themselves and drove them to engage in an increasing stream of public actions.[43]

STAKEHOLDERS of the NICE Appraisal process

7.3. Patient, Associations, Advocacy groups

The public actions of this group of stakeholders can be classified in two periods: prior 2006, when decisions of PCTs to refuse trastuzumab funding were appealed by patients and the result with no exception was the granting of treatment, and during 2006, when for the first time a patient brought her case to court. All those cases received wide public coverage and we could establish their chronology from the various press articles we had in our documentation.

In October 2005, nurse **Barbara Clark**, 49, threatened Somerset Coast Primary Care Trust with a Judicial Review, but the Trust backed-down before the case and provided her with the treatment. The appeal to the exceptional treatment panel of the Somerset Coast Primary Care Trust was grounded on patient's exceptional circumstances - Mrs. Clark has a child with a life limiting condition. Barbara Clark was the first patient to go public in her fight for the treatment.[46, 47]

In November 2005, **Elaine Barber**. North Stoke PCT reversed an initial decision not to fund trastuzumab, after discussions between the patient and the trust chief's executive and after the release of a press statement by the health secretary that the trust ruling was in conflict with other trusts decisions [48, 49]

Amanda D'Argue and **Alyson Cooper** were among few other patients who received funding for their treatment following public actions against the ruling of their trusts.[50]

The case of the 7 patients from North Staffordhire who organized an advocacy group called "Fighting for Herceptin" (see photo 1 and 2) was also widely publicized. Eventually all of them received the funding for their treatment before the end of their campaigning program. [51] "Fighting for Herceptin" group started their activity soon after June 2005 by meetings with the local health authorities. They appeared in national papers, on BBC programmes, they organized tens of events, collected signatures for their campaign and eventually arrived to manifest in front of Downing Street 10 on September 2005. [52] (photo 1 and 2)

Photo 1: "Fighting for Herceptin" in front of Downing Street 10.

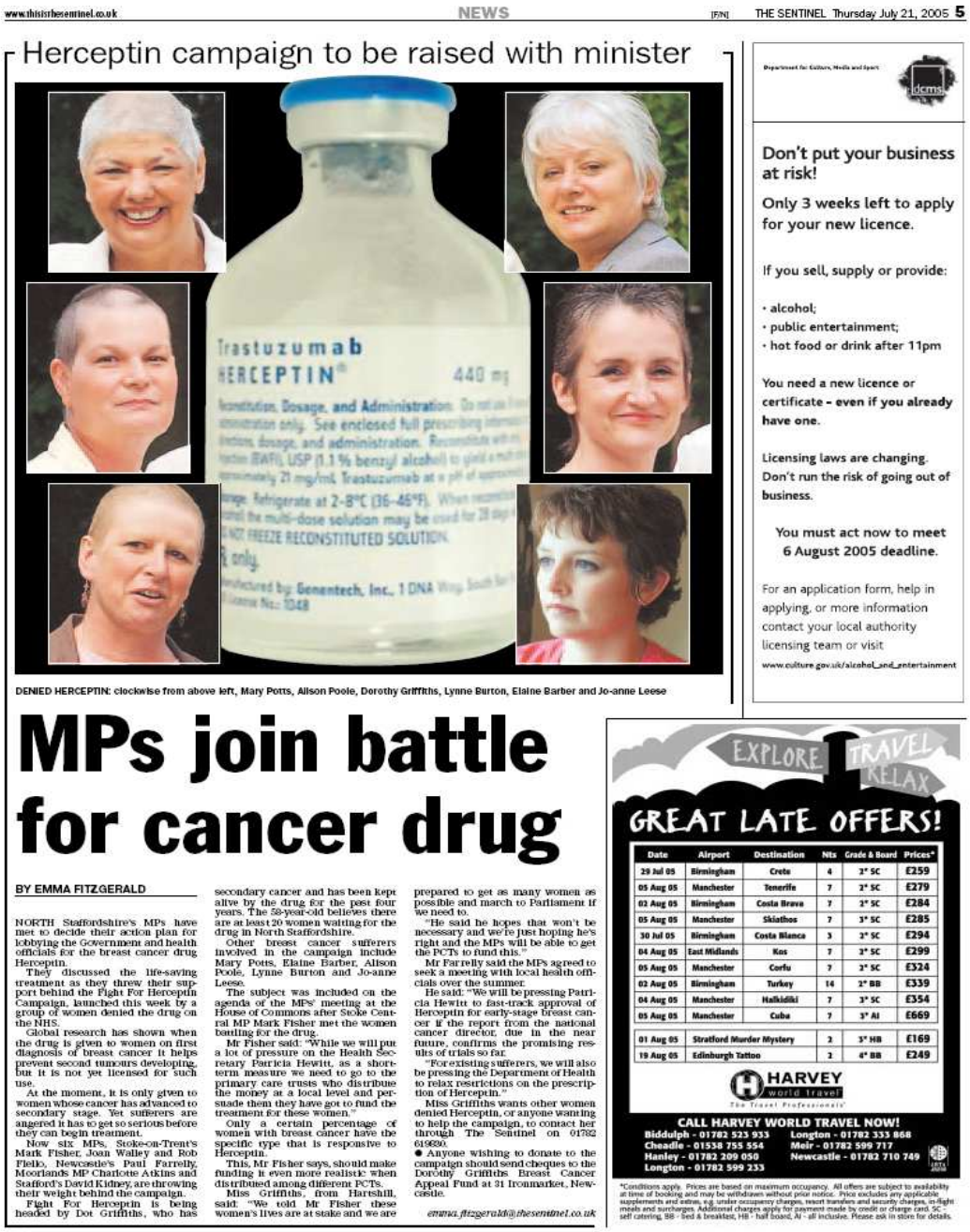
Ann Marie Rogers.

This is the most mediatized patient case in the whole cohort of individual stories regarding early breast cancer patients in quest for treatment with trastuzumab.

Ann Marie Rogers was the first patient to go to court in Britain, in a trial to force the NHS to fund her treatment with trastuzumab. The case received wide national press coverage and the story was reported closely by media outlets such as BBC news, SKY News, The Sun, but also medical press like British Medical Journal.

1. In January 2006 Ann Marie Rogers, received the right to appeal against a decision by Swindon Primary Care Trust to refuse the treatment with trastuzumab. The judge ordered Swindon PCT to fund the treatment until a full court hearing.
2. In February 2006 the hearing takes place at a High Court in London. Ann Marie Rogers claims that Swindon PCT is breaching her human rights in refusing to fund the treatment. As well, she claimed that the trust operated "an arbitrary, irrational and unlawful policy" against the decisions of the Department of Health. Mrs. Rogers considered that the decision of Swindon PCT is "equal with a death sentence"[36].
3. The High Court Judge rejected the appeal, deciding that Swindon's PCT decision was not unlawful, nor was it a breach of the European Convention of Human Rights.
4. The judge gave Mrs. Rogers permission to appeal and ordered Swindon PCT to pay for the treatment on an interim basis until the appeal court's decision.
5. In April 2006, Ann Marie Rogers brought her case to the London Appeal Court. The judges unanimously ruled that Swindon PCT has acted irrationally and unlawfully in refusing treatment to Ann Marie Rogers. The ruling stated that once the cost was considered irrelevant to the funding decision, the PCTs should fund all patients who could benefit from treatment. On the contrary, if cost was a constraint, then PCTs would act lawfully by deciding to reserve funding for other exceptional cases.

Exactly at the same time and under this public pressure NICE was running the Single Technology Appraisal process for the evidence of clinical cost effectiveness of trastuzumab in the early breast cancer. Meantime, in Bruxelles, the EMEA regulatory approval process was taking place.



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Herceptin campaign to be raised with minister

DENIED HERCEPTIN: clockwise from above left, Mary Potts, Alison Poole, Dorothy Griffiths, Lynne Burton, Elaine Barber and Jo-anne Leese

MPs join battle for cancer drug

BY EMMA FITZGERALD

NORTH Staffordshire's MPs have met to decide their action plan for lobbying the Government and health officials for the breast cancer drug Herceptin.

They discussed the life-saving treatment as they threw their support behind the Fight For Herceptin Campaign, launched this week by a group of women denied the drug on the NHS.

Global research has shown when the drug is given to women on first diagnosis of breast cancer it helps prevent second tumours developing, but it is not yet licensed for such use.

At the moment, it is only given to women whose cancer has advanced to secondary stage. Yet sufferers are angered it has to get so serious before they can begin treatment.

Now six MPs, Stoke-on-Trent's Mark Fisher, Joan Walley and Rob Flello, Newcastle's Paul Farrelly, Moorlands MP Charlotte Atkins and Stafford's David Kidney, are throwing their weight behind the campaign.

Fight For Herceptin is being headed by Dot Griffiths, who has secondary cancer and has been kept alive by the drug for the past four years. The 58-year-old believes there are at least 20 women waiting for the drug in North Staffordshire.

Other breast cancer sufferers involved in the campaign include Mary Potts, Elaine Barber, Alison Poole, Lynne Burton and Jo-anne Leese.

The subject was included on the agenda of the MPs' meeting at the House of Commons after Stoke Central MP Mark Fisher met the women battling for the drug.

Mr Fisher said: "While we will put a lot of pressure on the Health Secretary Patricia Hewitt, as a short-term measure we need to go to the primary care trusts who distribute the money at a local level and persuade them they have got to fund the treatment for these women."

Only a certain percentage of women with breast cancer have the specific type that is responsive to Herceptin.

This, Mr Fisher says, should make funding it even more realistic when distributed among different PCTs.

Miss Griffiths, from Harehill, said: "We told Mr Fisher these women's lives are at stake and we are prepared to get as many women as possible and march to Parliament if we need to.

"He said he hopes that won't be necessary and we're just hoping he's right and the MPs will be able to get the PCTs to fund this."

Mr Farrelly said the MPs agreed to seek a meeting with local health officials over the summer.

He said: "We will be pressing Patricia Hewitt to fast-track approval of Herceptin for early-stage breast cancer if the report from the national cancer director, due in the near future, confirms the promising results of trials so far.

"For existing sufferers, we will also be pressing the Department of Health to relax restrictions on the prescription of Herceptin."

Miss Griffiths wants other women denied Herceptin, or anyone wanting to help the campaign, to contact her through The Sentinel on 01782 619890.

● Anyone wishing to donate to the campaign should send cheques to the Dorothy Griffiths Breast Cancer Appeal Fund at 31 Ironmarker, Newcastle.

emma.fitzgerald@thesentinel.co.uk

Foto 2: Press article - Fighting for Herceptin

Cancerbackup (http://www.cancerbackup.org.uk/Home) **, Breaktrough Breast Cancer** (http://www.breakthrough.org.uk/) and **Breast Cancer Care** (http://www.breastcancercare.org.uk/) were among the numerous advocacy groups that sustained publicly and with high voice the trastuzumab funding fight in 2005 and 2006.

1. In a general statement about the length of NICE's approval process, the Chief Executive of Cancerbackup declared: "cancer treatment should be examined within 3 months of a license being granted".[54]

2. Immediately after the news of Ann Marie Rogers's winning appeal, the Chief Executive of Breaktrough Breast Cancer said publicly: "It is vital that this decision is now reinforced by NICE guidance being issued this summer. The fast track approval of drugs by NICE is welcomed but we need to ensure that once approved, guidance is implemented fully and that patients receive the drugs recommended"[55].

3. At the news of trastuzumab being granted the licence for use in the early stages of breast cancer, the spokesman of the Breakthrough Cancer charity reacted: "this is great news and should persuade any hesitating doctor or primary care trust to offer Herceptin to suitable patients. The full licence confirms Herceptin is safe and effective in early breast cancer"[56]

Patient groups provided support and information to patients and the public all the period we have in our study. As well, the 3 patient groups mentioned above were actively involved in the NICE appraisal process of trastuzumab as stakeholders and representatives of patients and patients organizations. [24]

There is a growing public debate about the societal role and the influence of the patients group in their actions for wider treatment access. Medical authors launch warnings on the damages generated by "the access advocacy", through which the pharmaceutical companies would weaken research, licensing and appraisal.[57]

Official voices sustain that the funding relation between drug companies and the advocacy groups in the future "will do the patient organizations an immense amount of damage and the confidence in their neutrality will dissipate" – Michael Rawlins, chairman of NICE. [58]

Recent surveys show that between 33 and 60% of the European patient groups receive industry funding. [58] It is not clear how big is this financial support and neither if it may undermine the group's independence.

Directly related to our case, Cancerbackup, one of the most active advocates of trastuzumab public funding, declared publicly that 9% of its financial resources are from industry. [58]

In an online survey conducted this year by BMJ, the following results were recorded to the question: "should patient groups accept money from the pharmaceutical industry?": 16% responded yes and 84% said no. [59]

Beyond that debate, it is obvious that the overwhelming part of the advocacy work is done in moral integrity and with a great educational role for the large public. The patient advocacy may be seen today as the link between a public with little knowledge and understanding of the theoretical aspects of the health matters and health professionals and policy makers that are looking to obtain scientific evidence for evidence based decisions. [60]

7.4. Opinion Leaders.

As a public voice, their role in generating interest and high expectations of the treatment was quintessential. Their declarations ranged from calls for moderation, balanced approach and thorough analysis of all elements in the play, with an increased accent towards considering the safety profile of the drug and the lack of strong evidence for efficacy markers [61] to ecstatic, enthusiastic vis à vis of the introduction of a drug that seemed to be a milestone in the treatment of breast cancer, years after

the introduction of taxanes. [21] Their comments and articles fueled the medical press during the period and were constant sources of references for the lay press.

7.5. Practicing physicians.

This category of stakeholders had rather a low public profile along the whole adoption process. Undoubtedly, an enormous amount of dialogue took place between the practicing clinicians and their patients in the meantime, regarding the efficacy and the appropriateness of this drug in individual situations. This generated expectation and request from the patient side for the early adoption of the treatment.

7.6. NHS (National Health Service)

NHS includes 152 regional primary care trusts (PCTs) that commission health services for a population of up to about 600,000.

NHS spends £10.3 bn a year on drugs and costs are raising rapidly. [62]

It is considered today that NHS resources are overexploited through a phenomenon termed "the tragedy of commons" – individual patients are acting rationally in seeking expensive treatments that generate marginal health benefits, because the costs fall on the common resource of NHS. [14]

At the end of 2005 the NHS had debts of around £620m for the financial year, with approximately 5% of the primary care trusts being responsible for the biggest part of the deficit. In this context, the intervention of the secretary of state for health in favor of free funding of trastuzumab to an individual patient went highly criticized in parliament.[63]

Prior trastuzumab case, the NHS organizations were little involved in the NICE appraisal process, most probably because of their low capacity for assessing effectiveness and prioritization. Realizing that they will be confronted with dramatic resource allocation decisions, the Primary Care Trusts, via the trastuzumab appraisal process, became active players in the adoption and seem more prepared to contribute to it by offering to the NICE appraisal the wider perspective, beyond the cost effectiveness assessments of the individual drugs. [24]

7.7. The drug company.

According to the STA rules, Roche was the sole source of the clinical and cost effectiveness evidence for the current appraisal. [24] An independent review has followed, however, in the process, the manufacturer was asked to submit only the evidence that it considered appropriate.

In the period, Roche sponsored health enconomic publications related to population access to newest cancer therapies. A 2005 sponsored report of the Karolinska Institute was republished 2 years later and was highly echoed by the UK lay media.[70] The report criticizes NICE for not enabling faster access of the medicines to the UK market (Wilking N, Jonsson B, 2005).[64]

There is relatively scarce public evidence of the relation between the drug company and patients or advocacy group in our case. Except the public declaration of funding made by the Cancerbackup organization, we retrieved Roche in a public spot when Professor Lisa Jardine, a patient with breast cancer herself, accused the company that tried to persuade her to run a public fight for free access to the treatment.[65] Roche denied the accusations and seems to have gone off the public stage for the period until submission of the evidence for the extension of their drug license, in February 2006.

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8. END OF PROCESS AND IMPLICATIONS OF THE TRASTUZUMAB CASE.

In June 2006, 2 weeks after trastuzumab received approval for use in early breast cancer by EMEA, NICE published the draft guidance for England and Wales. Separate guidance for Scotland was issued the previous week by the Scottish Medicines Commission. [66]
The drug is recommended as a treatment option for women with early stage HER2 positive breast cancer after surgery, chemotherapy and radiotherapy, if applicable. [66]

In July 2006 Newbury and Community Primary Care Trust appealed against the draft guidance. The appellants declared that they did not want to prevent the use of the drug but they asked clarification on the following points: 1) type of HER2 patients who should receive the treatment 2) the appropriate moment of start of treatment 3) the length of the treatment 4) the impact on the NHS resources 5) the long term risk and benefits of trastuzumab. [24]

In August 2006 a NICE panel dismissed the appeal and issued the final guidance for use of trastuzumab in early breast cancer. [67] However, NICE included in the final guidance responses to several points of the appeal clarifying aspects related to the start of treatment and the type of patients. [24]

The final guidance recommends the use of trastuzumab based on findings that the drug is clinical and cost effective. The guidance recommends 3 weeks cycles of treatment for one year or until recurrence, whichever is the shorter period. The guidance recommends cardiac function assessment and limits the drug use in patients at cardiovascular risk.[24]

The marginal cost per quality adjusted life year was found to be in the range of £3400 for the weekly dose regimen. Reviewing the data for the metastatic breast cancer, the evidence review group found that the marginal cost per QALY gained in this setting is ranging from £16,000 to £33,000. [24]

8.1. Implications of the trastuzumab adoption process:

1. NICE decided to short cut its own assessment timelines and developed "the single technology appraisal" process. A whole cohort of cancer medicines are to benefit from the process, so we can say that from that perspective the adoption process of trastuzumab was a revolutionary one.

2. The single technology appraisal process is taking place during and not after the regulatory review and that contributes massively to the shortening of the appraisal duration.

3. The trastuzumab case provoked a heated public debate about the NHS current functioning. It re stated the responsibilities of the local PCT management in making rational use of resources and the role of NICE as provider of guidance and support tools for economic decisions. It put the spot on the need of resource re allocation by the promotion of generic substitution and the possibility of introduction of a new drug reimbursement system. [68]

4. The innovation itself and more explicitly the evidence that was subject of the NICE independent review was submitted only by the manufacturer, and the nature and quality of it depended solely on the manufacturer's judgment of appropriateness. The innovation itself suffered changes in the adoption process: there is now a " test" for trastuzumab – that is mandatory for patients prior treatment and it predicts treatment success.

5. The industry funding of the patient organizations went in to a more in-depth scrutiny in that period. The Association of British Pharmaceutical Industry called for its members to disclose charity funding. Voices are raising in favor of stricter national regulations for charities and disclosure of the relation between charities and industry is now requested.[58]

6. The rule of rescue. The trastuzumab adoption process provoked a highly moral and philosophical debate about the fundaments and the role of the society in saving distressed individuals life vs. more rational use of resources for ensuring "the greatest good for the greatest number". The NICE Citizen Report Rule of Rescue was published in January 2006, in the midst of the trastuzumab public storm. [45]

9. FINDINGS AND THEORY BUILDING

What type of adoption and diffusion model can we recognize in the trastuzumab case?
Are we in the "efficient choice perspective" (Abrahamson, 1991)[2] where all NHS organizations were convinced of the effectiveness of the drug? Was the decision to reimburse trastuzumab rational?
In the run of this process, the scientific evidence was lagging behind adoption and ambiguity regarding the effectiveness of trastuzumab persisted for the whole period during which free access to this drug was granted to few individual patients. Therefore, at all times before NICE final guidance, we would define our case as one of over adoption. (Denis et al., 2002) [3]

The Department of Health's statement that the funding decisions of trastuzumab should not be based on cost arguments solely, but should consider the individual circumstances, recalls the intense public pressure the health system had to face in this period. From a model perspective, that situation recalls rather the Abrahamson's paradox, where organizations are in search of "political efficiency" instead of "technical efficiency". According to it, a technically inefficient innovation which is supported by external groups will be adopted if the political costs of not conforming to external pressures will exceed the technical costs of adopting it. [2] In our case the political cost for a government would have been that of loosing popularity and for NICE of increased government scrutiny and pressure.

A coalition of actors with highly different backgrounds emerged to defend the fast adoption of trastuzumab. It was by a common reading of the associated risk and benefits and by sharing the same value judgements that the group of patients, advocacy associations, politicians and industry managed to break the reluctance of a system that was installed to be a guardian of evidence-based decisions.

During this period a series of Primary Care Trusts decided to fund trastuzumab based on the fact that other trusts decided to do so. It is the classical "fad perspective" from the Abrahamson model [2], where organizations unsure about the efficiency of the innovation are relying on prior decisions of similar organizations and thus are looking for legitimacy.

In the same period, a final judgement of an Appeal court together with some rulings of the Secretary of State for Health, made us look more closely at the "forced-selection perspective" from Abrahamson's diffusion model. [2]

Undoubtedly, the final decision of adoption and its speed was influenced by the high public profiles of the individual patient cases of "exceptional" nature.

The fact that various Primary Care Trusts funded at different times in that period the treatment based on the existence of "exceptional circumstances" tends to confirm the proposal by Denis et al. [3] according to which the process of diffusion is a matter of negotiation of this periphery - in our case regarding the economic decision and the indications of use.

In order to reach the conclusion that trastuzumab is an effective option in the treatment of the early-stage breast cancer, the adopting institution, the appraisal process and the innovation itself suffered a number of significant structural changes (see implications).
that were the result of intense negotiations, therefore the current trastuzumab adoption model moves closely to the political fluid model described by Maguire.[2]

10. CONCLUSIONS

Back to our research questions, we found that the context of the adoption process has changed and this change was the ferment of further process changes. The theories of rational models, being centered on the overwhelming role of the scientific evidence and on the decisive influencing power of adopting institutions are clearly of limited relevance. Today's context of adoption decisions is characterized by 1) increased quantity and quality of the information flow, 2) efficient informal networking that conveys education and information on public health issues, and 3) an increased number of participants conscious of their societal roles. With the diminishing role of the scientific evidence, the external financial, political and emotional pressures become the key decision factors. In this context, the trastuzumab adoption process was one of high fluidity, with multilocular decision making and of greatly accelerated speed. It was a dynamic process with multiple variables: place of decision making, number and influence of the various stakeholders. The nature of the innovation coupled with the set of values and goals of the players had the most important role in the final decision of the adoption.

The structure of the adoption process and the timelines suffered changes when the clash between the strong rational arguments and the value judgments based on moral and emotions occurred. The dynamic of those changes reflects and parallels the dynamic of the deep societal changes, therefore we believe for the future that there cannot be given adoption processes for long period of times, only a common frame of negotiation could be agreed upon.

Moreover, the adoption process of a health technology tends to be an ever rolling process, since once with wider uses, doctors and patients are tempted to seek utility of a treatment in other disease areas.

Today, a health care adoption system is required extreme elasticity – since at the moment of adoption it is not prepared to absorb the new innovation - see the costs of adoption of trastuzumab and the need to refuse other important cancer treatments in order to accommodate the budgetary changes. Under those circumstances the system leaves a continuous process of adaptation and the long term outcomes in terms of resource allocation of a specific adoption decision are difficult to predict on a strictly rational basis.

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12. ANNEX A

Chronology of trastuzumab adoption milestones.
Adapted from BMJ (Wells J, Cheong-Leen C. NICE appraisals should be everyone's business. BMJ 2007; 334:936-8) and Bulletin de Cancer (Buron C et all. Reflexion on innovation diffusion factors: the case of Herceptin. Bull Cancerr vol94, n3, mars 2007)

March 1998: FDA decides "fast track approval procedure" for trastuzumab. Development of a test for identification of patients eligible for trastuzumab therapy

July 1998: Presentation at ASCO of phase III clinical trial results showing trastuzumab in association with chemotherapy slows disease progression and increases tumour shrinkage in patients with metastatic breast cancer

September 1998: US FDA approval of use of trastuzumab in the treatment of metastatic breast cancer HER2 positive patients

August 1999: Switzerland becomes the first European country to approve the commercialization of trastuzumab

August 2000: EMEA approval of use of trastuzumab in the treatment of metastatic breast cancer HER2 positive patients

December 2000: Genenetech/Roche in collaboration with other industry cancer therapy leaders launch phase III clinical trials to evaluate the efficacy of trastuzumab in adjuvant treatment of the breast cancer

March 2002: NICE approves trastuzumab for metastatic breast cancer

August 2002: Genentech receives FDA approval to insert label information concerning the FISH test for detecting the breast cancer gene

May 2005: Abstracts of preliminary results from trials of trastuzumab in early breast cancer presented at American Society for Clinical Oncology conference

June 2005- October 2005: Various public actions from patients and patient associations against decisions of PCTs to refuse funding of treatment with trastuzumab.

September 2005: NICE announces a new approval process for life saving drugs, labeled Single Technology Appraisal

October 2005: Secretary of State for Health, Patricia Hewitt demands publicly a fast track NICE approval process for trastuzumab

October 2005: A few patients receive NHS funded treatment for early breast cancer as "exceptional" cases, some after high profile appeal actions

November 2005: Publication in NEJM of the final results of 3 trials evidencing an improvement on overall survival rates, disease free survival rates in Herceptin breast cancer treated patients in adjuvant setting

January –April 2006: Judicial action of Ann Marie Rogers against Swindon Primary Care Trust

February 2006: Roche applies for a European license for the drug to be used "for the treatment of patients with HER2 positive early breast cancer following surgery, chemotherapy . . . and radiotherapy (if applicable)"

June 2006: EMEA grants license for use in early breast cancer

June 2006: NICE publishes draft guidance on use in early stage breast cancer after a single technology appraisal for trastuzumab

July 2006: Newbury and Community Primary Care Trusts appeals against NICE draft guidance on the use of trastuzumab

August 2006: NICE rejects appeal and publishes final trastuzumab approval and guidance requiring NHS implementation within 3 months.[6]

13. ANNEX B

Timelines of the STA process. Guide to the Single Technology Appraisal Process. September 2006. Appendix B. Available at: http://www.nice.org.uk/page.aspx?o=STAprocessguide