Appeal against Final Appraisal Determination

**Multiple Technology Appraisal (MTA) - Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of TA86)**

This joint Appeal is submitted by [redacted], RCP registrar on behalf of the following organisations:

Patient organisations
Sarcoma UK
GIST Support UK
Rarer Cancers Foundation

Professional/medical organisations
Association of Cancer Physicians (ACP)
The Institute of Cancer Research (ICR)
NCRI (NCRI) Sarcoma Clinical Studies Group
Royal College of Physicians (RCP)
Royal College of Radiologists (RCR)
Joint Collegiate Council for Oncology (JCCO)

This appeal is on two grounds:

1. **The Institute has failed to act fairly.**

We believe that the draft FAD is unreasonable and represents an unfair use of process and breach of trust.

2. **The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted.**

We believe that key evidence has been discounted by a restrictively narrow Scope. As a consequence, the draft FAD offers unreasonable recommendations and conclusions.

The reasons for appeal are outlined below and take into account the background to this appraisal:

Establishing a Scope for the Appraisal

TA86 was published in 2004 and approved the use of imatinib for treating metatstatic and unresectable GIST, with certain limitations. At the time of this appraisal evidence was due to be published concerning the efficacy of the escalated dose (up to 800mg/d). The NICE Appraisal Committee at the time ruled that as this evidence had not been published it could not be considered. It was published shortly prior to the release of the FAD. The FAD for TA86 did however state that a review would occur in 2007:

*'9.2 The guidance on this technology will be reviewed in October 2007.'*

This new evidence was considered by the European Medicines Agency (EMEA) and the licence for imatinib for GIST was amended in August 2005 to include use of the escalated dose on failure of imatinib at standard dose.

Clinical practice, supported by research, has moved quickly in this disease. It is a rare disease and international studies are the only way of ensuring that clinical research can attain statistical significance. Even then the distribution of patients is such that prospective studies are not easy and retrospective series of the whole patient cohort or of sub-groups is the primary route forward.

The stated review of TA86 was not taken forward by NICE in 2007. Only following pressure from patient and professional organisations to NICE did the review of the appraisal take place.

An initial consultation took place in January 2008 (nb due to an acknowledged problem with the NICE database at the time, the RCP (which coordinates responses to NICE oncological appraisals for the NCRI/RCP/RCR/ACP/JCCO) did not receive this consultation request). Among the published responses to the expert submissions is the following:

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| Institute of Cancer Research | I am concerned that the timetable has slipped. I was one of the physicians involved in treating this disease who has been arguing strongly for the timetable to be brought forward, not delayed.<br>Since the original appraisal, for which I acted as a clinical advisor, a great deal has been published regarding dose, the consequences of discontinuing therapy, the impact of specific mutations on progression free survival and so on.<br>….(references)….<br>I feel that the above demonstrates quite clearly the need for an urgent review of the original appraisal, which is now totally out of date and in some respects out of step with clinical practice world wide. | Comments and highlighted studies noted. After taking these comments into consideration, particularly with regard to the availability of, and new evidence relating to, the 800 mg dose of imatinib, we consider it appropriate to proceed with the review of guidance TA86. |

The response from NICE clearly acknowledged the existence of new evidence, and gave information that a full review of TA86 was intended. A draft Scope for the review Appraisal was then published in July 2009. It contained the following stated objective, which was open to consultation:

**Appraisal objective**

To appraise the clinical and cost effectiveness of imatinib within its licensed indication for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours which have progressed on treatment at a dose of 400 mg/day.

This was not a full review, as promised. No indication was given as to why only a narrow sub-set of a complex clinical situation was selected. Both the patient and professional communities understand that the clinical situation described in the Scope is complex, individual to each patient, requires comprehension of their disease/treatment pathway, and requires expertise to ensure that each patient is appropriately treated. In this circumstance it was not considered that a review could be meaningful without looking at the treatment of the disease from beginning to end and various aspects of the pathway were explored in responses to the Scope consultation:

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| **UK, Rarer Cancers Forum, Sarcoma UK Submitted on behalf of the responders by SarcomaUK** | However for one group of patients, those with an Exon 9 mutation in c-Kit, there is now good evidence that escalating to a dose of 800mg/d during the first few months of treatment delays the development of resistance. This may apply to the Exon 11 group too as it is apparent that some patients receiving 800mg day (regardless of mutation status) achieve long term disease free survival (>7 years). This is a small group of patients who were randomised to 800mg per day in the Phase 3 trials starting in 2001. | Comment noted. If the evidence allows, subgroup analysis by mutational type will be considered and any costs associated with subtyping should be included in the economic analysis. See under 'other considerations' in the final scope |
| **NCRI/RCP/RCR/ACP/JCCO** | At the time of the first STA on imatinib for the treatment of GIST it was already known that there was a progression-free survival advantage for imaitnib 800 mg daily compared with 400 mg, albeit the full paper had not been published. It is now well established that patients with exon 9 mutations in KIT experience superior progression-free survival on imatinib 800 mg daily and are more likely to respond to the higher dose. The combined data from 1640 patients treated in both the European and North American trials have been used to confirm this finding. These patients were also more likely to benefit from sunitinib in the registration trial but this was apparently because these patients had progressed quickly on imatinib and were much less likely to have developed secondary mutations capable of conferring resistance both to imatinib and sunitinib.<br>The other group of patients requiring specific attention are those with no identifiable mutations in KIT or PDGFRA, i.e. so-called "wild-type" disease. This most commonly occurs in young women, often presenting with profound anaemia and multifocal disease arising initially in the stomach. Limited clinical experience and laboratory data appear to demonstrate that sunitinib is a superior agent compared with imatinib in this patient population. | Comment noted. If the evidence allows, subgroup analysis by mutational type will be considered and any costs associated with subtyping should be included in the economic analysis. See under 'other considerations' in the final scope |

These submissions made it clear that the respondents were making the assumption that in order to achieve the appraisal objective a full consideration of the clinical pathway and the applicability of imatinib was necessary. We believe that the NICE response, using the phrase 'if the evidence allows…' is significant.

The final Scope was then published in August 2009. The Appraisal objective was unchanged from the draft.

The ‘other considerations’ referred to in the responses above made clear the approach that was being taken.

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| **Other considerations**<br>Guidance will only be issued in accordance with the marketing authorisation.<br>If evidence allows, subgroup analysis by mutational type will be considered and any costs associated with subtyping should be included in the economic analysis. |

We believe that this was wholly misleading. The marketing authorisation only permits dose escalation on relapse after taking standard dose imatinib. The evidence for dose escalation by mutational sub-type, rather than purely on relapse, is contained in a meta-analysis of the three largest clinical studies which, under NICE rules of evidence, was disallowed by the Evidence Review Group because; ‘*No/insufficient data for escalated dose patients’.*

NICE is a public body charged with meeting the needs of the NHS, its patients and the wider public. We believe that the above description of fact establishes:

1. A failure to keep an explicit promise regarding TA86
2. A failure to keep an implied promise (2008 consultation)
3. A failure to explicitly communicate at the time of the Draft Scope the limited nature of the proposed review
4. Passing off a disallowable item of evidence as acceptable in order to placate responders.

The Appraisal conclusions are unreasonable because of the inadequate scope. We believe that the Institute has failed to act fairly in that there has been a repeated ‘breach of trust’ compounded by inadequate process.

## Choice of Technology Comparator

NICE processes require comparison between existing and new technologies to arrive at the ICER which provides the economic argument for acceptance of the new technology. This is a core requirement and the choice of comparison is always important.

The Draft Scope put forward the following comparisons:

- the strategies of continued dose and escalated dose imatinib will be compared with each other
- sunitinib
- best supportive care

In response to the Draft Scope the following responses were among those considered:

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| **NCRI/RCP/RCR/ ACP/JCCO** | The biggest problem with attempting to compare higher dose imatinib with sunitinib in GIST that is refractory to imatinib 400 mg daily is the lack of direct comparative data. A clinical trial is underway to address this. However, what is often difficult to determine from such studies is the survival advantage to be derived from sequential effective treatments. | Comment noted. No action required. |

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| **Health Services Research Unit/Health Economics Research unit, University of Aberdeen** | One of our clinical advisers commented that the key comparison for clinicians will be dose escalation of Imatinib versus Sunitinib following first line failure on lower dose Imatinib. Appropriate that best supportive care is also included as a comparator. There are no other comparators that should be included. | Comment noted. Scope amended accordingly. |

The final Scope for the Appraisal contained the following comparators:

- sunitinib
- best supportive care

The two responses above are significant.

The first was provided by expert clinicians with extensive experience of treating GIST. Many of them are research authors, including first authors, on GIST related studies. They are also members of specialist sarcoma MDTs, acting as a referral point for other doctors treating GIST, and members of the NCRI Clinical Studies Group for Sarcoma which sits at the heart of the initiation and peer review of clinical trials. Their views were supported and submitted jointly on behalf of major professional organisations and patient groups.

The second was submitted by the Economic Review Group selected by NICE to undertake the review for this appraisal. As far as we are aware, the clinical adviser has not been an investigator on any of the international clinical studies in GIST, nor published papers on the subject.

We believe that it is unreasonable that NICE chose to favour the latter submission. NICE was given the authoritative opinion that there was no valid comparator data, as was confirmed during the Appraisal, and yet chose to disregard this. In favouring advice from its own contractor we believe that NICE has acted unreasonably. It represents an unfair use of process.

We would additionally comment that, on this occasion, the way NICE reviewed the commentator input on the draft Scope was not transparent. We believe that where clinical opinions differ it is reasonable for a third specialist opinion to be sought. There is no evidence that this was undertaken. As a result we have concerns that the decision to select the Aberdeen submission may have been made administratively. If this is the case, it would further support this appeal.

## Fairness to Consultees and Expert Witnesses

Para 4.3.3 of the FAD contains the following:

*'The Committee noted that consultees had requested the review based on the belief that a large amount of clinical evidence about imatinib had been published since 2004. The Committee further noted that during the scoping process for this review consultees and commentators for this appraisal were given another opportunity to comment on the appropriateness of this review. The Committee was reminded that, at the time of the review proposal, the manufacturer of imatinib was seeking to extend the marketing authorisation for 800 mg/day imatinib for unresectable and/or metastatic GISTs and that the manufacturer supported the review going ahead. However, in their submission and*

*during the Committee meeting, the manufacturer stated that no new evidence had emerged since 2004 on the effectiveness of increased doses of imatinib after disease progression on 400 mg/day imatinib.'*

The consultee belief that there was a large amount of new clinical evidence remains true. Critically important is that evidence published late in 2004 was notified to the committee when TA86 was in preparation. As mentioned previously, consideration was refused as the data was at that time unpublished. In addition, there is the meta-GIST study. This was discounted by the ERG owing to the narrow scope and the interpretation it placed on that. It is the very strong view of our experts that this is a significant study and has influenced worldwide clinical practice. The statement contained in the above abstract of the FAD is thus untrue. The importance of this evidence was once again notified to NICE in the response to the ACD but the consultees' comments were not reported to the second appraisal hearing.

Given that there was:

- a clear statement from NICE in 2004 that a full review would take place in 2007
- an acknowledgement from NICE that the review was appropriate in 2008, with the recognition that there was new evidence to support a full review

We believe that the submission of the draft scope was open to misinterpretation. There was no account of this history when senior NICE staff made their statement to the Committee. No consultee, or expert witness, was invited to that meeting (other than as a member of the public) so the statement could not be challenged.