NICE Consultation on Proposed Changes to the Technology Appraisal Programme Phase 2

Views from Costello Medical

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Introduction

In October 2017, NICE consulted on amendments to the current technology appraisal process. The aim of the proposals was to generate capacity to increase the number of topics processed through the current four appraisal committees to 75 appraisals per year.

Since then, many stakeholders, including industry, academia and Appraisal Committee members, have provided comments on the proposed amendments. Having reviewed these comments, NICE have updated their proposed changes to the technology appraisal process and provided a draft version of a new process guide. This updated process guide is now out for consultation until **5pm 1st March 2018**. The new guide presents a number of changes to NICE's processes that we believe will have important impacts for submitting manufacturers. This commentary presents our views on the key changes.

The Impact of NICE's New Proposed Timelines

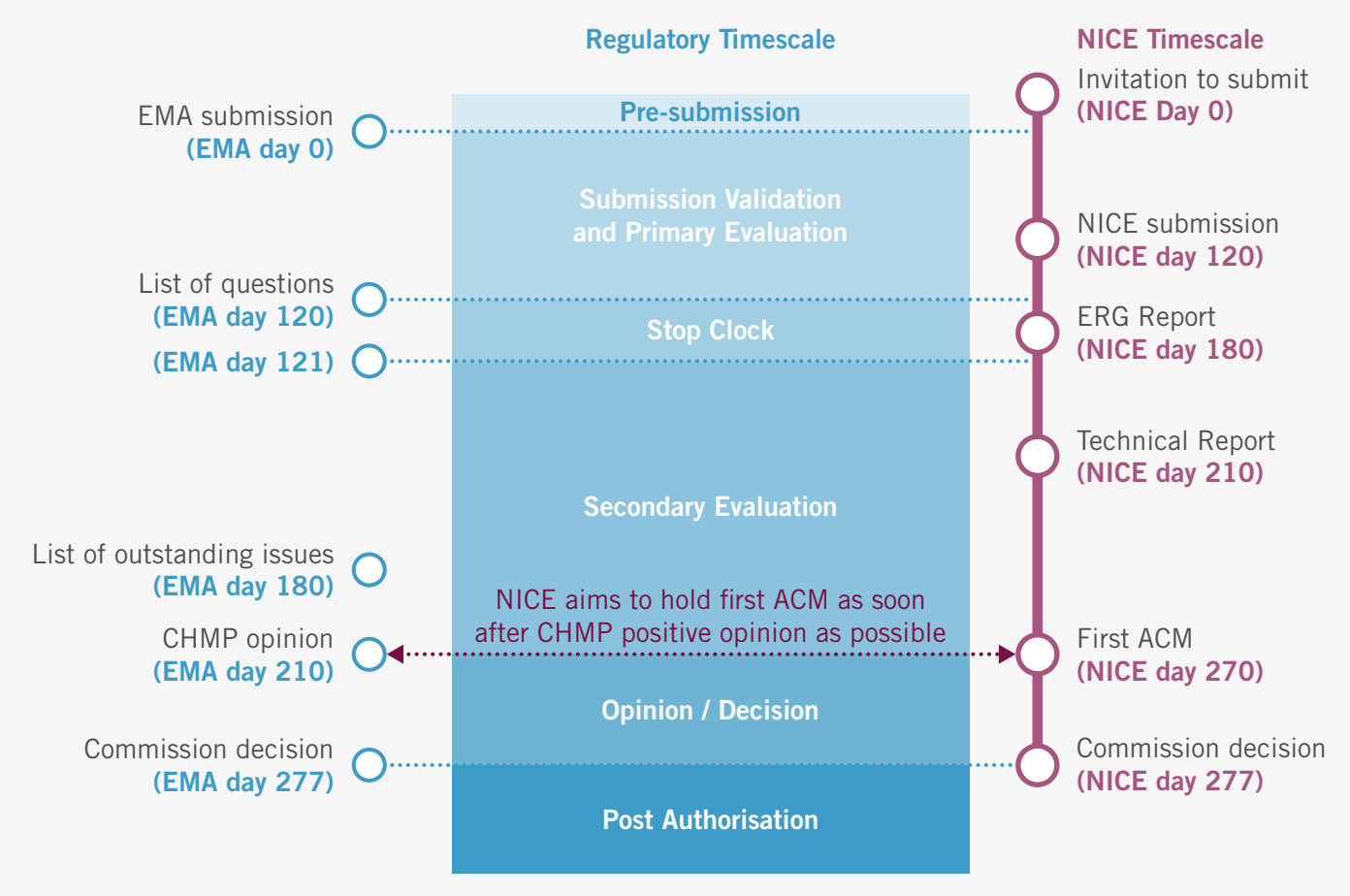
NICE have proposed new processes that target NICE guidance within 90 days of marketing authorisation for all appraised products. As per the current process, NICE aim to hold the first Appraisal Committee meeting as soon as possible after a positive Committee for Medicinal Products for Human Use (CHMP) opinion has been obtained, or the equivalent from the Medicines and Healthcare products Regulatory Agency (MHRA).

However, extensions to the timelines between submission and first Appraisal Committee meeting (currently ~84 days; proposed 150 days) and between invitation to submit and submission date (currently ~63 days; proposed 120 days) mean that the date of submission to NICE is likely to fall considerably earlier in the regulatory process. The timelines for a technology to receive regulatory approval from the European Medicines Agency (EMA) are presented in Figure 1, alongside how the proposed NICE process fits with these. Interestingly, NICE have proposed that an ACD or FAD may be published prior to regulatory approval, although final guidance would only be given after final regulatory approval.

In our view, the proposed timelines have a number of key implications for submitting manufacturers:

- Manufacturers may potentially face considerably more uncertainty around their licence at the time of developing their NICE submission, which could have knock-on effects for the scope and decision problem addressed in the technology appraisal. In our experience, population wording and the licensed dose are key factors that can often change over the course of regulatory discussion and that may therefore generate uncertainty for the NICE submission. Regulatory uncertainty also has the potential to increase the risk of delays or withdrawals of company submissions to NICE, and pose difficulties for scheduling of workflow on the part of the manufacturer and NICE. Efficient development of the NICE submission dossier will potentially require more flexible thinking as to which sections of the template can be completed at an earlier stage and which sections are simply too vulnerable to extensive changes.
- Cost-effectiveness models, systematic literature reviews and indirect treatment comparisons will need to be developed early relative to the regulatory process (with implications for data availability issues – see below) and models will need to be developed with the flexibility to adapt for potential changes throughout the NICE process. Where pricing decisions are informed by cost-effectiveness modelling, will Pharma companies feel comfortable to take these decisions at an earlier stage relative to knowing the final licence of their product than they currently do?
- Data availability to inform the submission and the model development will be a key issue for Pharma to resolve. Strict internal data sharing policies can sometimes limit availability of data to affiliates until certain regulatory milestones are reached. Will Global functions be prepared to provide the necessary data to UK affiliates at an earlier stage of the regulatory process, or else accept that a greater burden of the evidence generation for NICE submissions will fall on them? The alternative of simply seeking to shorten the timeframe over which the NICE submission is assembled would not seem to represent a viable option without sacrificing submission quality. Similarly, where post-hoc analyses of trial data (e.g. specific subgroups) are required to address the specific UK context, will central statistical functions at Pharma companies have the capacity to handle such requests whilst simultaneously dealing with responses to the EMA as part of the regulatory process?

Figure 1: Overview of EMA regulatory approval timelines alongside the proposed NICE appraisal timelines



This figure illustrates how milestones in the NICE process would fall against milestones in the regulatory process assuming a 0 day stop-clock at Day 120 and based on NICE's aim to tie the first ACM to CHMP positive opinion. ACM: Appraisal Committee meeting; CHMP Committee for Medicinal Products for Human Use; ERG: Evidence Review Group; EMA: European Medicines Agency; NICE: National Institute for Health and Care Excellence.

Concerns Over Confidentiality

The draft NICE process guide appears to aim for reductions in the amount of information considered confidential in manufacturer submissions and push for increasing public availability of all information relevant to the ultimate decision – manufacturers should be prepared to be pushed hard by NICE on this point. In general, we view moves towards increased transparency as a positive step for good scientific practice and ultimately beneficial in allowing robust assessment of cost-effectiveness of future novel therapies. However, there are legitimate reasons why some data in NICE submissions need to remain confidential, in terms of protecting both commercial interests and integrity of future academic publications. NICE propose that all information marked as confidential, except confidential patient access schemes (PASs) or commercial access arrangements, will be released to consultees and commentators – this includes competitor manufacturers. This raises some concern for the protection of clinical data confidentiality prior to publication.

The NICE process guide also states that Evidence Review Groups (ERGs) will incorporate comparator PAS discounts in a confidential appendix, but that an incremental cost-effectiveness ratio (ICER) range that uses the comparator discount will be made publicly available. Unless the ICER ranges provided are wide enough as to be meaningless, we envisage that it will be very difficult for NICE to take this approach without implicitly revealing the comparator PAS to a reasonable degree of accuracy if analyses using the comparator at list price are available in the manufacturer submission. To avoid this, we would expect to see NICE issue strict and clear guidance to submitting manufacturers on the information that must be marked as confidential in their submission

in order to protect the comparator PAS (i.e. ICERs using the comparator at list price). Without such guidance (and perhaps even with it), protection of the comparator PAS relies on a diligent submitting manufacturer and ultimately places a considerable onus on the comparator manufacturer (acting as a commentator) to be pro-active in thoroughly checking the submitting manufacturer's submission. Furthermore, it is unclear when in the process the range of ICERs for the comparator at PAS price will be published. If this is as part of the technical report, and therefore at the same time as the manufacturer submission, then it is feasible that combinations of ICERs that allow the comparator PAS to be calculated could be circulated before the comparator manufacturer has had an opportunity to perform this safeguard check. If this is the process, are NICE offering to guarantee a check of this themselves prior to circulation of the technical report? We believe more clarity over this process is needed to reassure manufacturers.

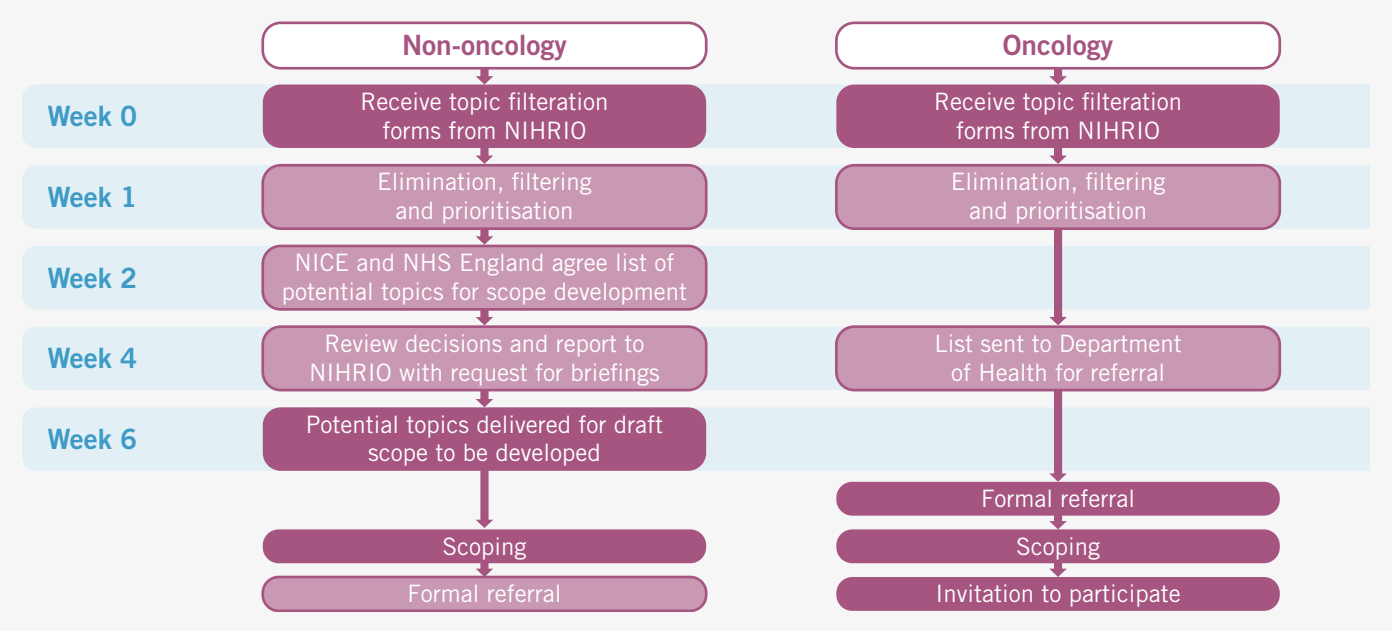
A Risk to the Timely Appraisal of Non-Oncology Therapies?

In the proposed changes to technology appraisals, NICE have indicated that all oncology technologies will be referred for assessment, with scoping to follow the early referral of oncology indications. Non-oncology technologies will go through a more involved process, including scoping prior to formal referral. The latter process is slightly longer and includes four different points at which decisions will be made about whether the technology will be appraised **(Figure 2)**. For oncology technologies there will be two points for decisions.

Does This Differential Approach Present a Risk to The Timely Appraisal of Non-oncology Technologies?

The new NICE process guide states that appraisals are scheduled into NICE's work programme **on formal referral**, and the dual process would therefore appear to have the potential to create situations where oncology appraisals (of which NICE acknowledge there are expected to be many) are rapidly (and somewhat automatically) planned into NICE's workflow, committing NICE capacity, whilst non-oncology appraisals are caught in a slower process. NICE aim for their new processes to increase their capacity generally, which should circumvent this issue. However, if the idealised capacity gains are not achieved and this poses a risk to NICE's aim to achieve guidance within 90 days of marketing authorisation for all appraisals, the differential

Figure 2: Overview of topic selection stages for non-oncology and oncology topics, including the decision points



■ denotes stage when a decision is made on whether the technology continues in the appraisal process. Abbreviations: NICE: National Institute for Health and Care Excellence; NIHRIO: National Institute for Health Research Innovation Observatory; NHS: National Health Service.

processes outlined above would appear to have the potential to place this risk disproportionately on non-oncology technology appraisals. NICE may need to be prepared to demonstrate flexibility in their application of the processes and their scheduling to mitigate against this. A parallel with the Scottish Medicines Consortium's (SMC) Patient and Clinician Engagement (PACE) process springs to mind; lately the SMC have been operating a programme of deferrals on the basis of capacity constraints, with priority given to PACE candidates (and therefore disproportionately oncology therapies). Timely appraisal of non-oncology products has suffered in this case.

Introduction of the Technical Team

NICE have recommended the introduction of a technical team. This team will form scientific and technical judgements on the manufacturer submission and ERG report and summarise these judgements in a technical report, on which stakeholders have the opportunity to consult. This aims to allow scientific and technical judgements on the submission and economic model to be consulted on and reached prior to the Appraisal Committee meeting, which NICE hope will allow the Appraisal Committee to discuss a more "final" proposition and negate the need for a second Committee meeting for the majority of appraisals. Committee meetings should be more streamlined as a result of this. We believe this has the potential to represent a positive step, as it should reduce the need for manufacturers to "second-guess" NICE's likely judgements on the key technical approaches and assumptions made by themselves and the ERG in advance of the Committee meeting. The ultimate aim of hopefully providing a mechanism for faster patient access through reducing the number of Committee meetings is also a desirable goal.

Based on our experience of involvement in decision problem meetings, discussions on ERG clarification questions and NICE Appraisal Committee meetings, the success of this new approach will be heavily dependent on how constructively parties on all sides approach the technical engagement. This means:

- Willingness from manufacturers to engage with the process and seriously consider the judgements and requests from the technical team, which in theory aim to pre-empt ultimate Committee opinion. If requested changes are not followed through by manufacturers prior to the Committee meeting, then this would likely result in a technology not being recommended, particularly considering the concurrent changes to limit submission of new evidence after the Committee meeting.
- Manufacturers will need to be comprehensive in their provision of data and analyses in their submission in order to limit the likelihood of extensive requests by the technical project team, or else accept that the period of engagement with the NICE technical team post-submission could represent an intense step in the process.
- Under the current process, the first 'signal' received by manufacturers as to the challenges to their submitted approach is the ERG report. From this point, manufacturers have three weeks prior to the Committee meeting to be considering what analyses may be necessary, and then the period following the Committee meeting and until the 20 working day consultation on the ACD ends in which to prepare any analyses required to address potential Committee concerns. Under the new process, new evidence will not be accepted after the Appraisal Committee meeting (unless specifically requested by the Committee) and the first 'signal' received by the manufacturer as to the challenges to their submitted approach is the technical report. Manufacturers have only 20 working days to respond to this, including submitting any new evidence analyses. As we see it, the new process therefore gives manufacturers considerably less time from receipt of the first 'signal' from the ERG/NICE until the deadline for providing any final evidence. Manufacturers will therefore need to be prepared for this; not least by making the most of the opportunities for engagement with the technical team that NICE now offer during submission preparation. On NICE's side, they would likely argue that they still offer 20 working days for consultation on preliminary judgements. However, this would not acknowledge that the new process removes the time that manufacturers currently have post-ERG report and pre-ACD consultation to start to prepare the data they may need for their response based on early signals from the ERG. Should the NICE technical team envisage that their report will generate a need for an involved response from the manufacturer, we would hope that there would be a level of pragmatism in forewarning manufacturers of this so that they have an opportunity to respond in an evidence-based manner under reasonable time constraints.

Summary

- The proposed changes to the NICE technology appraisal process should increase the capacity of NICE and provide a number of potentially valuable opportunities for increased engagement with NICE throughout the appraisal process.
- The earlier timing of the NICE submission deadline relative to regulatory timelines is likely to provoke the need for considerable changes in how Pharma approach submissions, in particular with regards to efficiently managing the increased uncertainty around submission development. UK affiliates and Global functions will need to work together to develop solutions regarding data availability, earlier development of the evidence base and earlier decision-making (e.g. regarding positioning and pricing).
- More reassurance from NICE is warranted in terms of how the proposed alterations to handling of confidential data will guarantee protection of data that does legitimately need to remain confidential in nature.
- The differential referral processes for oncology and non-oncology therapies would appear to have the potential to bias the commitment of NICE capacity in favour of oncology appraisals in the event that NICE's capacity-increasing aims are not fully realised.
- In so far as the ERG report currently provides a useful 'signal' as to the further evidence manufacturers may need to generate, the new process would seem to restrict the time available to manufacturers for this evidence generation.

Costello Medical

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Further Assistance

Costello Medical has worked on over 80 HTA submissions and almost 40 NICE submissions, and our HTA and Health Economics division specialises in the delivery of these projects to the highest quality. This experience has helped inform the opinions summarised in this commentary. If you would like any further information or to discuss this commentary further, please do not hesitate to contact Matt Griffiths at: matt.griffiths@costellomedical.com.

