NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Review Proposal Project (RPP) decision paper

Review of TA187; Infliximab and adalimumab for the treatment of Crohn's disease

Final recommendation post consultation
The guidance will remain on the static list and the recommendations will be incorporated into the forthcoming clinical guideline.
Rationale
Stakeholders have indicated that they do not consider an update of TA187 within the forthcoming clinical guideline to be appropriate as any such update would have led to the funding direction for infliximab and adalimumab mandated in TA187 being removed. After further consideration in discussion with the developer, it has been agreed that the partial update of CG152 (Crohn's disease management) will incorporate the recommendations from TA187, thus preserving the funding direction.

1. Background

This guidance was issued in May 2010.

At the Guidance Executive meeting of 26 June 2017 it was agreed that we would consult on the recommendations made in the GE proposal paper. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

The guidance should be updated in an on-going clinical guideline. That we consult on this proposal.

3. Rationale for selecting this proposal

TA187 was added to the static list in March 2011. In March 2015 the Institute considered the available evidence and decided that the guidance should remain on the static list as no new robust new evidence was available that would be likely to lead to a change in the existing recommendations.
The Institute is now proposing to undertake a partial update of the clinical guideline on Crohn's disease management (CG152). During surveillance a considerable amount of evidence was identified which assessed the efficacy of anti-TNF therapy for maintenance of remission of Crohn's disease after surgery.

Currently TA187 does not provide any recommendations for anti-TNF therapy for maintenance of remission of Crohn's disease after surgery. The update to CG152 provides an appropriate context for these recommendations to be made, especially

as the recommendations can then be placed into wider context within clinical practice.

Subsequently, it is recommended that the recommendations made in TA187 should be updated in the upcoming partial update of the clinical guideline CG152. Upon the publication of the new clinical guideline, TA187 will be superseded and the guidance withdrawn.

4. Summary of consultee and commentator responses

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Respondent: Almirall Ltd **Response to proposal:** No comment	**Comment from Technology Appraisals** -

Respondent: Amgen **Response to proposal:** Agree AMGEN are supportive of the approach that the guidance should be updated in the forthcoming partial update of clinical guideline CG152, assuming that the guideline update reflects in its entirety the availability of licensed biologics for appropriate treatment of Crohn's disease.	**Comment from Technology Appraisals** Comment noted. Following stakeholder feedback and further consideration in discussion with the developer, the Institute has decided that the recommendations from TA187 should be incorporated in the forthcoming clinical guideline.

Respondent: Abbvie UK **Response to proposal:** Disagree Abbvie would like confirmation that the withdrawal of TA187 would coincide with the publication of new Technology appraisal guidance (TAG) which includes the guidance for the use of adalimumab and infliximab currently contained within TA187. Abbvie would only support the withdrawal of TA187 if this is the intention. This is necessary to guarantee the mandatory funding for the use of adalimumab and infliximab in line with the TA187 guidance since such funding is associated with TAGs but not with Clinical Guidelines. Secondly, Abbvie would suggest that the paediatrics extension to the adalimumab licence to treat Crohn's Disease which was granted after the publication of TA187 should be incorporated into the new Technology appraisal guidance issued to coincide with the withdrawal of TA187. This would ensure availability to licenced biologic therapy options for children with Crohn's disease for which conventional therapies have failed. Infliximab was included within TA187 for this patient group.	**Comment from Technology Appraisals** Comments noted. Following stakeholder feedback and further consideration in discussion with the developer, the Institute has decided that the recommendations from TA187 should be incorporated in the forthcoming clinical guideline.

Respondent: MSD **Response to proposal:** No comment We welcome the addition of guidance on the use TNF-alpha inhibitors after surgery, due to the high volume of literature available; however we do not endorse the use of infliximab in this population. We have no comments on the proposal paper, but for your information we have included the literature for the main study concerning infliximab for crohn's disease. [1] Stephen B Hanauer, Brian G Feagan, Gary R Lichtenstein, Lloyd F Mayer, S Schreiber, Jean Frederic Colombel, Daniel Rachmilewitz, Douglas C Wolf, Allan Olson, Weihang Bao, Paul Rutgeerts. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial, The Lancet, Volume 359, Issue 9317, 2002, Pages 1541-1549, ISSN 0140-6736, http://dx.doi.org/10.1016/S0140-6736(02)08512-4.	**Comment from Technology Appraisals** Comment noted.

Respondent: The British Society of Gastroenterology **Response to proposal:** The incorporation of TA187 into CG152 is appropriate and should include discussion of the areas outlined below. **Anti-TNF and thiopurine therapy post-surgery** A pivotal study regarding this issue is the POCER trial that identified a group of post-surgical patients that were at high risk of progression as determined by colonoscopy/faecal calprotectin assessment. Those treated actively with azathioprine, escalating to adalimumab on the basis of colonoscopy at six months, had reduced endoscopic relapse at 18 months. There was no evidence presented regarding progression to a further requirement for intestinal surgery. The TOPPIC study regarding the use of thiopurines post-surgically showed that mercaptopurine therapy prevents clinical disease recurrence, but only in those continuing to smoke cigarettes. References De Cruz et al. Lancet 2015;385:1406 (POCER trial) De Cruz et al. APT 2015;42:867 (POCER trial) Jones et al. APT 2014;39:1253 (systematic review) Mowat et al Lancet Gastroenterol Hepatol 2016;1:273 (TOPPIC trial) **Biologic withdrawal** The timing and appropriateness of anti-TNF withdrawal needs consideration in updated CG152 guidelines. Evidence from STORI study suggests only individuals in deep remission should be considered for withdrawal. The role of faecal calprotectin measurement in this respect needs further evaluation. A recent systematic review has suggested 50% of patients withdrawn from antiTNFs will remain in remission after 2 years but the proportion in remission will decrease with time. References Louis et al. Gastroenterology 2012;142:63 (STORI study) Torres et al Gastroenterology 2015;149:1716 (Systematic review) **Biosimilars** The role of biosimilar infliximab needs to be emphasised in controlling costs. The recent	**Comment from Technology Appraisals** Comments noted. Following stakeholder feedback and further consideration in discussion with the developer, the Institute has decided that the recommendations from TA187 should be incorporated in the forthcoming clinical guideline.

NORSWITCH study reveals equivalence compare with originator drug.[e-publication August 2017 Lancet] **Co-prescribing of anti-TNF with immunomodulators and other biologics.** The need for and appropriateness of co-prescribing of thiopurines with antiTNFs is an important area to address in the review of guidance. The evidence for higher remission rates for infliximab in combination with thiopurines has been shown in treatment-naïve patients (SONIC study). There is also evidence for benefits in systematic reviews and metanalysis for infliximab with thiopurines. Evidence for combination therapy of adalimumab and thiopurines is much weaker, and cannot be recommended. **Therapeutic drug monitoring (TDM)** Whilst the quality of data regarding TDM of antiTNFs was not considered high in the NICE TA on this topic the use of TDM has been adopted widely in routine clinical practice. The revised guideline should include a discussion of the TDM in the management of patients with Crohn's disease on antiTNFs, with a number of studies clarifying the cost-savings and clinical benefits of drug level and antidrug antibody measurement in directing therapy choices in patients with secondary loss of response to infliximab or adalimumab. **Paediatrics** Special consideration with respect to children should be incorporated in guidance notably the role of liquid enteral diet. The guidance should include recommendations on use of adalimumab for induction of remission in children with moderate to severe active Crohn's disease. (Now licensed for use in children)	

Respondent: Crohn's and Colitis UK **Response to proposal:** Disagree We recognise the value of incorporating new evidence into the process for the partial update of the clinical guideline. However, we cannot support the withdrawal of the technology appraisal on the basis that this would lose both the funding direction for the NHS and a significant patient right enshrined in the NHS Constitution. "The NHS is legally obliged to fund and resource medicines and treatments recommended by NICE's technology appraisals. The NHS Constitution states that patients have the right to drugs and treatments that have been recommended by NICE for use in the NHS, if their doctor believes they are clinically appropriate." (NICE website) The impact of Crohn's Disease on all aspects of an individual's life can be profound due to its relapsing and remitting nature, the fact that it can occur anywhere in the gastrointestinal tract and the effect of various treatment options, including surgery. The stigma attached to the symptoms involved make it difficult for people to talk about even with those closest to them, which can serve to isolate people and lead to anxiety and depression. With the peak diagnosis period being the teens and twenties, these factors are even more challenging to deal with. We have highlighted below some personal stories, which serve to illustrate this. *"Crohn's Disease is an incurable and relapsing condition, which blights my life. I am an experienced professional teacher and a trustee of a local charity but my ability to contribute to my community, to wider society, and to pay my taxes, is limited by the impact of the disease. It forces me to work part-time when I would otherwise work full-time and I have regular episodes of sick-leave, roughly every 12-18 months. The latest period of sick-leave will last six weeks, which is a burden on my employers. The impact on my family and social life is huge. I haven't been able to travel abroad for over two years."* *"I'm an active divorced 60 year old woman now who feels the impact of my symptoms have precluded me from having a regular social life and finding a partner. On the surface I'm a confident outgoing woman but emotionally I'm crying inside and feel completely isolated. I work full-time, my employers are aware of*	**Comment from Technology Appraisals** Comment noted. Following stakeholder feedback and further consideration in discussion with the developer, the Institute has decided that the recommendations from TA187 should be incorporated in the forthcoming clinical guideline.

my condition and are tolerant. I still travel but with all of my fingers and toes crossed and exercise as much as I can. I gave up my gym membership because my symptoms include constant flatulence, which is embarrassing beyond words but not to be beaten, I walk outdoors on my own instead to clock up my 10,000 steps a day. This terrible disease has robbed me of my life in many ways and at times I have felt living on into my even older age is pointless, but my saving grace is that I have three boys whom I want to see marry and be happy. I'd hate for any of them to be diagnosed with this disease but am aware it may be a possibility. Nobody truly understands what it's like to have Crohn's unless they themselves are patients. My friends can't comprehend why a 'woman like me never remarried'. It's easy, I'm too embarrassed to even contemplate sharing a house with a man. The psychological effects keep me in like a hermit crab at the weekends." Increased use of biologics for Crohn's Disease, supported by TA187, has been a major development in the treatment of IBD and positively life-transforming for some patients with Crohn's Disease. Biologics are high cost therapies, the value of which has been more widely recognised over the last decade, with greater familiarity through use in clinical practice and additional research. Biosimilars are now being produced for both infliximab and adalimumab and newer biologics, such as vedolizumab and ustekimumab offer important additional treatment options for patients and clinicians in the battle to control Crohn's Disease and restore quality of life to patients. Nonetheless, within the context of an NHS focused on resource limitations and cost-savings, there is considerable scrutiny by managers and commissioners over the use of these drugs. Technology appraisals confer a highly significant right to treatment where this has been determined to be the most appropriate option by a clinician. Consequently, while we support the incorporation of more recent evidence for the use of infliximab and adalimumab into the update to the clinical guideline, we could not support the withdrawal of the technology appraisal and associated funding direction as part of this process. Instead, we would advocate some means of updating the technology appraisal alongside the guideline update in order to prevent any erosion of existing patient rights to treatments which have been	

determined by NICE to be both clinically and cost-effective. This would also serve to maintain a level playing field in terms of status, in relation to the newer biologics, which have been subject to more recent appraisal. We would look forward to the opportunity to contributing further and to acting as a conduit for the experiences and input of people with IBD throughout the review process.	

Respondent: CiCRA - the specialist charity for children and young adults with crohns and colitis **Response to proposal:** Agree Further to your review and based on advice from the chair of our medical advisory panel, we support the updating of TA187 by NICE to include indications following surgery. We support NICE convening a committee to help gather evidence on the use of influximab and adalimumab to prevent relapse after surgery.	**Comment from Technology Appraisals** Comment noted. Following stakeholder feedback and further consideration in discussion with the developer, the Institute has decided that the recommendations from TA187 should be incorporated in the forthcoming clinical guideline.

Paper signed off by: Meindert Boysen, 15 February 2018

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