National Institute for Health and Care Excellence

Medical technologies evaluation programme

MT539 3C Patch System for treating diabetic foot ulcers

Consultation comments table

Final guidance MTAC date: 15th October 2021

There were 80 consultation comments from 12 consultees

The comments are reproduced in full, arranged in the following groups:

- Recommendations (comments 1-4, n=4)
- Patient Population (comments 5-10, n=6)
- Treatment Setting (comments 11-17, n=7)
- Clinical Evidence (comments 18-21, n=4)
- Stopping Rule (comments 22-33, n=12)
- Wound Size Measurement (comments 34-38, n=5)
- Treatment Timescale (comments 39-43, n=5)
- UrgoStart Use (comments 44-46, n=3)
- Economic Model (comments 47-62, n=16)
- Further Research (comments 63-67, n=5)
- General comments (comments 68-80, n=13)

#	Consultee ID	Role	Section	Comments	NICE response
Recommendations					
1	2	Healthcare Professional	General	*Are the recommendations sound and a suitable basis for guidance to the NHS?* I feel that the Leucopatch is a useful addition to the few evidence-based therapies that we have for DFU treatment - and should be supported by NICE	Thank you for your comment. The committee acknowledged that for some people 3C Patch might fulfil an unmet need in diabetic foot ulcer care. However the committee also heard from clinical experts that currently it is unclear who these patients will be. This in combination with the generalisability issues from the main RCT, and the uncertainty around the cost saving led the committee to decide not to change the recommendations.
2	7	Healthcare Professional	General	*Are the recommendations sound and a suitable basis for guidance to the NHS?* If the devise is being used by an experienced clinician then I think the recommendation to use the 3C patch should be adopted	Thank you for your comment. The committee acknowledged that 3C Patch would be used in a multidisciplinary diabetic foot ulcer clinic by people who are appropriate trained in using the 3C Patch system. Please also see additional response to comment 1. However, they decided the recommendation should remain unchanged.
3	9	Company	General	*Are the recommendations sound and a suitable basis for guidance to the NHS?* The company does not believe that the recommendations are sound, nor that they are a suitable basis for guidance to the NHS. The recommendations are based on the findings of the EAC model, which the company believes to be deeply flawed. The company has previously set out detailed criticisms of this model and does not believe these have been adequately addressed. Given the gravity of these issues, this model should not be used as a basis for guidance or recommendations without an independent health economic opinion on the detailed criticisms presented by the company. It will be important for this expert to consider the combined impact of the EAC model's	Thank you for your comment. Please see NICE's response to these comments in the clinical and economic evidence sections (comments 18-21 and 47-62).

				assumptions and inputs, not merely to consider each point in isolation. The recommendations are also based on the committee's doubt as to whether the RCT results were clinically meaningful. We believe this doubt was based on a misunderstanding; the committee discussion focused on the 12-day reduction in median time to healing, rather than on the 50% increase in the proportion of patients who achieved healing (34% with 3C Patch versus 22% with standard care, with the differential largely maintained at 52-week follow-up). We consider this difference and the consequent reduction in days of ulcer care (approximately 4,300 fewer days of ulcer care in the 52-week period for the 132 3C Patch patients relative to standard care patients) highly significant from both a clinical and a cost perspective.	
4	9	Company	1.1	The Recommendations section states that the 3C Patch system delivers clinical benefit but the cost analysis is unlikely to be cost saving, yet the Guidance does not give a research recommendation as would be expected for a committee decision where there is uncertainty around either the clinical or cost effectiveness but not both. The clinical evidence is seen as solid with respect to the outcomes of the RCT, the unmet need and innovative aspects of the product are supported by the EAC and the committee. We would ask for a change to a research recommendation and would consult with clinicians to gather evidence (for example using Delphi panel or SHELF methodology) to address the following areas of uncertainty: (a) At what stage would the stopping rule be applied, with what degree of healing & can it be applied in reality? (b) What is a reasonable (and conservative) discontinuation rate to apply in the economic model? Would everyone really continue for 20 weeks? (c) We would also seek to clarify and confirm the most appropriate costs to apply in the economic model. In its various verbal and written communications with the NICE technical team and Committee, Reapplix has raised concerns about aspects of the economic model on which the EAC has relied regarding its advice to the Committee. We continue to have serious concerns regarding the EAC	Thank you for your comment. The External Assessment Centre (EAC) was asked to comment on the further research suggested. It stated that the key uncertainties in the cost modelling are the proportion of patients who would discontinue treatment with 3C Patch at 5 weeks and the corresponding rate of healing for those left on treatment with 3C Patch for the remaining 15 weeks. This would not be addressed by research recommendations suggested here. The methodologies suggested would be useful for informing what the stopping rule in clinical practice might be and how long patients might continue to receive the patch. However, the rate of healing in the patients remaining on 3C Patch would need to be demonstrated prospectively as part of a clinical trial. Similarly, for those who discontinue use of the patch the healing rate would be best demonstrated in a clinical trial setting. Hence our recommendation that a clinical trial be conducted in which a discontinuation rule that is reflective of what would be used in clinical practice is implemented. Regarding point c, it is likely clinicians would be best placed to comment on resource requirements rather than costs to

				model; Their model excludes a large portion of DFU costs and underestimates many of the associated costs leading to a reduction in cost savings as well as inaccurately and disproportionately allocating costs to 3C Patch. The EAC presented no validation of their cost inputs or model outputs, and the company believes their costs cannot be reconciled with study evidence and NHS datasets. The combined impact of these errors is substantially to inflate the cost of 3C Patch, and substantially reduce the cost of standard care. With regard to how infections have been modelled, Reapplix's model took full account of these, so the EAC's work is adding inappropriate additional costs to 3C Patch. We ask the Committee please to consider seeking a second health economic opinion on both the model and its assumptions, from a qualified third party, similar to a DSU. The differences of perspective between Reapplix and the EAC are so fundamental that we believe they demand such an additional review. Second, the Committee has referenced what it sees as a number of outstanding uncertainties relating to clinical aspects of this appraisal. We are confident that a clear way forward can be found to provide answers to set the Committee's mind at rest on many of these. We should like to undertake research to provide further insight from a much wider group of clinical experts across England, than has so far been possible. This research would be in the form of either a rigorous Delphi Panel or a SHELF elicitation. Given that such research would take time to undertake to an appropriately high standard, we ask the Committee either to consider making an interim "in research" recommendation with an exceptional review date of perhaps a year or, better, allow a pause in the current process to give us time to complete the proposed research. We continue to remain committed to working with NICE to achieve a positive outcome from this appraisal. The draft guidance does not reflect the certainties with which we know that our product can be used, consistent with generating cost savings for the NHS.	be applied in the economic model. Some of the key uncertainties remaining around the costs used in the model include the resource use required for those with unhealed ulcers and any differences that may be seen between treatment arms. The methodologies suggested would likely help to address this particular uncertainty. In response to the comments surrounding the validity of the EAC's economic model, EAC's are independent academic centres and they are responsible for the quality assurance of their own work and the conclusions they draw from the available evidence. It is not appropriate for NICE to request additional scrutiny of this work. If any further evidence is generated this can be reviewed as part of the standard guidance review and update process. Please see NICE's responses to comments 47 and 53 on the economic model. The committee considered this information provided but decided that the recommendation should remain unchanged. A further potential research section (section 4.10) was added to the guidance to outline the key uncertainties where further research is warranted. This section highlights the areas of uncertainty that have been identified during the guidance process. They can help inform the company and the system in case there is additional studies planned following the publication of this MTG. The committee however, concluded that although further research could be conducted, on balance it was unlikely to result in a cost-saving case for 3C Patch based on the decision problem evaluated in this guidance. Section 4.6 was amended to acknowledge the proposed SHELF elicitation or Delphi panel to address some of the uncertainties.
Patient Population					

5	3	Healthcare Professional	4.5	*3C Patch could have an impact on service organisation, depending on how they are currently structured* My experience is that the patients who meet the criteria of truly hard to heal wounds is in reality extremely small. The reality is that you only use 3CP on at most 2 patients per month with a maximum of 3 weeks of applications. the actual impact on the clinics is so minimal that it is absorbed amongst the workload. Before using the intervention we thought the impact would be more than it actually turned out to be when the patients were correctly selected for treatment. This isn't a product that should be used in centres that are not MDT's or do not have the ability to take blood from patients as the patient should be thoroughly assessed and vetted to ensure they have been medically and surgically managed before even contemplating an intervention such as this. this is not a dressing such as urgostart that is low skill, relatively low cost. etc	Thank you for your comment. Section 2.7 of the guidance states the intended use of 3C Patch, highlighting use on ulcers not healing despite standard wound care and the use of the device in a multidisciplinary team (MDT) setting. Section 4.5 of the guidance listed the adjustments needed to include 3C Patch use in their practice and acknowledged that 3C Patch has a relatively limited impact on appointment times. The committee heard from experts who said that they would expect 3 to 4 people a week (at a large centre) to be eligible for 3C Patch usage and amended section 4.5 to reflect this.
6	8	Healthcare Professional	General	*Are the recommendations sound and a suitable basis for guidance to the NHS?* 3c patch would not be used for for many individuals within the diabetic foot clinic, i would estimate there would be only 1-3 patients per week that fit the criteria we would use. Those wounds that despite all treatment options healing is not occurring this included NICE recommended dressings , casting , antibiotics etc. It is easy to incorporate the 3c patch in to a clinic appointment it just require organization. Foot clinics are very busy today i have been in a morning clinic with 42pts in it of which one i would like to use 3c patch on. A gentleman who if we don't achieving healing will opt for a below knee amputation as he can no long live a life of staying off his feet to try and aid healing when there is little change in the wound. he needs to get on with life. If 3c patch does not work then this will be the outcome, he's 51, fit and well diabetes very well controlled! he deserve this option. It is not for all but where we need it, we should have	Thank you for your comment. Please see NICE's response to comment 5. The committee's recommendations do not limit the use of 3C Patch to treat diabetic foot ulcers in the NHS. The committee considerations (section 4.1 to 4.2) acknowledged that the patch is biologically plausible and that the main evidence presented was from a well-conducted randomised controlled trial done mostly in the UK. However, the committee were unable to recommend the use of this technology cost savings were found not be robust. Please see additional responses to comments 1 and 2.

				the ability to offer something that has proven to heal in trials and clinical practice wounds that i had looked after for years!!! not 4 weeks!!!	
7	9	Company	4.4	*Blood sampling and blood disorders could affect appropriateness of 3C Patch treatment* The last part of this statement cannot be found in the supporting document - where does this statement come from? The patients attending the committee meeting very clearly mentioned that, in order to heal his foot after two years, he would not mind giving blood each and every day if that was what it takes and he would also not mind coming to the hospital daily if that avoids an amputation.	Thank you for your comment. The comments summarised within the committee discussion are based on expert and committee member opinions discussed within the committee meeting. Section 4.4 has been further amended to reflect expert opinion.
8	9	Company	4.1	*The committee recognised that there is an unmet need for new treatments for hard-to-heal diabetic foot ulcers and that 3C Patch is biologically plausible* (a) With this draft decision the Committee will deny clinicians and patients an evidence based treatment alternative at the end of the treatment pathway. As the patient in the Committee meeting mentioned, he would have lost his foot if 3C Patch had not have been available. While there might be uncertainties around the practical aspects of when to start and stop using 3C Patch and the specific health economics, there is no doubt that this product can help preserve limbs and lives. Since 3C Patch will only be used AFTER UrgoStart and other advanced alternatives have not led to adequate healing, there is no risk of unpredictable costs caused by 3C Patch. It is a product for a small group of patients not healing with any other available advanced product. But for this population it will most likely make all the difference and not recommending it despite the outcomes of a well-conducted RCT which proved its positive impact, seems unethical. 3C Patch is explicitly recommended by the International Working Group on the Diabetic Foot which includes well-regarded UK clinicians. The current decision would exclude a treatment that is in the IWGDF guidelines from being used in the UK and available to UK patients and caregivers.	Thank you for your comment. a) The committee's recommendations do not limit the use of 3C Patch to treat diabetic foot ulcers in the NHS. The committee considerations (section 4.1 to 4.2) acknowledged that the patch is biologically plausible and that the main evidence presented was from a well-conducted randomised controlled trial done mostly in the UK. However, the committee were unable to recommend the use of this technology cost savings were found not be robust. Please also note that there is a clear difference between a budget impact analysis that refers to the overall cost impact to the NHS arising from a potentially small group of patients and the health economic evaluation conducted as part of the guidance development that shows that 3C Patch is unlikely to result to cost saving for the NHS independently of the size of the population. Please also note that although the RCT was well conducted there were uncertainties around the generalisability of the results in clinical practice. The additional limitations of the main RCT are outlined in sections 3.3 and 4.2 of the guidance. Please see additional responses to comments 1 and 2.

				(b) The Committee queried whether the treatment programme could be followed. This is not supported by the Committee's own experts who state that: "From this, it can be assumed that it might not be necessary to change the patch each week as missed visits in the trial did not appear to make any significant differences to the outcome." (page 456 of the supporting documentation). And on pages 472 following the experts state: "...the number of people being treated with a patch at any one time would probably mean the impact would be minimal." and "It would be difficult at first as the clinics are already over capacity, but if it healed patients quicker then that would of course release capacity in the longer term." and "I think this would be practical there are many reasons why treatment need to be more often than every 2 weeks."	b) Although the committee queried whether the treatment program would be followed, section 4.1 of the guidance also communicates the views of clinical and patient experts who said that 3C Patch treatment program would likely be adhered to if progress is seen. Section 4.5 addresses the practicalities of incorporating 3C Patch into clinics and the likely patient numbers.
9	3	Healthcare Professional	3.2	*The main clinical evidence comprises 4 studies, 1 of which is a randomised controlled trial* I strongly disagree with the statement that a reduction of less than 50% is not routinely used in clinical practice. I am a clinical expert and this is a rule that we is used in clinical practice to determine hard to heal wounds. There is ample evidence that wounds that have not reduced by 50% in 4 weeks will not be healed in 12 weeks and will need other interventions in order to heal. This is a standard measure that is used in order to establish healing trajectory in diabetes foot clinics across the country.	Thank you for your comment. The committee heard that a 50% wound area reduction rule is used in clinical practice to determine if an ulcer is hard to heal. The statement 'Entry into the treatment phase of the trial was determined by a decision rule (failure to respond to standard care provided in the run-in period, based on a reduction of less than 50% in ulcer area). Clinical experts stated that this rule is not routinely used in practice to judge response to treatment on the 50% rule to determine a hard to heal ulcer' was removed from section 3.2 as a result.
10	12	Professional Society	General	*The larger the number of patients on whom the technology may be used, the greater the likelihood that a national evaluation is important.* Although there is a large population of people with diabetic foot ulceration (DFU) the size of the population of people with DFU who have failed to respond to high-quality optimized care is uncertain.	Thank you for your comment. Please see NICE's response to comment 5 on population size. Section 4.5 of the guidance document notes clinical expert opinion that the 3C Patch use would make up a relatively small proportion of their foot clinic referrals.
Treatment Setting					
11	5	Healthcare Professional	4.5	*Are the recommendations sound and a suitable basis for guidance to the NHS?*	Thank you for your comment.

				4.5: in secondary care/MDT settings - where the most difficult to heal wounds are looked after, there would be the facility to manage phlebotomy etc. Hence it may not be suitable/feasible for an over all recommendation across all footcare settings, but for those who require secondary care input it is very achievable.	The committee heard that 3C Patch could be used anywhere were there were there was the appropriate expertise (multidisciplinary team) to manage the ulcer and administer the patch. It heard that this does not need to be in secondary care if the appropriate resources are available in the community. Section 2.7 was amended to reflect this.
12	6	Healthcare Professional	2.4	*Current care for DFUs (as outlined in NICE's guideline on Diabetic foot problems: prevention and management) includes offloading, debridement, control of ischaemia, and use of dressings. It recommends that clinical assessment and patient preference are used when choosing dressings, but healthcare professionals should choose the lowest cost dressing that is likely to achieve the desired results.* We are a regional diabetic foot team with acute clinics twice weekly. During the trial this treatment modality offered a further layer to our options. It was only considered once all other options had been tried. In many cases the patients would, at this point be considering lower limb amputation. All patients at this point were willing to try any options available. This has shown benefits in this group of patients. My feeling is that we owe our patients all options and we have seen results with this. It is contradictory not to allow patients this choice, when amputations are very costly, in terms of both monetary and personal value.	Thank you for your comment. This evaluation has been limited to the treatment of diabetic foot ulcers that are not healing despite standard wound care. The committee heard from a patient expert who agreed that they were willing to try any options available. The committee heard that the Game et al. randomised controlled trial (RCT) did not show any significant reduction in amputations (although amputation rate was low in the trial and the trial was not powered to detect a significant difference). As a result the amputation rate between the 3C Patch and standard care groups, used for the economic modelling, were considered equivalent. As the technology was unlikely to be cost saving the committee was not able to make a positive recommendation. Please see additional responses to comments 1,2 and 8.
13	6	Healthcare Professional	2.4	*offloading, debridement, control of ischaemia, and use of dressings.* All of this is standard first line care in diabetes foot MDT teams. Nobody would consider moving to more expensive or more high level interventions without trying the standard level care initially. We need more alternatives in our armoury. This has proven useful, but should be reserved for regional centres of excellence , with the staffing and skills to make best use.	Thank you for your comment. Please see NICE’s response to comment 11 on treatment setting and comment 5 on patient population.
14	6	Healthcare Professional	4.1	*The committee also acknowledged that there is an unmet need for new treatments for hard-to-heal diabetic foot ulcers (DFUs) and that not all treatments will work for all ulcers. The committee were concerned that the treatment program,*	Thank you for your comment.

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<td>with weekly appointments and blood draws, would be difficult to follow for some people.

Most of the patients in this category are already attending specialist diabetes foot secondary care clinics weekly. This doesn't add to this existing cost.</td>
<td>The committee acknowledged that there is differing practice around the frequency of appointments in standard care, with some experts sayings fortnightly, some weekly.

The EAC did additional scenario analysis where the standard care also had weekly appointments. This is with an outpatient cost in standard care of £111.66 per week (increased from £78) vs £125.24 per week with 3C Patch (which reflects the additional time for an outpatient appointment due to the centrifuge element). District nurse visits have not been altered so there are still slightly fewer visits in the 3C Patch arm per week. 3C Patch is still cost incurring.

Model A (without infection health state)
<table>
<tr><th>Key results</th><th>3C Patch</th></tr>
<tr><td>Total costs</td><td>£12,540,923</td></tr>
<tr><td>Cost per patient</td><td>£12,541</td></tr>
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Model B (with infection health state)
<table>
<tr><th>Key results</th><th>3C Patch</th></tr>
<tr><td>Total costs</td><td>£12,007,538</td></tr>
<tr><td>Cost per patient</td><td>£12,008</td></tr>
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The committee decided not to amend the guidance in response to this comment.</td>
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<td>15</td>
<td>6</td>
<td>Healthcare Professional</td>
<td>4.5</td>
<td>Some clinical experts stated that 3C Patch has a relatively limited impact on appointment times. This is because the appointments have been structured to accommodate blood taking and centrifugation time. Some centres also have podiatrists and nurses trained in blood taking or have phlebotomists available to help with 3C Patch preparation.

Indeed.
This is all standard behaviour in acute diabetes foot centres.</td>
<td>Thank you for your comment.</td>
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16	9	Company	4.5	*3C Patch could have an impact on service organisation, depending on how they are currently structured* All experts state that after an initial implementation 3C Patch will not impact or stretch the system in a negative way (supporting document pages 470 following [redacted] even stated the opposite: "It would be difficult at first as the clinics are already over capacity, but if it healed patients quicker then that would of course release capacity in the longer term."	Thank you for your comment. Please see NICE's response to comment 5.
17	11	Healthcare Professional	General	*Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?* Weekly visits to a secondary care clinic are standard for many total contact casting devices, utilising the 3C patch would be on a similar basis. A case series with an urgostart experienced population and the use of 3C patch could be undertaken. In clinical practice patients selected for 3C patch are carefully selected it may be in the use of URgostart if there has been limited impact/ reduction in wound size after 4 weeks the 3C patch would be considered.	Thank you for your comment. Please see NICE's response to comment 14 on weekly clinic visits. Please see NICE's response to comment 63 on further research.
Clinical Evidence					
18	2	Healthcare Professional	General	*Has all of the relevant evidence been taken into account?* It is interesting that the NICE document states that "the committee were also uncertain of the clinical importance of the difference in healing time and healing rate shown in the evidence." However, the Game et al. RCT showed a 50% increase in healing (34% v 22% with standard care) of hard to heal DFUs, and the differential in the proportion of patients healed was largely maintained at 52 week follow up. This is surely a very important observation. I was a member of the advisory group at the beginning but had to resign as the meetings clashed with my main diabetic foot clinic - but did emphasize my views on the Game trial which showed strong evidence of the efficacy of the product.	Thank you for your comment. The committee heard clinical expert opinion which felt that the difference in healing rate was clinically meaningful. Please also note that although the RCT was well conducted there were uncertainties around the generalisability of the results in clinical practice. The additional limitations of the main RCT are outlined in sections 3.3 and 4.2 of the guidance. The committee decided to remove the statement on the clinical importance of the difference in healing time (as referred to in your comment) from section 4.2.

19	9	Company	3.6	*Evidence does not support 3C Patch reducing the risk of amputation or ulcer infection and direct clinical evidence for the other company-claimed benefits is limited* (a) It is incorrect to claim that the study did not provide direct evidence of reduced demand for ulcer care and follow-on treatments. The study demonstrated both an increase in the proportion of patients who achieved healing within 20 weeks (34% in the 3C Patch group versus 22% in the standard care group), and reduced time to healing (median days to healing in those who healed 72 in 3C Patch versus 84 days in standard care). Both were statistically significant differences. Two points follow: first, less ulcer care was required within the 20 weeks for 3C Patch patients, second, healing 12 more patients out of a 100 means there are 12 fewer patients per 100 who require ongoing ulcer care and follow-on treatments beyond 20 weeks. Data from the Game et al. RCT indicate that the difference between the two trial arms was largely maintained at 52-week follow-up, even though all patients received standard care from week 20. At 52 weeks, 54.55% of 3C Patch patients and 44.03% of standard care patients had achieved healing. In other words, over a year many fewer days of ulcer care were required for 3C Patch patients than for standard care patients (approximately 4,300 days of ulcer care were averted in the first year for the 3C Patch cohort relative to standard care, 269 days for each additional patient who healed with 3C Patch). Multiple studies indicate that hard to heal DFUs can last for many years. Some never heal. Achieving healing in 12% more patients is therefore likely also to lead to reduced demand for ulcer care and follow-on treatments in subsequent years. (b) The clinical submission provided data from the Game RCT dataset on quality of life. This showed that there was a statistically significant improvement in EQ-5D score of 0.14 for patients who became ulcer free during the 20-week trial period. As indicated above, a statistically significantly higher proportion of 3C Patch patients achieved ulcer healing than	Thank you for your comment. a) Section 3.6 of the guidance was clarified to acknowledge that a reduced time to healing seen, however, no data on demand for NHS care across outpatient, community, primary and inpatient settings were presented. b) The quality-of-life data presented was mentioned in section 3.6 of the guidance and reviewed in full within the EAC's assessment report. The committee acknowledges in section 4.1 of the guidance that diabetic foot ulcers can reduce quality of life.

				standard care patients. The findings on quality of life were validated with reference to other studies. Multiple studies indicate that quality of life is substantially higher for people who achieve ulcer healing than for those with continued ulceration. All clinical experts consulted agree that ulceration is associated with substantial decrements to quality of life and that healing is associated with substantial improvement in quality of life. Diabetic foot ulcers have substantial impacts on mobility and ability to perform normal tasks; they are often painful, smelly, and can impact relationships. Clinical experts agree that healing an additional 12% of patients with hard to heal DFUs will lead to substantial improvements in quality of life.	
20	9	Company	4.2	*Randomised controlled trial evidence shows improvements in ulcer healing proportion and time to healing but the clinical importance of the observed benefit is uncertain* (a) It is important to recognise that a large proportion of the patients in the trial had protease-modulating dressings in the run-in period and in the standard care arm during the intervention period. See also comment on 3.2. (b) The company firmly believes that a 50% increase in the healing rate for hard to heal DFUs, as observed in the RCT, (34% versus 22%) is clinically meaningful and important. Healing 12 more patients out of a 100 means there are 12 fewer patients per 100 who require ongoing ulcer care and follow-on treatments beyond 20 weeks. The 12 day difference in median time to healing between 3C Patch and standard care relates only to those for whom healing was achieved in each arm. The main benefits arise from the substantial increase in the proportion of patients who healed with 3C Patch (as above, 34% versus 22%). The trial data indicate that the differential between the two arms was largely maintained at 52 weeks. This means that a substantial proportion of additional patients were healed in the 3C Patch arm over the long term (approximately 4,300 days of ulcer care were averted in the first year for the 3C Patch cohort relative to standard care, 269 days for each additional patient who healed with 3C Patch).	Thank you for your comment. a) The committee heard that only 2% of people had protease modulating dressings during the run-in, when using the British National Formulary dressing classifications. The committee were concerned about the whether the classification of some dressings as protease modulating (for the 40% valued used for the run-in period) was appropriate. As a result, the committee decided to amend section 3.2 to use the BNF classification. Section 4.2 discusses the committee and expert opinions on whether UrgoStart use would have affected the outcome of the clinical trial. b) Please see NICE's response to comment 18. Please also note the additional responses to comments 1,2 and 8 about the issues with generalisability of the RCT results in clinical practice.

21	12	Professional Society	General	*The extent to which a medical technology claims measurable benefit to patients over currently available health and social care system technologies in terms of its impact on quality of life or life expectancy.* *Claimed benefits:* • *Heals more wounds and reduces wound healing time.* • *Helps to avoid wound-related complications, including amputation and infection, reducing the need for further treatment.* • *Improves quality of life through reduced ulcer duration and the avoidance of complications, enabling people to return to activities of daily living sooner and avoid long term reduction in quality of life.* There is one well-designed RCT (Game et al 2018) which suggests that use of the product achieves clinically significant improved time to healing in patients with diabetic foot ulceration (DFU) who have received high quality optimized care (offloading, control of foot infection, ischaemia and wound debridement) in specialist diabetic foot clinics but failed to heal. The sample was predominantly male, but this is in line with the ratio of men in the population of interest so not an issue of concern. There is a second prospective observational study (Londahl et al 2015) but this is a pilot study designed to report safety and feasibility so not designed to answer questions of effectiveness.	Thank you for your comment. The committee acknowledged this review of the quality of clinical evidence.
Stopping Rule					
22	4	Healthcare Professional	4.7	*The stopping rule applied in the 3C Patch arm of the company model is not appropriate*	Thank you for your comment. The committee heard from clinicians that advanced wound measuring devices would improve the tracking of wound

				clinicians are assessing these wounds regularly without the advanced wound measuring systems. As previously mentioned no clinician would continue to use any woundcare product beyond 6 weeks if there is no improvement noted in the wound as seen in recorded measurements using a paper rule and photography and accurate wound description	area measurement, however, less advanced methods (such as paper rulers and photography) are still sufficient to track ulcer healing. Clinical experts agreed that ulcers would be routinely reviewed and if no improvement is seen (there has been no significant change to the healing trajectory) then changes to the treatment options used would be considered. They stated, however, that a 50% stopping rule would not be used as it is too strict and there is more variability in clinical practice. Sections 3.11 and 4.6 of the guidance acknowledge this and section 4.6 of the draft guidance was removed.
23	5	Healthcare Professional	4.7	*Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?* Not entirely 4.7 - stop rule follows a basic cornerstone of clinical practice within wound care/diabetes. We regularly use the measure of 50% reduction in wound size over a 4 week period as measure of progress and effectiveness of wound care regime. Hence the guidance from the manufacturer seems very sensible - especially when working with an expensive product.	Thank you for your comment. Please see NICE's response to comment 22 on the stopping rule.
24	6	Healthcare Professional	3.3	*The EAC noted the way the intervention was delivered in the trial did not align to the company's proposed treatment pathway. The company stated that 3C Patch use should be reviewed after 4 to 6 weeks and stopped if there has not been a 50% reduction in ulcer area. This stopping rule was not followed in the clinical trial because everyone in the treatment group had 3C Patch until healing or up to 20 weeks. The EAC considered this an important limitation of the evidence base.* The reality is that off trial the patch would be stopped at 4 - 6 weeks if no improvement was seen. On trial, we had to adhere to the pathway.	Thank you for your comment. Section 3.3 was amended to acknowledge the company's proposed pathway which states that if adequate progress in healing has not been seen, such as a reduction of 50% or more in ulcer area then the treatment would be stopped. The committee acknowledged that treatment would be stopped if no progress is seen after 4 to 6 weeks and that this was not done in the clinical trial. The committee also heard from clinical experts that there is variability in clinical practice around the choice of a cut off as a discontinuation rule.
25	7	Healthcare Professional	General	*Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?*	Thank you for your comment.

				I feel that the stopping rule is achievable when the devise is being used by experienced clinicians	Please see NICE's response to comment 22 on the stopping rule.
26	7	Healthcare Professional	3.11	I disagree that the stopping rule is unlikely to be followed. It is common practice that if healing isn't taking place then a review of treatment is undertaken. This is usually undertaken at every appointment. Although specialist equipment for measuring ulcers is not widely available a simple measurement of diameter using the supplied ruler or a photograph would allow for adequate assessment of the ulcer. This is standard care for the assessment of any ulcer when using any dressing. I feel that it would suffice for the 3C patch.	Thank you for your comment. Please see NICE's response to comment 22 on the stopping rule.
27	7	Healthcare Professional	4.7	I disagree that the stopping rule would not be easy to implement. Experienced clinicians, would be able assess the whether or not the wound has reduced by 50% with photographic evidence or a measuring rule. I also feel that patients wouldn't necessarily agree to continue with the treatment unless they are able to see that a notable difference was been achieved.	Thank you for your comment. Please see NICE's response to comment 22 on the stopping rule.
28	9	Company	3.2	(b) Every DFU treatment pathway guide includes an area reduction review at a certain time and certain volume (e.g. in %) to assure the treatment is working e.g. the Leicester pathway suggests to change the treatment if after 4-6 weeks the wound has not decreased by approx. 30%. Wound size and reduction measurement is a standard procedure to access treatment success. 3C Patch does not change the standard procedure nor does it request a more accurate measurement than currently used as standard of care. c) The stopping rule proposed in the clinical pathway is not strict in regards to 50%. The 50% rule is given only as an example of adequate progress toward healing. It is widely accepted across NHS MDT diabetic foot clinics that changes in size/depth can be obtained using simple measurement tools, eg paper grids. Furthermore, objective wound measurement is acknowledged to be just one of several considerations made by clinicians when judging adequate progress toward healing. See also comment on 4.6 regarding devices to measure ulcer area.	Thank you for your comment. b) Please see NICE's response to comment 22 on the stopping rule. c) The committee amended section 3.3 of the guidance to reflect this, please see NICE's response to comment 24. Please see NICE's response to comment 34 on measurement devices.

29	9	Company	3.3	It is common practice to review the treatment progression and success regularly and adjust the treatment if healing results are not adequate. All committee experts agree with this practice (pages 470 - 471 in the Supporting Documentation) as well as the “non-committee” experts whose feedback was part of the submission. Therefore, even though it diverts from the RCT protocol, the review and discontinuation if adequate healing does not occur is the realistic scenario to be used as the basis for a broader 3C Patch implementation. It is common, well-published practice to move chronic wounds to the next level of treatment and products when the ulcer does not reduce sufficiently in 4 weeks. This is the official definition of a chronic wound, e.g.: “When wounds fail to achieve sufficient healing after 4 weeks of standard care, reassessment of underlying pathology and consideration of the need for advanced therapeutic agents should be undertaken” (Challenges in the Treatment of Chronic Wounds, Adv Wound Care (New Rochelle). 2015 Sep 1; 4(9): 560–582.)	Thank you for your comment. Please see NICE’s response to comments 22 and 24.
30	9	Company	3.11	*The EAC revised 3C Patch discontinuation rates in the model* See also comment for section 3.3. The majority of experts agree with a review and stopping if progress is not adequate after e.g. 4 weeks. They all agree that they would not use a product that does not have an effect. (see Page 470 and 471 of the Supporting Documentation). Therefore, a stopping rule is already a standard rule in wound care. It needs to be further identified what the exact criterion for adequate wound healing with 3C Patch is. But the committee experts did not state that a stopping rule in general is unlikely to be implemented. The opposite is the case (see p470 of Supporting Documentation): a stopping rule is common practice. Wound size and reduction measurement is a standard procedure to access treatment success. 3C Patch does not change the standard procedure nor does it request a more accurate measurement than currently used as standard of care.	Thank you for your comment. Please see NICE’s response to comment 22 and 24 on the stopping rule.
31	9	Company	4.7	*The stopping rule applied in the 3C Patch arm of the company model is not appropriate*	Thank you for your comment.

				See also comments made for sections 3.3, 3.11 ad 3.15. (a) The stopping rule proposed in the clinical pathway is not strict in regards to 50%. The 50% rule is given as an example of adequate progress toward healing, and it is acknowledged that clinical judgement will be applied. In the economic model the 50% rule was used as a proxy. Given that it is acknowledged that a stopping rule would be needed, the EAC base case, which allows no discontinuation, is not considered a fair or reasonable representation of how 3C Patch would be used. (b) According to the committees experts it is not appropriate to not have a stopping rule (pages 470 following). It is common practice to review wound healing progress and stop a specific treatment if healing is not adequate. Therefore, removing the stopping rule is not realistic. As noted above, we would ask for a change to a research recommendation and would consult with clinicians to gather evidence to address the stage at which the stopping rule should be applied and the criteria for stopping.	Please see NICE's response to comment 22 and 24 on the stopping rule, it was acknowledged that treatment would be stopped if sufficient healing progress has not been made. The committee recognised that the rule was used as a proxy in the economic model. However, the committee acknowledged the EAC evaluation of the evidence which noted the limitations in the proposed discontinuations rate. Specifically, the company assumed 58% of people receiving 3C Patch are discontinued at the 5-week review and the healing rates in the company's model were based on an unplanned post-hoc analysis, rather than based on a pre-planned analysis of the clinical evidence. This led to uncertainty in the cost modelling because the probability of healing with 3C Patch in weeks 6 to 20 was a key driver in the company model. The committee decided not to change the recommendations for this technology.
32	11	Healthcare Professional	General	*Has all of the relevant evidence been taken into account?* I do not believe the stopping rule is significantly dissimilar to the majority of clinical practice in real world diabetic foot clinics. Accurate measuring tools are not widely available often it is a crude measure with a paper ruler or measuring guide on a scalpel handle. Never the less many other treatments would be stopped in 4-6 weeks for example certain offloading techniques would often be reviewed at a similar interval for the clinician to stop and think about the effectiveness of the treatment and other potential reasons for lack of progress. This could be reviewed with some case series applying this in clinical practice.	Thank you for your comment. Please see NICE's response to comment 22 and 24 on the stopping rule and comment 34 on wound size measurement.
33	1	Healthcare Professional	3.3	In relation to the paragraph: *The intervention delivered in the trial did not align to the company's proposed treatment pathway. The company stated that 3C Patch use should be reviewed after 4 to 6*	Thank you for your comment. Please see NICE's response to comment 22 and 24 on the stopping rule.

				weeks and stopped if there has not been a 50% reduction in ulcer area. This stopping rule was not followed in the clinical trial because everyone in the treatment group had 3C Patch until healing or up to 20 weeks ***"The EAC considered this an important limitation of the evidence base**".* In my opinion this stopping rule is important clinically and I would argue 'real life evidence' of expert practice that the EAC have overlooked and not considered. All new treatments started on a patient would be reassessed and in our local area 4 weeks is the usual time frame we would give (unless deterioration was seen earlier) before making a judgement to change treatment.	
Wound Size Measurement					
34	1	Healthcare Professional	3.11	In relation to paragraph: *'It also noted that clinical experts stated that the stopping rule used in the company model was unlikely to be implemented in clinical practice.* ***This is because accurately measuring ulcer size would need specialist equipment*** *and 3C Patch treatment would likely continue if any significant improvement in ulcer size is seen when compared with previous treatments. Therefore, the EAC changed the discontinuation rate to 0% (meaning everyone in the treatment arm would continue 3C Patch until healing or for 20 weeks)'* Clinicians are skilled at monitoring wound progress with simple tools such as photographs, measurement devices (paper rulers or grids) and shared discussions with patients and reviewing documentation. Judgement on wound progress with respect to carrying out invasive surgical procedures, changes in treatments (antibiotics and offloading) and changes in dressings are all routinely made	Thank you for your comment. The committee acknowledged that digital devices for accurately measuring ulcer area are not widely available across the NHS. Section 4.6 of the draft guidance has been removed in response to consultation comments. Section 3.11 has been amended to remove the statement on specialist equipment. Section 4.6 of the final guidance has been amended to remove the statement that the stopping rule is not easy to implement due to a lack of specialist equipment, instead it acknowledges that a lack of specialist equipment may make accurate wound tracking more difficult.

				in clinically practice without 'specialist wound care measurement devices' and the 3C patch assessment criteria in the pathway is no exception to this. The EAC comment that specialist equipment would be required to make this assessment is incorrect in my view as this has not been the required best practice for any NICE recommendation with regards to wound care treatments to date and therefore should not be the recommendation in this case. The clinical expert comments based on 'objective measurement' maybe biased from the framing of the question and perhaps should be reviewed?	
35	4	Healthcare Professional	4.6	*Devices to accurately measure ulcer area are not available across the NHS* In reality it will take many years for any such wound measuring device to be easily available in the NHS. Should that lack of resource be a reason not to use a product?	Thank you for your comment. Please see NICE's response to comment 34 on wound measurement devices. The committee acknowledged that access to digital ulcer-size measuring devices should increase over time but that this is not a limiting factor preventing the use of this device.
36	5	Healthcare Professional	4.6	*Are the recommendations sound and a suitable basis for guidance to the NHS?* 4.6: does not seem relevant as this is the case with regards evaluation of any foot wound.	Thank you for your comment. Please see NICE's response to comment 34 and 35.
37	6	Healthcare Professional	3.11	*It also noted that clinical experts stated that the stopping rule used in the company model was unlikely to be implemented in clinical practice.* I disagree. We have technology within our secondary care acute diabetes foot service to accurately measure wounds and determine progress. We measure using ab infra red 3D camera. This treatment modality should be reserved for centres such as ours, who can monitor progress.	Thank you for your comment. Please see NICE's response to comment 34 on wound measurement devices. The committee acknowledged that some centres have access to more advanced wound area measuring devices.

				It isn't a routine intervention. But it has proven to be very useful.	
38	9	Company	4.6	*Devices to accurately measure ulcer area are not available across the NHS* 3C Patch does not need any additional or more accurate devices to be implemented than any other wound care product. This is NOT a barrier to adoption as wound healing measurement for 3C Patch has to be no more precise and accurate than with any other product. Many of the experts already use simpler tools (e.g. ruler) plus clinical judgement to determine wound progress as discussed at the Committee meeting. Every DFU treament pathway guide includes an area reduction review at a certain time and certain volume (e.g. in %) to assure the treatment is working. E.g. the Leicester pathway suggest to change the treatment if after 4-6 weeks the wound has not decreased by approx. 30%. Wound size and reduction measurement is a standard procedure to access treatment success. 3C Patch does not change the standard procedure nor does it request a more accurate measurement than currently used as standard of care.	Thank you for your comment. Please see NICE's response to comment 34 on wound measurement devices.
Treatment Timescale					
39	3	Healthcare Professional	General	*Are the recommendations sound and a suitable basis for guidance to the NHS?* No I do not believe so. The treatment timescales for treatment used in the analyses are not in reality what are used. Treatment times are much shorter. Implications for services are also much less than is being suggested here. The actual patients that this intervention can be used on is extremely small and it should only be in a specialist MDT setting. This inference here is that this would be on a scale similar to the use of urgostart. this is completely incorrect.	Thank you for your comment. Please see NICE's response to comment 5 on patient population size and treatment setting. 3C Patch has been considered as an option for treating hard to heal diabetic foot ulcers which have not healed despite best standard care, this includes UrgoStart. The committee acknowledge that this population would be smaller than that of UrgoStart. The treatment timelines used in the assessment of the evidence is based on the design of Game et al. RCT, which continued treatment for 20 weeks. In the trial, the median time to healing in those who healed within 20 weeks (in the 3C Patch arm) was 72 days (10.2 weeks). Clinical experts noted that patients would not receive 20 weeks of treatment with 3C Patch outside of the trial if improved healing is not seen.

40	3	Healthcare Professional	2.5	As regular users of 3CP in diabetes foot ulceration we have never used this intervention for more than 4 applications in wounds that have gone on to fully heal. It is never used to wound closure.	Thank you for your comment. Please see NICE's response to comment 39.
41	4	Healthcare Professional	3.11	*The EAC revised 3C Patch discontinuation rates in the model* In the trial the median time to heal was 10 weeks. In general wound care settings no practitioner would continue using a product after 6 weeks if that wound was failing to improve. Wounds should be assessed regularly for improvement. IN this case if the wound showed no improvement at week 6 then I would expect 3c patch to be stopped not continued until 20 weeks. This is not standard practice so why is it suggested here? Specialist measuring equipment is not available to most locations in the NHS but most locations surely have access to photography and some form of paper measure which is used to show reduction in wound size	Thank you for your comment. Please see NICE's response to comment 39 on treatment timescales and to comment 34 on wound measurement devices.
42	6	Healthcare Professional	1.1	*The clinical evidence on ulcers that are not healing shows that using 3C Patch led to more ulcers healing at 20 weeks and faster ulcer healing. But, cost analysis for 3C Patch showed that the clinical benefits seen in the trial are unlikely to lead to cost savings in practice.* Having taken part in the clinical trial and used this product on many consenting patients, we were interested to see that in most cases a positive response was measurable within 3 - 5 applications. We would be able to assess probable benefit within this time and agree whether to continue with the treatment. Therefore in most cases, length of treatment would be much length than 20 weeks.	Thank you for your comment. Please see NICE's response to comment 39 on treatment timescales.
43	8	Healthcare Professional	General	*Has all of the relevant evidence been taken into account?* I don't feel that the evidence has been correctly interpreted. In clinical practice i would not consider 3c patch after 4 weeks of alternative treatments as this would be far too early. In clinical trails i witnessed patients who had had diabetic foot problems for may years be offered a chance to heal or significantly improve the wound size by using 3c	Thank you for your comment. The company's clinical pathway stated that 3C Patch would be considered for hard to heal DFUs in cases where best standard of care as recommended by NICE (including offloading, debridement, control of modifiable factors, and use of dressings such as UrgoStart and other protease

				patch. A foot problem can have devastating effects mental well being not just physicals. I am not such this was taken into consideration.	modulating and advanced dressings where appropriate) have failed to promote ulcer healing. It is likely that best standard of care would be tried for at least 6 weeks before 3C Patch is considered. During this time progress towards healing should be reviewed regularly and the patch should only be considered in cases where ulcer area has not reduced by 50% or more during the 4-week period prior to proposed use. The committee acknowledged that ulcers could have negative effects on physical and mental wellbeing and is acknowledged in sections 4.1 and 4.6 of the guidance.
UrgoStart Use					
44	3	Healthcare Professional	4.2	*Randomised controlled trial evidence shows improvements in ulcer healing proportion and time to healing but the clinical importance of the observed benefit is uncertain* As a user of 3cp in clinical practice outside of a clinical trial all my patients have had urgostart and this has failed before considering use of 3cp. In the small subset of patients with truly hard to heal wounds the true cost of achieving healing through use of 3cp is difficult to measure as for the patient the gains in QOL are immeasurable.	Thank you for your comment. The committee acknowledge the company's clinical pathway which states that 3C Patch would be considered for hard to heal DFUs in cases where best standard of care as recommended by NICE (including offloading, debridement, control of modifiable factors, and use of dressings such as UrgoStart and other protease modulating and advanced dressings where appropriate) have failed to promote ulcer healing. Limited quality of life data was collected as part of the trial and is discussed in section 3.6.
45	6	Healthcare Professional	4.2	*However, they were unsure if the results of the current study would have been different if UrgoStart had been used by everyone in the run-in period.* We use Urgostart when indicated. It doesn't work for all, but would always be tried prior to considering the 3c patch, as it is less invasive.	Thank you for your comment. Please see NICE's response to comment 44.
46	9	Company	3.2	(a) The Experts stated that UrgoStart would not have changed the outcome of the RCT as it is used on less severe wounds – see page 453 of the Supporting Documentation: "Therefore, it is possible that some patients in the 3C Patch trial would have had ulcers that could be considered 'harder to heal' ulcers than those in the UrgoStart trial. Therefore, the experts doubt this would have made any difference to the outcomes of the Game trial because the patient groups would likely be different in	Thank you for your comment. The committee heard from clinical experts who agreed that it is unlikely that UrgoStart use would affect 3C Patch outcomes as they have different mechanisms of action. However, the committee were uncertain on the healing rates following 3C Patch use on the population with ulcers that have failed to heal following UrgoStart use.

				clinical practice."" 3C Patch is used in wounds where other advanced products including UrgoStart did not result in adequate wound healing. Therefore, there is no conflict or negative impact of UrgoStart not being the standard of care at the time of the 3C Patch RCT. See also comment on 4.2.	
Economic Model					
47	2	Healthcare Professional	General	*Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?* I feel that the EAC's economic model on which NICE have based their recommendations seriously underestimates the NHS costs of diabetic foot ulcers and therefore the savings from a higher healing rate. For example, they have not included any costs for inpatient care in situations where the foot ulcer is not the cause of the admission. The earlier published analysis of HES data (by the leading health care economist with expertise on the diabetic foot, Marion Kerr) shows that DFUs are associated with substantial increases in length of stay in such admissions, and that this is a major cost driver. There are also errors and omissions in the analysis of outpatient, community and primary care costs. I think NICE's use of an economic model that underestimates the cost of standard care for DFUs is very troubling, and if unchallenged may set a precedent. Many of us have worked hard for such a long time to increase understanding of the human and financial costs of DFUs. I would also point out that Dr Kerr wrote the chapter on the costs of DFU care in the 5th edition of the book 'The foot in Diabetes' (Wileys, 2020) of which I am the senior editor.	Thank you for your comment. The External Assessment Centre (EAC) was asked to respond to this comment. They note that the EAC uses the Kerr paper throughout the evaluation. Generally, rather than apply modelling assumptions, the EAC have tried to weight costs and resource use from Kerr and other published sources using trial data provided in the unpublished Farr et al. paper. Consistent with previous NICE guidelines for similar treatments such as Urgostart, trial data was used to weight cost elements such as inpatient costs in the base case of the model. The EAC believe that by using costs from Kerr with resource use data from Farr it has captured the relevant costs to the decision problem. Furthermore, an additional scenario is presented below. In this scenario, the model uses the following: - Weekly inpatient cost for those with unhealed ulcers as per the company model (£92.51). This is calculated from Kerr et al and is applied equally to both treatment arms (whereas in the EAC base case analysis this is weighted by the number of severe infections and revascularisations reported in each treatment arm from Kerr). - Outpatient attendance is assumed weekly for both standard care and 3C Patch (which goes against clinical input that patients receiving standard care currently have fortnightly outpatient visits). For standard care the outpatient weekly cost is £111.66 using Kerr et al but removing the district nurse cost because this is applied separately. For 3C patch

					this is set at £125.24. This is the same as standard care but accounting for the longer appointment times with 3C patch. This therefore assumes the only difference between treatment arms in terms of resource use is a slightly longer appointment time with 3C Patch to account for additional time to make and apply the patch. It still incorporates a reduction in district nurse visits as reported by Farr et al. Despite these changes, the results are still significantly cost incurring, at around £500 per patient. The key drivers which are likely to change the direction of the results are the cost of the patch, the discontinuation rate at 5 weeks, and the healing rate in weeks 6 to 19. It is important to note that the cost of the patch used in both models is £150, weighted by the averaged used per week in the trial (£125.40). This is significantly more expensive than alternative treatments available. The alternatives currently used in standard care costed from NHS supply chain costs amounts to approximately £8 per week, based on average patches used per week. The committee decided not to amend the guidance in response to this comment.
48	4	Healthcare Professional	4.8	*Economic modelling is limited by the available clinical evidence and its relevance to the NHS clinical pathway* would a consensus piece be useful in this instance?	Thank you for your comment. Please see NICE's response to comment 63 on further research.
49	5	Healthcare Professional	4.9 and 4.10	*Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?* 4.9 & 4.10: The economic evaluation is sound with the framework of standard care for diabetic foot ulcers, but less so when looking at the hard to heal subset. The costings for patients who are failing to progress with standard care and may be facing long term non healing wounds, with ongoing care to prevent deterioration over a number of months/year	Thank you for your comment. The committee heard that the cost of ulcer treatment was one of the biggest cost drivers in the economic model. However, the economic model over a 2-year time horizon showed uncertainty as to whether 3C Patch use would lead to cost savings. The model included the cost of amputations. As the clinical evidence showed no significant differences in amputation rate between the 3C Patch and

				or those who progress to amputation may need to be considered.	standard care arm, the major and minor amputation rates were the same for both groups.
50	6	Healthcare Professional	3.14	*The company's base case results showed cost savings of £191 per person over 2 years when 3C Patch is used instead of standard care. But, the EAC's base case results found that 3C Patch is cost incurring compared with standard care. The incurred costs were £1,590 per person over 2 years when modelled without an infection state (model A) and £1,993 when modelled with an infection state (model B).* To be used for those in whom other interventions have failed. Any cost is worthwhile when comparing with that of lower limb amputation. To look at one off costs is short sighted.	Thank you for your comment. Please see NICE's response to comment 49.
51	6	Healthcare Professional	4.10	*Large savings in care costs would be needed to offset the cost of 3C Patch and there was insufficient evidence presented to show that care needs would be significantly reduced after 3C Patch treatment.* Cost saving can be measured at all levels. Not only institutional. Personal, psychological, social etc etc. Any opportunity to offer an alternative care to save limbs and improve quality of life needs to be considered. This treatment intervention was never intended to be a standard care for all health care settings. It is for centres of excellence, who offer expertise and hope to those in whom most other interventions have failed. It is so important to have choices. One size does not fit all.	Thank you for your comment. The Medical Technologies Evaluation Programme evaluates the cost consequences of introducing novel and innovative technologies to the NHS. This includes the direct NHS costs of implementing new technologies. Quality of life measures were also presented as part of the submission and presented in the EAC's assessment report. Please see NICE's response to comment 11 on treatment setting and comment 5 on patient population.
52	8	Healthcare Professional	General	*Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?* Again I feel there is not a cost that can actually be put on reduction in pain for an individual who suffers constantly as a result of a wound. The time of treatment would also vary considerably and many would not require a full 20weeks of treatment. However the on going cost for these chronic wounds by district nurses and on going appointment at the diabetic foot clinic would far out weight 20weeks of treatment. clinically we also see those individuals with	Thank you for your comment. Please see NICE's response to comment 49 and 51 on the economic model. The committee acknowledges in section 4.1 that 3C Patch may fulfil and unmet need to diabetic foot ulcer care. However, as the committee were uncertain whether the technology would lead to cost savings within the NHS, it was unable to make a positive recommendation for the technology.

				chronic wounds going on the develop multiple drug resistance to antibiotics as they need repeated courses. Cost is an important factor but so it the ability to give these difficult to heal individuals the right to heal and be able to get on with living	
53	9	Company	General	*Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?* The company does not believe that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. There are issues and inconsistencies with the interpretation and summaries, particularly with the health economics, and the company believe that an independent health economic expert should be appointed by NICE to assess the EAC model inputs and methods in detail, in the light of the company's comments. The main issues are around the following points: (a) Economics: The report is based entirely on the EAC model which we do not believe is robust or suitable for decision making. The EAC model excludes of a large portion of DFU costs (e.g. inpatient costs for extra length of stay in hospital admissions for other causes) leading to an underestimation of the costs savings from additional healing. In addition, many of the EAC-used costs are inaccurate and disproportionately allocated to the 3C Patch arm. The combined impact of these errors is to substantially inflate the cost of 3C Patch, and substantially reduce the cost of standard care. There is further detail in the company fact check response to the EAC report. The company's serious concerns over the many issues with the EAC modelling and use of the Farr data have not been adequately addressed. (b) Healing rate - Given the substantial decrements to QoL associated with DFUs, and the long duration of hard to heal DFUs (many lasting for years or never healing), it does not seem reasonable to question the clinical significance of this improvement. Healing 12% more patients means there are 12 fewer patients per 100 who suffer ongoing ulceration and follow-on complications beyond 20 weeks. The Game	Thank you for your comment. External assessment centres are independent academic centres and they are responsible for the quality assurance of their own work and the conclusions they draw from the available evidence. It is not appropriate for NICE to request additional scrutiny of this work. If any further evidence is generated this can be reviewed as part of the standard guidance review and update process. a) The EAC was asked to provide a response to this comment. It said that inpatient costs are captured in the EAC model using data from the Game RCT for the proportion of patients experiencing inpatient admissions in each arm and costs as reported by Kerr et al. and used in other NICE guidelines. By using the direct trial data from Farr et al., the EAC does not consider costs that were unrelated to the diabetic foot ulcer (DFU) and only considers DFU related admissions. Regression analysis by Kerr et al. suggests that people admitted to hospital with diabetic related issues, not because of DFU, would have an additional length of stay. However, it is likely that people admitted for different conditions who also have a hard to heal DFU will generally be in worse health which will lead to a longer stay, not necessarily linked specifically to the DFU. Therefore, this was omitted by the EAC. Increasing costs associated with unhealed ulcers in both treatment arms does not have a substantial impact on the results of the economic model because both arms are being impacted. The difference between the weekly cost applied to the unhealed ulcer health states in each treatment arm in the EAC model is

				RCT dataset indicates that the differential in healing was largely maintained at 52 weeks and we estimate that 269 days of ulceration were averted in the first year for each additional person who healed with 3C Patch relative to standard care, a total of 4,300 fewer days of ulceration for the 3C Patch cohort. We present these numbers here as the committee discussion focused largely on the 12-day median reduction in time to healing (3C Patch relative to standard care). We feel the primary point was overlooked; the much more significant impact is in averted ulcer care observed in the RCT dataset in weeks 21-52 owing to the significant increase in the proportion of patients who healed with 3C Patch. Owing to the very long duration of many hard to heal DFUs, it is likely that further days of ulceration are averted beyond week 52. (c) Urgostart: All protease modulating dressings were widely used in the run-in period, and in the intervention period for the standard care arm, along with a wide range of other first line dressings. Non-interactive dressings remain the most utilized dressings in the UK and should therefore also be considered relevant comparators for 3C Patch. UrgoStart may not be appropriate for all patients. (d) Infections costs: The company's economic model included all costs related to infection, and the healing rates in the RCT and the economic model took full account of any infection impact. It is possible that in the RCT patches were used more often in the context of infection than would occur in routine practice. If so, the company model will have over-estimated costs in the 3C Patch arm, and under-estimated savings relative to standard care. (e) Stopping rule: The report states that "a stopping rule would be needed in the economic model". Whilst there is some disagreement as to which stopping rule should be applied (and it may therefore be reasonable to model more than one stopping rule) it is not reasonable to base the decision on an economic model that has no stopping rule at all and this is supported by the views of the clinical experts sought by NICE. With robust cost inputs there is a high probability that 3C Patch is cost saving under a variety of stopping rule scenarios.	around £170, the majority of which is due to the cost of the patch itself. b) The committee heard that the Game RCT did follow up patients at 52 weeks but this data is unpublished and the was limited to a telephone follow up call rather than a clinic visit. The committee acknowledged that diabetic foot ulcers reduce quality of life as noted in section 4.1. The EAC were asked to respond to the comment on the reduced ulcer care in the 3C Patch group in weeks 21-52 due to the significant increase in the proportion of patients who healed with 3C Patch. It said that in the model those people with unhealed ulcers continue to accrue costs related to ulcer care until healing for up to 2 years. The same cost is applied to both treatment arms for those with unhealed ulcers beyond 20 weeks. The difference in healing seen in the trial at 20 weeks is reflected in the model. Therefore, these costs will be captured for those people remaining unhealed beyond 20 weeks in both treatment arms. The same healing rate beyond 20 weeks is applied as per the company model. c) Please see NICE's response to comment 20. d) Please see NICE's response to comment 58. e) Please see NICE's response to comment 22. The limitations around the use of a stopping rule are discussed in section 4.8 of the guidance. Please see NICE's response to comment 4 on the SHELF and Delphi methods.

				We would aim to seek clarification and consensus using Delphi and/or SHELF methodology for the following issues (and also see Comment for Section 1): (a) Exactly when would 3C Patch be used where there is also an infection? Would any additional costs be incurred when there is an infection, that wouldn't be with other interventions? (b) Healing rates – is the extra 12% healing from 3C Patch, on top of the 22% healing rate seen with SoC, clinically meaningful? (c) What are reasonable cost assumptions for the various different costs on which the EAC and Reapplix disagree? (d) Would 3C Patch stretch existing services; if so how and how easily can those issues be addressed? Would 3C Patch be difficult to use in practice, or require measurement tools that the NHS currently doesn't have? (e) To what extent does the use of other protease modulation dressings replicate the same efficacy of UrgoStart? Is the low usage of UrgoStart during the 3C Patch study a real issue?	
54	9	Company	3.10	*The EAC corrected cost errors found in the company's model* This is factually incorrect. The EAC made these changes to the company's model but they were not corrections to cost errors. The EAC did not state that these were corrections to errors. • The company model did not use relative costs. The changes made in the EAC model were modelling decisions, not error corrections. • There was no double counting in the company model. The EAC changed the way in which district nurse inputs were modelled and therefore removed district nurse inputs from the company model as leaving them in would then have resulted in double counting. • Applying the cost of training up front is a modelling decision, not an error correction.	Thank you for your comment. The EAC was asked to respond to this comment. They agreed that there was no double counting of district nurse visits in the company model, this correction was made in the EAC model because of they included the cost of district nursing separately this had to be removed from the outpatient/community cost applied. Regarding the application of absolute costs rather than relative, the EAC state that is an error not a modelling preference. It is less accurate to apply an incremental cost to a health state rather than applying the cost for that particular element in both treatment arms separately. This artificially decreases the cost of that particular health state (unhealed ulcer) and so the difference in costs of moving to different health states in the model becomes skewed.

					Regarding the training costs, they believe it is more accurate to apply these costs up front. There limited justification for applying the costs on a weekly basis and subjecting them to discounting when they can be applied up front which is when the majority would be expected to occur. The committee decided to amend the wording in section 3.10.
55	9	Company	3.12	*The EAC revised the healing rates in the model in line with published RCT data and its preferred discontinuation rates* It is important to understand this 0.6% in context. The weekly probability of healing in the company model is 0.057. The 0.6% refers to an absolute reduction in this rate to 0.051. This is a reduction of more than 10% in the probability of healing. This is not a small reduction. For balance it should also be stated that a movement of the same size in the opposite direction would substantially increase the savings arising from 3C Patch.	Thank you for your comment. The committee understood that this referred to the probability of healing with 3C Patch in weeks 6 to 19 being a key driver in the company model, and that a reduction of approximately 0.6% could result in the direction of the results changing. The committee decided to amended section 3.12.
56	9	Company	3.13	*The EAC made a number of amendments to the costs used in the base case model* (a) The Farr et al analysis is considered to be poor quality and has not been published. Further detail is set out in the comment on section 4.9. It is difficult to understand how can this be given priority over evidence from peer-reviewed publications? (b) It is incorrect to say that there were cost errors. See response under 3.10 above.	Thank you for your comment. a) The EAC were asked to provide a response to this comment. It said it used analysis by Farr (unpublished) within the model as it contains trial data from the RCT which is most relevant to the population for this evaluation. This was generally used to capture resource use from the trial in order to apply costs. Generally, the EAC still made use of the Kerr paper similar to the approach used by the company. Further to this, additional unpublished supporting information from the Kerr et al. paper was used in the company model but is not in the public domain and therefore not peer reviewed. By using Farr (unpublished), the EAC was able to combine RCT data alongside a transparent methodology for individual costs. The EAC deemed that the Farr et al. was of good quality and appropriate for inclusion. b) Please see NICE's response to comment 54.

57	9	Company	3.15	*The EAC's sensitivity analysis found the cost of index ulcers and discontinuation rate to be the biggest cost drivers* See also 3.3 and 3.11. All clinical experts agree that there would be discontinuation. No clinician is likely to continue using the patch for 20 weeks where no progress has been made. 0% discontinuation is therefore not a reasonable assumption. Also, this result has been generated using the EAC's base case cost inputs, which the company do not consider reasonable or evidence based, as explained in detail elsewhere.	Thank you for your comment. Please see NICE's response to comment 22 on the stopping rule. The committee acknowledged that a stopping rule would be used, however, there was uncertainty on what this rule would be and what the clinical outcomes would be if this rule is adopted. These uncertainties are listed in section 4.10 of the guidance.
58	9	Company	4.3	*3C Patch treatment should be halted whilst wounds have a moderate or severe infection* The company's economic model included all costs related to infection, and the healing rates in the RCT and the economic model took full account of any infection impact. No patient was excluded from the analysis because of infection. Clinical judgement was used in the RCT to determine whether a patch should be applied in the presence of infection, and in 22% of weeks in which infection or possible infection was recorded, no patch was applied. Patch use was resumed in these patients when clinical judgement indicated that it was appropriate. It is possible that in the RCT patches were used more often in the context of infection than would occur in routine practice. If so, the company model will have over-estimated costs in the 3C Patch arm, and under-estimated savings relative to standard care.	Thank you for your comment. The EAC was asked to respond to this comment. It stated that the company's economic model reflects the approach used in the RCT where 3C Patch use was continued whilst the ulcer was infected. Clinical experts confirmed that 3C Patch was likely to be discontinued if a serious infection occurred and restarted once the infection cleared. The EAC's Model B represented a scenario whereby use of 3C Patch was discontinued in patients experiencing a serious infection in line with comments received. The EAC felt it was important to reflect infection related discontinuation in the economic modelling which was not possible in the company model. The committee acknowledged the company submission which stated that the cost impact of wound related infections is incorporated in the economic model by means of weekly antibiotic prescribing costs estimated from the RCT dataset. It updated the wording to section 3.9.
59	9	Company	4.8	*Economic modelling is limited by the available clinical evidence and its relevance to the NHS clinical pathway* (a) The company model used a conservative healing rate for this group (0.0068, compared with 0.0138 for standard care), to ensure that the benefits of the patch were not overstated. This estimate was based on weekly healing	Thank you for your comment. A) The EAC was asked to provide a response to this comment. They acknowledged that that this value could be conservative because it does not account for any benefit of the 3C Patch seen over the first 5

				observed in the standard care arm for patients whose ulcers had not reduced in area by ≥50% in the first 5 weeks, and therefore takes no account of any potential benefit from 3C Patch over the first 5 weeks. (b) The very different cost estimates arise not only from application of the healing rates for the whole cohort, with no discontinuation, but also from application of very different unit costs. These are contested by the company, as outlined in detail in the company's fact check response to the EAC report. The company does not consider that these serious concerns have been adequately addressed.	weeks. However, there is no clinical data available with which to confirm this. B) Please see NICE's response to comments 47 and 56.
60	9	Company	4.9	*The EAC and company used different data sources in the cost modelling, which changed the direction of the cost case for 3C Patch* Farr et al. is not considered by the company to be a robust data source. Also, the EAC model is built substantially on non-significant cost differences reported in Farr et al. The issues related to Farr et al. as used in the EAC model were set out in detail in the company fact check response to the EAC report. The company does not consider that the response to that document adequately addressed these concerns. The company model was also based on direct trial evidence on resource use, including prescribing, dressings, district nurse visits etc, wherever robust data were available. It is important to note that Farr et al. did not have direct trial evidence on costs for crucial inputs in the EAC model such as inpatient care. The EAC applied unit costs from other sources, including repeating a mistake in Farr et al. by using the wrong cost from a NICE publication (Table 12, Appendix J NG 19). The unit cost used by the EAC (£6,249, uplifted to £7,052) relates to outpatient, primary and community care for a severe ulcer during the entire period of ulceration, as explained in the text on page 14 of Appendix J NG 19. It excludes inpatient costs and is not specific to infection. This cost is applied by the EAC to inpatient admissions for severe infection. The correct unit cost in the NICE document is the inpatient cost provided in Table 12, £3,848 (£4,343 in current prices). Given the	Thank you for your comment. Please see NICE's response to comment 47 and 56. The company fact check of the EAC report followed standard process. This is intended as an opportunity for the company to highlight any factual inaccuracies in the report. Factual inaccuracies reported by the company and confirmed to be a factual inaccuracies by the EAC, were corrected in the EAC report. The updated EAC report and fact check document were included in the public consultation. Any other comments that were deemed to be a difference in opinion, rather than a factual inaccuracy, were not amended.

				multiple errors identified by the company in the EAC model, and set out in the fact check, the company does not accept that this model is a robust foundation for assessing the costs and savings associated with 3C Patch.	
61	9	Company	4.10	*The company's base case is unstable and 3C Patch is unlikely to be cost saving* (a) The company's probabilistic sensitivity analysis found that the likelihood of 3C Patch being cost saving to the NHS was approximately 90% over 3 years. The EAC acknowledged that the distributions for model inputs for this analysis were appropriate. (b) The company does not accept that the EAC's model B is an appropriate model structure, nor that it provides an accurate representation of the relative costs of 3C Patch and standard care. The company's detailed criticisms of model B were set out in the fact check response to the EAC report. These criticisms have not been adequately addressed in the EAC's response. While the company model did not have a separate infection state, it fully reflected all infections recorded in the RCT dataset, and their impact on costs and healing rates. Clinical judgement was used in the RCT to determine whether a patch should be applied in the presence of infection, and in 22% of weeks in which infection or possible infection was recorded, no patch was applied. Patch use was resumed in these patients when clinical judgement indicated that it was appropriate. It is possible that in the RCT patches were used more often in the context of infection than would occur in routine practice. If so, the company model will have over-estimated costs in the 3C Patch arm, and under-estimated savings relative to standard care. (c) The company does not accept that the EAC's 2-way sensitivity analysis demonstrates that there are few combinations of discontinuation and healing rates that can lead to 3C Patch becoming cost saving, nor that only clinically implausible combinations are associated with cost savings. The EAC's 2-way sensitivity analyses are all based on the EAC model A and B base case cost inputs. The	Thank you for your comment. a) The committee acknowledged that p114 of the EAC's assessment report does say that 'The company also presented PSA results for 10,000 iterations of the model and reports mean probabilistic cost savings of £192 per patient over a 2-year time horizon. The EAC judged the distributions used to be appropriate'. b) Please see NICE's response to comment 58. c) The committee acknowledge that the EAC's 2-way sensitivity analysis was based on the EAC's model. Please see NICE's response to comments 53 and 56 on the cost inputs used by the EAC. d) Please see NICE's response to comments 53 and 56 on the cost inputs used by the EAC. e) External assessment centres are independent academic centres and they are responsible for the quality assurance of their own work and the conclusions they draw from the available evidence. The EAC were asked for a response to this comment. The stated that the validation checks performed by the company are always performed as standard for any model produced by the EAC. Model calculations are checked by a health economist separate to the project and standardised checklists are used to pressure test the model for errors. The model calculations (in Excel) were also verified by using the EAC inputs in the company model (in Treeage). Inputs are assessed using clinical expert opinion. The reasoning around the clinical and cost inputs used are justified in full in the EAC assessment report.

				company believes that these cost inputs are unsound. Detailed criticisms of these inputs were set out in the company's response to the EAC report. These have not been adequately addressed. (d) The company does not believe that these cost inputs used by the EAC are sound. Therefore use of the company's healing and discontinuation rates in combination with the EAC's costs is not a robust test of whether 3C Patch is cost saving . (e) The company does not consider the Committee's conclusion to be reasonable and does not accept that the cost-saving case presented was not robust. The model was based on the trial dataset, with other inputs sourced from peer-reviewed published papers, and published NHS data. Model inputs and outputs were subject to an extensive validation process, which was explained in detail in the submission. No such validation was reported for the EAC model. As explained above, the company believes that the trial demonstrates a significant reduction in care needs after 3C Patch treatment. The study demonstrated both an increase in the proportion of patients who achieved healing within 20 weeks (34% in the 3C Patch group versus 22% in the standard care group), and reduced time to healing (median days to healing in those who healed 72 in 3C Patch versus 84 days in standard care). Both were statistically significant differences. Two points follow: first, less ulcer care was required within the 20 weeks for 3C Patch patients, second, healing 12 more patients out of a 100 means there are 12 fewer patients per 100 who require ongoing ulcer care and follow-on treatments beyond 20 weeks. Data from the Game et al. RCT indicate that the difference between the two trial arms was maintained at 52-week follow-up, even though all patients received standard care from week 20. At 52 weeks, 54.55% of 3C Patch patients and 44.03% of standard care patients had achieved healing. In other words, over a year many fewer days of ulcer care were required for 3C Patch patients than for standard care patients (approximately 4,300 days of ulcer care were averted in the first year for the 3C Patch cohort	The committee heard that using either EAC costs within the company model or company costs within the EAC model led to 3C Patch being cost incurring. The committee felt that this led to sufficient uncertainty in the cost case for the technology not to be recommended. f) Please see NICE's response to comment 19.

				relative to standard care, 269 days for each additional patient who healed with 3C Patch). Multiple studies indicate that hard to heal DFUs can last for many years. Some never heal. Achieving healing in 12 more patients in every 100 is therefore likely also to lead to reduced demand for ulcer care and follow-on treatments in subsequent years. (f) The company does not accept that insufficient evidence was presented to show that care needs would be significantly reduced after 3C Patch treatment, as outlined above.	
62	12	Professional Society	General	*Costs will be considered from an NHS and personal social services perspective.* The RCT (Game et al 2018) did not undertake a cost-effectiveness evaluation. The item cost of the 3C Patch is £150 per patch (excluding VAT) plus clinician and technician time to prepare the product. These costs will exceed the costs of current standard practice. However, if the product is clinically effective, the cost benefits of healing may outweigh the costs of care with the 3C Patch. More information is needed.	Thank you for your comment. Cost effectiveness evaluations are outside of MTEP's process and methods, please see the programme's methods guide.
Further Research					
63	4	Healthcare Professional	4.2	*Randomised controlled trial evidence shows improvements in ulcer healing proportion and time to healing but the clinical importance of the observed benefit is uncertain* Given urgostart was not around at the time of the trial then would it not be worth further trials putting the 2 products together? At the time of the trail the 3C patch was used against the advanced dressings available to clinicians	Thank you for your comment. Section 4.10 was added to the guidance to list potential additional research which could be done to address clinical and economic uncertainties. The committee acknowledged that further research could be done in an UrgoStart experienced population. However, the committee decided not to alter their recommendations.
64	4	Healthcare Professional	4.10	*The company's base case is unstable and 3C Patch is unlikely to be cost saving*	Thank you for your comment.

				is further research warranted?	Please see NICE's response to comment 63.
65	5	Healthcare Professional	4.2	*Has all of the relevant evidence been taken into account?* Yes. 4.2 - although the evidence gap noted here is valid with regards Urgostart, the trial was set up before the data with regards Urgostart was available. High quality studies prior to the publication of the Urgostart data remain valid and should not be discounted. The committee state uncertainty of the results if Urgostart had been used in the run in period - hence a recommendation for further research into this (taking into account Urgostart in the protocol) would seem very appropriate for the 3C system (and in fact any other dressing/intervention in this area going forward).	Thank you for your comment. Please see NICE's response to comment 63.
66	5	Healthcare Professional	General	*Are the recommendations sound and a suitable basis for guidance to the NHS?* General comment - Although there is currently not the evidence consider recommending for standard care of diabetic foot ulcers, there is a potential for this to have benefit for the very hard to heal ulcers. Hence would benefit from further research in this group.	Thank you for your comment. Please see NICE's response to comment 63.
67	11	Healthcare Professional	General	*Are the recommendations sound and a suitable basis for guidance to the NHS?* Further information/ case series around use of stopping rule and in urgostart usage within real world clinical practice would be useful	Thank you for your comment. Please see NICE's response to comment 63 on the inclusion of UrgoStart in a trial on 3C Patch. Please see comment 4 for the EAC's view on the use of a stopping rule in research.
General Comments					
68	3	Healthcare Professional	General	*Has all of the relevant evidence been taken into account?* Yes although I believe some of the clinical expert evidence is questionable.	Thank you for your comment.
69	7	Healthcare Professional	General	*Has all of the relevant evidence been taken into account?*	Thank you for your comment.

				yes	
70	9	Company	General	*Has all of the relevant evidence been taken into account?* Yes.	Thank you for your comment.
71	6	Healthcare Professional	4.1	*The committee acknowledged that for some people 3C Patch might fulfil an unmet need in DFU care.* Absolutely.	Thank you for your comment.
72	10	Professional Society	General	ABCD feedback to NICE re 3C patch - from a variety of our members We at Wolverhampton Diabetes Centre were involved with the Leucopatch Trial a few years ago I was one of the named collaborators in the study conducted by Frances Game: https://pubmed.ncbi.nlm.nih.gov/30243803/ The 3C patch was previously called Leucopatch, and the trial did indeed show an improvement in healing - albeit slowly Bear in mind that diabetes foot ulcers generally are slow to heal - if at all However, the study did show a reduced time to heal and a reduced ulcer size at 20 weeks (some of our patients have had ulcers for years) The study did have limitations however, and the study unfortunately did not show any change in amputation nor infection risks. It was also unfortunate that NICE could not recommend this treatment on the basis of health economics (or lack of evidence to support this in the study) The upfront cost of the kits (centrifuge was loaned) was likely the main prohibiting factor, each kit costs £150 for 3 “patches” There is a potential risk of patch failure in the centrifuge (aka the patch did not develop in the centrifuge, and a repeat blood extraction may need to be done to the patient) which the NICE recommendation did not mention - but we	Thank you for your comment. In response to the feedback from the first member, the guidance (sections 3.1 to 3.6) summarises the outcomes of the Game et al. RCT. The committee understood that the use of 3C Patch was likely to be cost incurring, even without the failure of patch development, and so could not recommend the use of this device in the NHS. The cost evaluation of the technology is limited to evaluating the resources and expected outcomes associated with the technology under consideration compared with current comparators and healthcare pathways defined in the scope, in line with the programme’s methods guide. In response to the second member, the committee acknowledged that hard to heal wounds would be existing for longer than 4 weeks. Section 4.1 acknowledges that there could be challenges associated attending appointments in secondary care.

				had been aware of this as one of the local centres conducting this trial I am unable to comment on the health economics behind their recommendation to decline this as a long term solution (the section in point 4.8 pretty much sums up the uncertainty in the health economics based on the study's limitations) I suspect the health economics were only calculating the "medical" cost of this treatment (aka, the 3C kit, centrifuge upkeep, nurses' healthcare times to apply the patch, blood venesection costs, etc), I am unsure if the health economics calculated the "true cost" of a non-healing ulcer (some of which can last for months/years) - loss of productivity in the patient, loss of income (and tax), the increased need for patient's healthcare, increased need for social support, foot offloading, and increased health support at home, etc. I think a true calculation of the benefits of earlier healing of a Diabetes Foot Ulcer using such treatments should take into account all of these factors and financial implications. Kind regards [redacted] [redacted] Consultant Physician, Diabetes & Endocrinology [redacted] Royal Wolverhampton NHS Trust Wolverhampton Diabetes & Endocrine Centre WV10 0QP	

				Hello [redacted], After reviewing I would agree with the recommendation of not supported. Good comments raised about standard of care would now include UrgoStart which wasn't necessarily standard care in the original studies. Also the consideration of using 3C Patch at 4 weeks where standard care hadn't healed the ulcer at least by 50% is ambitious. In some wounds due to aetiology you would be happy to have 40% reduction as long as it was moving in the right direction. Good observation around limitations of measuring for such targets to be applied to treatment initiation. As services are moving closer to home the availability to undertake 3C Patch applications is reduced and would stay as secondary care interventions. They clearly have a role to play but would be special initiation, rather than at the levels on consideration they discuss. [redacted]	
73	8	Healthcare Professional	General	*Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?* The reality is that there are patients that we need this product for as with out it there are likely to require surgical intervention that may mean they loose a limb as the wound will become infected. For other healing is not the only outcome if i can make that wound smaller and less leaky and therefore improve there quality of life that is an achievement also as it buys them time.	Thank you for your comment. In section 4.1 of the guidance the committee acknowledges that there is an unmet need for new treatments for hard-to heal diabetic foot ulcers (DFUs) and that not all treatments will work for all ulcers. It acknowledges that DFUs reduce quality of life.
74	2	Healthcare Professional	General	*Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?* No	Thank you for your comment.
75	5	Healthcare Professional	General	*Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?*	Thank you for your comment.

				No	
76	7	Healthcare Professional	General	*Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?* No	Thank you for your comment.
77	9	Company	General	*Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?* No	Thank you for your comment.
78	12	Professional Society	General	*The extent to which the technology is likely to reduce use of staff or facility resources* This technology may reduce use of staff and facility resources through improved healing in patients with DFU who have received high quality optimized care (offloading, control of foot infection, ischaemia and wound debridement) in specialist diabetic foot clinics but failed to heal. This could lead to less clinician time for dressing changes etc, reduction in amputations and associated rehabilitation. However, the benefits reported in this study may not be achievable in patients who have not received high-quality optimized care outside diabetic foot clinics.	Thank you for your comment. The committee acknowledged that improved ulcer healing would lead to a reduction in costs. However, in the economic model, the cost savings associated with improved healing did not offset the costs associated with 3C Patch use, when compared to standard care.
79	12	Professional Society	General	*The greater the impact of the disease or condition on quality of life or life expectancy, the greater the likelihood that a national evaluation is important.* *For technologies aimed at treatment, consideration should take into account the likely degree of improvement in life xpectancy, disease severity and quality of life, paying particular attention to conditions that are associated with social stigma.* Diabetic foot ulceration is associated with a greatly increased risk of amputation and mortality. It is also self-evident (and supported by a body of qualitative evidence) that people with chronic wounds have	Thank you for your comment. Section 4.1 of the guidance states that there is an unmet need for new treatments for hard-to heal diabetic foot ulcers (DFUs) and that not all treatments will work for all ulcers. The committee acknowledged that DFUs reduce quality of life.

				reduced quality of life due to the symptoms of chronic wounds which include pain, malodour, and excessive exudate. These factors can contribute to reduced mobility, depression, loss of esteem and self-neglect.	
80	12	Professional Society	General	*Is the technology likely to contribute to the sustainability agenda, for example, less energy usage or less waste generation during production or clinical usage?* The company claims the 3C Patch reduces the use of energy and raw materials because of faster healing times and reduced use of single-use dressings. It also claims the 3C Patch reduces the environmental impact because of less travel to appointments. There is no published evidence to support these claims.	Thank you for your comment. The committee acknowledged that there is no published evidence to support any of the company's sustainability claims.

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