National Institute for Health and Care Excellence

IP1790 Restorative Neurostimulation to Activate the Lumbar Multifidus for chronic mechanical low back pain

IPAC date: 14 July 2022

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1	Consultee 1 Company	**Lay description and 2.3**	'on the lower back' Later in the guidance document it is stated that the device is implanted in the upper buttock. In practice the device is implanted in the upper buttock or lower back according to patient preference. We therefore recommend that all references/text to implantation site is amended to refer/include to both implantation sites -the lower back and upper buttock for consistency and accuracy.	Thank you for your comments. **IPAC considered and amended lay description as follows:** 'Low back pain of unknown cause (non-specific) can be long term (chronic) and difficult to treat (refractory). In this procedure, a cut is made on the lower back or upper buttock and a small battery-powered device (neurostimulator) is placed under the skin. Two wires are placed near the nerves that control the muscles either side of the spine (lumbar multifidus lmuscles) and connected to the neurostimulator. After the procedure, the patient uses a remote control to stimulate the nerves using low-voltage electricity. This is usually done twice a day for about 30 minutes. The aim is to stimulate the lumbar muscles and reduce pain.
2	Consultee 1 Company	**Lay description**	in the surgical procedure the two wires are placed near the nerves and not on the nerves. It is more accurate to say near the nerves rather than on the nerves.	Thank you for your comments. See response to comment 1.
3	Consultee 1 Company	**Lay description.**	the correct name of the muscle is the lumbar multifidus muscles. It is more accurate to say lumbar multifidus muscles.	Thank you for your comments. See response to comment 1.

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4	Consultee 1 Company	**Lay description**	It is more accurate to say that the aim is to stimulate the medial branch of the dorsal ramus to elicit episodic contraction of the lumbar multifidus and reduce pain.	Thank you for your comments. This is a lay description and therefore the wording used is simple language. IPAC considered and amended the statement in lay description as follows: 'the aim is to stimulate the lumbar muscles through its nerve supply and reduce pain'.
5	Consultee 6 NHS professional University Hospital Southampton	**1**	"In my opinion, Multifidus stimulator should be available on a routine basis – Standard or Special arrangement- for these difficult to treat subset of chronic low back pain sufferers. The assessment should be done in an MDT manner, which should have the implanter (Neurosurgeon or pain physician), a pain psychologist, pain physician, neuromodulation nurse specialists, physiotherapist etc., and the outcome data should be collected via the National Neuromodulation Registry (NNR)."	Thank you for your comments. IPAC considered your comments and amended 1.1. Data collection via the National Neuromodulation Registry (NNR) was recommended in 1.2. In section 1.4 of the guidance, IPAC recommended patient assessment through an MDT and amended the wording slightly to those with experience in pain management and of neuromodulation stimulation procedures.
6	Consultee 7 Genesis Research Services	**1.1**	"The baseline risks of the stimulator are favourable compared to spinal cord stimulator (SCS) devices approved by NICE. There is a favourable safety profile in comparison to published SCS safety data (Eldabe literature review > 400 subjects and Hayek multicentre review of 234 subjects). All adverse events were comparable or less. This included infection, implant site discomfort, lead fracture and malfunction. With the ReActiv8 implant there were no lead migrations due to the lead design frequently seen with SCS. The surgical interventions	Thank you for your comments. The IP programme does not assess the efficacy and safety of comparator interventions.The committee did not compare the evidence for safety for this procedure with that for spinal cord stimulation and state that the evidence should be better than that for spinal cord stimulation.

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			for system explants and lead replacements were less than SCS. The theoretical risk of adverse events is less than SCS due to the extra-spinal placement of the leads. This is therefore a procedure that carries less risk than a conventional SCS device that is already NICE approved for clinical use."	
7	Consultee 7 Genesis Research Services	**1.1**	The RCT outcomes of 120 days must be evaluated in the context of the time it takes to restore function to the of the spinal stabilizers. Statistically and clinical meaningful improvement was seen in VAS at 120 days. Disability, quality of life and patient satisfaction showed improvement at 120 days and continued to improve beyond this. The patients included in the ReActiv8 B study had, on average, 14 years of lower back pain with almost all the days impacted in the previous year. Reversal of long-term inhibitory effects and functional muscle loss of the spinal stabilisers continues well beyond the 120-day study period. The guidelines should consider the durability of the therapy as evidenced by the gradual sustained restorative effect seen in the 1, 2- and 4-year follow up data. There is currently no other treatment available that could deliver these profoundly positive restorative results in the management of patients with refractory CLBP that would meet the inclusion criteria for this device. All of my implanted patients utterly failed high utilization of standard medical care. Decrease opioid use and health care utilization and return to work outcomes were achieved. These are achieved in the high health care utilization, difficult to treat, functionally disabled cohort of patients. This has been a life changing therapy for these patients.	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered all the evidence and changed the recommendation in 1.1.

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8	Consultee 8 on behalf of The British Pain Society	**1.1 & 1.3**	"1.1 The BPS is of the opinion that this treatment should have its position raised to being available on the NHS on the grounds of reducing complication rates as the treatment providers have gained experience with implantation allied with development of the underlying technology, e.g implantable leads, to the point where complication rates are minimal and sit below known complication rates accepted for spinal cord stimulation which is a NICE accepted similar technology. The evidence assessment does not take into account the combination of difficulties of evaluating changes in pain scoring when used as a primary outcome and that the study was designed similarly to previous neuromodulation studies which were all spinal cord stimulation where there is an immediate effect at 3 months. This is a long-term restorative therapy where excellent results are seen at 1, 2 and now 3 years in patients. All secondary outcomes, assessing functional and patient well being, were positive in outcome and , in the opinion of the BPS, should hold greater strength in overall treatment evaluation rather than the shorter term VAS pain score changes. The BPS is aware that further evidence is currently undergoing peer-review prior to publication which is expected to strengthen the evidence base to support implementation of this treatment. The BPS would ask the committee to delay proceedings to allow this evidence to be provided prior to a final decision as moving forward without doing so would delay treatment for a specific sub-population of patients until after the usual consultation review in several	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1. IP guidance is advisory and not a commissioning mandate to recommend that this treatment should be available on the NHS. The IP programme does not assess the efficacy and safety of comparator interventions.The committee did not compare the evidence for safety for this procedure with that for spinal cord stimulation and state that the evidence should be better than that for spinal cord stimulation. IPAC also considered comments around difficulties of evaluating pain scores and use of short term VAS scores in the RCT (Gilligan 2021).

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			years' time. This would be a significant detriment to those patients."	
9	Consultee 9 International Neuromodulation Society	**1**	In summary, as the members of the Executive Committee of the International Neuromodulation Society and representing our more than 2500 members, we believe that multifidus muscle stimulation therapy has been proven safe and effective in high quality peer reviewed studies and that long term efficacy is of great clinical significance. In light of this data, combined with the lack of effective therapies once physical therapy, pharmacotherapy and injection therapy have failed, we believe that this therapy should be made clinically available to the patients who suffer greatly from chronic mechanical back pain with multifidus muscle dysfunction. Thank you for your consideration of our request.	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1.
10	Consultee 10 NHS professional NHS - Royal Brompton & Harefield hospitals	**1.1**	There is a well conducted RCT and 2 well conducted trials which all show favourable results at 1 and 2 years. I feel this therapy should be available to the small cohort of patients who will benefit from this treatment, without further research.	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1.
11	Consultee 11 NHS professional	**1.1**	**1.1 Evidence on its efficacy is inadequate in quantity and quality.**	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year

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			Response: The committee may wish to consider the below: a) The MS device is the only implantable neuromodulation device to be compared against a sham device in a rigorous double blinded design. Such a design has not been applied on such a scale in a parallel design for other pain devices recommended by NICE for low back pain. (please see NICE MTG41) b) Furthermore, having contributed to the design of the Gilligan et al 2021 study I will point out that the design has several issues which in retrospect contribute to the lack of significance on the primary outcome, these include: • The setting of a primary outcome at 120 days in a rehabilitative therapy where the effects accrue over time was in retrospect too early a point to observe the impact of the therapy, the 120-day point was however dictated by ethical considerations. • The choice of a dichotomised primary outcome around the 30% VAS reduction and no intake of medication for any indication impacted the statistical significance since nine patients who took analgesics for acute transient pains unrelated to the low back were counted as therapy failures even when they had reported >30% improvement VAS.	follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1. The IP programme does not assess the efficacy and safety of comparator interventions. The committee did not compare the evidence for safety for this procedure with that for spinal cord stimulation.

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			c) I am pleased to note that the committee observe that in the Gilligan 2021 study • LBP-VAS was significantly in favour of the therapeutic stimulation treatment group (-3.3 compared with -2.4; difference of -0.9 cm; 95% CI -1.6 to -0.1 cm; p=0.032). • The cumulative-proportion-of-responders analysis showed that therapeutic stimulation was superior to sham-control (p=0.0499). • I will also point out that all secondary outcome measures at 120 days point to the superiority of the intervention over control barring resolution of low back pain which is not expected to occur at 120 days. d). Two-year data from Gilligan et al study (Neurosurgery submitted June 2021) is to our knowledge, available and confirms the longevity of the response to MS therapy. • Four-year data from the Deckers 2018 (Mitchell B et al. Durability of the Therapeutic Effect of Restorative Neurostimulation for Refractory Chronic Low Back Pain. Neuromodulation 2021; E-pub ahead of print.DOI:10.1111/ner.13477) demonstrates longevity of the response to MS therapy. Data from the UK based PMCF study (Thomson et al, Pain and Therapy submitted July 2021) will shortly become available and would complement existing up to date MS device implant data in clinical practice in an NHS setting.	

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12	Consultee 12 Department of Anesthesiology, Perioperative and Pain Medicine Division of Pain Medicine Pain Management Center Harvard Medical School BRIGHAM AND WOMEN'S Health Care	**1, 2, 3**	Thank you for the opportunity to comment on the provisional recommendations on “Restorative Neurostimulation to Activate the Lumbar Multifidus for Chronic Mechanical Low Back Pain”. I am the principal investigator for the ReActiv8-B pivotal clinical trial (clinicaltrials.gov identifier: NCT02577354) which evaluated the efficacy and safety of a restorative-neurostimulation treatment for patients with chronic low back pain secondary to multifidus muscle dysfunction, and lead author on the related publication considered in your provisional recommendations. A manuscript reporting on the two-year outcomes is currently under review at a prominent peer-reviewed journal. Chronic low back pain (CLBP) secondary to impaired neuromuscular control of lumbar spine stability is often referred to as mechanical or musculoskeletal CLBP. It represents an important unmet clinical need, especially for patients who are severely impacted by pain and disability, effective treatment options are lacking. In the pivotal trial, we studied an implantable neurostimulation system which targets the neuromuscular control of lumbar spine stability. It invokes a rehabilitative, restorative mechanism leading to improvements that accrue over time and are maintained when the system is dormant between sessions. To avoid confusion with spinal cord stimulation, the term “restorative neurostimulation” is used to describe this new type of neurostimulation. Spinal cord stimulators are commonly used for the	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1. IPAC considered your comments about ‘restorative neurostimulation’ but decided not to amend.

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			treatment of radicular-CLBP post spine surgery. These systems, which employ sensory nerve stimulation to mask the perception of neuropathic pain while stimulating, are not effective in patients with musculoskeletal CLBP. While the interpretation of any trial should depend on the totality of the evidence (i.e., the primary, secondary, and safety outcomes) and not just a single end point, the following may provide additional justification: ▪ The primary endpoint was 'inconclusive' in terms of treatment superiority; that is, while it did not meet statistical significance, the confidence interval is compatible with a clinically meaningful treatment effect. ▪ The cumulative-proportion-of-responder-analysis (CPRA) of the primary endpoint data (before dichotomization) showed a statistically significant difference suggesting treatment superiority at 120 days. This supporting intention-to-treat analysis, which has greater statistical power than the dichotomized primary outcome, was prespecified in the protocol and statistical analysis plan. ▪ The primary outcome measure (improvement in low back pain VAS) showed a statistically significant and clinically meaningful difference in favor of the treatment at 120 days. ▪ In contrast to the immediate effect seen with analgesic treatments, restorative neurostimulation follows gradual rehabilitative trajectory which varies	

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			by patient. Consequently, the treatment effect continued to grow beyond 120 days. ▪ Patients were included based on “severe and disabling chronic low back pain” as eligibility criteria required pain intensity of at least 6 on a 10-cm visual analog scale (VAS) or numerical rating scale from 0-10 (NRS) and at least a disability impact of 21 on the Oswestry Disability Index (ODI). Furthermore, in the ReActiv8-B RCT candidates were required to have had pain on more than half the days in the prior year. These patients were refractory to conventional medical management including medication and physical therapy for their low back pain. This is a difficult to treat patient population with few remaining effective therapeutic options. In light of these arguments I believe that it is appropriate to consider the secondary- and long term outcomes in a more constructive interpretation than a “negative trial”: ▪ The secondary outcomes, including disability, quality of life and patient satisfaction, consistently showed a statistically significant and clinically meaningful difference at 120 days in favor of the treatment. ▪ Treatment durability is demonstrated by the statistically significant and clinically substantial one-year improvements which are sustained through two years (manuscript submitted and under peer-review). ▪ The incidence of serious procedure- or device-related adverse events compared favorably to that reported in the literature for other neuromodulation therapies for chronic pain.	

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			In conclusion, I believe that this unique therapeutic approach addresses an important unmet clinical need in a well defined subset of chronic low back pain patients for whom we had no effective solutions before. Based on the totality of evidence of the ReActiv8-B pivotal trial, these patients appear to receive an important clinical benefit from a therapy with a well characterized and favorable safety profile. Thank you for considering my comments in your recommendations.	
13	Consultee 13 NHS professional Consultant in Pain Medicine and Neuromodulation The Walton Centre NHS FT, Liverpool	**1.1**	My experience undertaking 11 procedures as part of a post marketing clinical follow-up study (PMCF) is that this is an extra spinal, safe and efficacious procedure and I therefore do not agree that this procedure should be restricted to research use only and deprive patients of a possible therapeutic approach. The procedure is intended for a carefully selected group of patients, for whom other treatments have failed. In my experience this is a restorative treatment in which the pain-relieving effect develops over time and is then sustained. Moreover, the procedure has a favourable safety profile compared to other intra spinal (epidural) neuromodulation procedures.	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1. IPAC considered your comments about 'restorative neurostimulation' but decided not to amend.
14	Consultee 13 NHS professional Consultant in Pain Medicine and Neuromodulation	**1**	In summary I would highly recommend that this procedure to be made available for the specific group of NSCLBP patients who may benefit from it. As it is a new treatment I think it is only appropriate that ongoing arrangements should be in place for further clinical audit.	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-

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	The Walton Centre NHS FT, Liverpool			A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1.
15	Consultee 14 NHS professional President on behalf of the Neuromodulation Society of UK & Ireland and board members	**1**	The Neuromodulation Society of UK & Ireland (NSUKI) is the only multidisciplinary society involving Pain Clinicians, Neurosurgeons, Neuromodulation Nurses, Psychologists and Physiotherapists involved in the practice of spinal cord stimulation. NSUKI thanks NICE for IPG draft on Neurostimulation of lumbar muscles for refractory non-specific chronic low back pain. Some of the NSUKI members have long term experience of using this technology in patients with refractory low back pain.	Thank you for your comments.
16	Consultee 14 NHS professional President on behalf of the Neuromodulation Society of UK & Ireland and board members	**1.1**	Spinal cord stimulation is a therapy used to provide pain relief whilst ReActiv8 multifidus muscle stimulation is a restorative therapy targeted at rehabilitating the multifidus muscles that have experienced neural inhibition. Similar to most rehabilitative therapies, the effects of multifidus muscle stimulation would only be noticeable few months later. The primary outcome measure in the Gilligan 2021 study was a composite of 30% VAS reduction with no	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.

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			increase in medication at 120 days. This study has showed a non-significant difference to active sham on the primary outcome. However, we take the view that the study results when analysed globally point to a different conclusion: a) The prespecified cumulative-proportion-of-responders ITT analysis which has greater statistical power than the dichotomised primary outcome and was based on primary outcome data showed a significant difference between the treatment and control groups at 120 days. Furthermore, the improvement in pain intensity (VAS) showed a clinically meaningful and statistically significant between-group difference at 120 days. This warrants interpretation of the totality of data. b) The secondary outcomes, including Oswestry Disability Index (ODI), quality of life (EQ-5D), subject global impression of change (SGIC), clinician global impression of change (CGI) and patient treatment satisfaction (TSQ) consistently showed a statistically significant and clinically meaningful difference at 120 days in favour of the treatment. c) In contrast to an immediate treatment effect seen with analgesic treatments such as spinal cord stimulation, restorative neurostimulation follows a more gradual rehabilitative trajectory which varies by patient. Consequently, the treatment effect for	IPAC considered your comments, all the evidence and changed the recommendation in 1.1.

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			most patients continued to increase after 120 days. d) The one-year improvements in secondary outcome measures are clinically substantial, and statistically significant for all outcome measures. (Gilligan 2021) e) The long-term recovery trajectory also results in increasing responder rates over time for both pain (VAS) and disability (ODI). f) After unblinding at 120 days the proportion of patients in the treatment group with a 50% or greater improvement in VAS increases from 45% to 64% at 1 year. g) The proportion of remitters increases from 34% at 120 days to 51% at one year. h) Similarly, the proportion of patients with a 15-point improvement in ODI increased from 59% to 69% of patients at 1 year. i) 49% of patients who were on opioids at baseline have voluntarily either eliminated (28%) or reduced (21%) their use. The secondary outcome measures in the study includes important parameters essential for day to day function of the patients whilst VAS only reflects pain intensity. The above data interpreted with the rehabilitative mechanism of action of the therapy where effects accrue over time, in our view points to a superiority of the treatment over sham, a view	

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			shared by the FDA in their analysis of the same data.	
17	Consultee 14 NHS professional President on behalf of the Neuromodulation Society of UK & Ireland and board members	**1.1**	**Evidence on its efficacy is inadequate in quantity and quality.** The Gilligan et al 2021 study is to our knowledge the only study comparing a neurostimulation therapy to an active sham in a rigorous parallel group rigorous double-blind design. This study was conducted under strict guidelines and supervision from FDA. Hence, in our opinion this study is of higher quality than most neurostimulation studies. We believe this to be the case especially by comparison to NICE recommended SCS devices were sham controlled studies are of small size and report an overall mixed response as confirmed by NICE's own assessment (https://www.nice.org.uk/guidance/mtg41) and the literature (Duarte RV.et al.. Systematic review and meta-analysis of placebo/sham controlled randomised trials of spinal cord stimulation for neuropathic pain. Pain 2020;161(1):24-35.) 1-year data of Gilligan study supports the more gradual rehabilitative trajectory restorative effect hypothesis. The longevity of the therapeutic effect of multifidus stimulation is confirmed in the publication of our experience of the 4 year follow up of the Reactiv8-A study cohort (Mitchell B et al. Durability of the Therapeutic Effect of Restorative Neurostimulation for Refractory Chronic Low Back Pain. Neuromodulation 2021; E-pub ahead of print.DOI:10.1111/ner.13477)	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1. The IP programme does not assess the efficacy and safety of comparator interventions. The committee did not compare the evidence for safety for this procedure with that for spinal cord stimulation.

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			Recently submitted UK data from post marketing follow up study (Thomson et al Pain and Therapy submitted July 2021) as well as the two 2 year follow up from the Reactiv8-B study data (Neurosurgery submitted June 2021) add to the quantity of the evidence and confirm the durability of the response to the therapy. Based on the literature of neurostimulation therapies, we conclude that evidence for Multifidus Stimulation for a specific sub-group of patients experiencing chronic low back pain due to multifidus dysfunction is superior to other neurostimulation therapies recommended by NICE at the same stage.	
18	Consultee 15 NHS professional Consultant in Anaesthesia and Pain Medicine Leeds Teaching Hospitals NHS Trust	**1**	Draft recommendations I thank NICE for IPG draft on Neurostimulation of lumbar muscles for refractory non-specific chronic low back pain. My feedback reflects my use of this therapy in patients with refractory low back pain in research context (not done any commercial as was awaiting NICE guidance).	Thank you for your comments.
19	Consultee 15 NHS professional Consultant in Anaesthesia and Pain Medicine Leeds Teaching Hospitals NHS Trust	**1.1**	**Evidence on its efficacy is inadequate in quantity and quality.** ReActiv8 multifidus muscle stimulation is a restorative therapy targeted at rehabilitating the multifidus muscles that have experienced neural inhibition. This is very different to Spinal Cord Stimulation. As this is a rehabilitative therapy results get better with time. We have seen this is our clinical practice. This is very different to SCS as the results can fade with time in	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.

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			some patient's; we noticed a cumulative increase in effect with time on rehabilitation. As per the FDA advice for a pivotal study, Gilligan 2021 study used 30% VAS reduction with no increase in medication at 120 days as a primary outcome. This study has showed a non-significant difference to active sham on the primary outcome. However, the study results when analysed with a pre-specified Intention to treat analysis than the dicotomised primary outcome shows a difference that is significant in the groups at 120 days. All the secondary outcomes such as Oswestry Disability Index (ODI), quality of life (EQ-5D), subject global impression of change (SGIC), clinician global impression of change (CGI) and patient treatment satisfaction (TSQ) showed a significant difference at 120 days in favour of active treatment.	IPAC considered your comments, all the evidence and changed the recommendation in 1.1.
20	Consultee 15 NHS professional Consultant in Anaesthesia and Pain Medicine Leeds Teaching Hospitals NHS Trust	**1.1**	**Evidence on its efficacy is inadequate in quantity and quality.** Mitchell B et al. Durability of the Therapeutic Effect of Restorative Neurostimulation for Refractory Chronic Low Back Pain. Neuromodulation 2021; E-pub ahead of print.DOI:10.1111/ner.13477, this is a 4 year follow up study. I understands that there are further studies with longer term follow up is currently under peer review and expected publication soon (Co-author). Based on the literature of neurostimulation therapies,	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.

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			the evidence for Multifidus Stimulation for a specific sub-group of patients experiencing chronic low back pain due to multifidus dysfunction is superior to other neurostimulation therapies recommended by NICE at the same stage.	IPAC considered your comments, all the evidence and changed the recommendation in 1.1.
21	Consultee 16 NHS professional Senior lecturer and consultant in Pain medicine and neuromodulation Barts Health NHS Trust and QMUL	**1**	At Barts Health NHS Trust, we are the largest European implanters of the Multifidus reactivate therapy. We have a robust MDT setting (Pain physician, neurosurgeon, and a psychologist) where patients are screened through a rigorous methodology to be deemed suitable for this procedure. Less than 5% of patients reviewed in MDT were deemed suitable for this therapy in 2020 (pre-COVID). A typical patient will have a mechanical low back pain and would have undergone physio- therapy and low back pain management pathway outlined by NICE NG59. The typical patient is keen go back to work and ready to engage with the therapy. The MRI will confirm the non-suitability of any neurosurgical target. Our cohort of 16 patients in the Reactiv8-B trial and subsequent 9 commercial non study patients have all gone back to work following therapy, substantiating not just physical but the economic benefit of the therapy as well. Patients with 2-year f/u have demonstrated >50% pain relief with significant reduction in medications. We feel that this therapy is particularly suitable for young and middle age population, that allows them to come off their medication, regain their core strength and return to work.	Thank you for your comments and sharing your research and clinical experience. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1. data collection via the National Neuromodulation Registry (NNR) was recommended in 1.2. In section 1.4 of the guidance, IPAC recommended patient assessment through an MDT and amended the wording slightly to those with experience in pain management and of neuromodulation stimulation procedures.

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			At Barts Health NHS Trust, we have been following these patients in our routine neuromodulation programming clinic and no extra burden is noted in management of these patients. Our real-world clinical results are comparable with the published evidence (Gilligan 2021) which shows cumulative outcome being clinically and statistically significant at 120 days. The benefit continues with >50% VAS improvement at 12 months which further sustained at 24 months. It is important to understand that the secondary outcomes, including disability, quality of life and patient satisfaction, consistently showed a statistically significant and clinically meaningful difference. This research evidence is very much comparable to our clinical experience in non-research patients. In contrary to an immediate treatment effect seen with pharmacological treatments, restorative neurostimulation by the virtue of its core muscles strengthening and resultant spine stability properties provides a more gradual relief with ongoing rehabilitative trajectory. Consequently, the treatment effect for most patients continued to increase after 120 days. Our outcome measurement data demonstrate substantial patient satisfaction with very meaningful benefit from the therapy in terms of ability to resume their dream professions and leading productive life. These patients have happily	1.5 about further research was also slightly amended.

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			contributed to the feedback video recordings to help other patients making informed decisions. Our experience clearly demonstrates that this therapy is safe and effective and would be extremely beneficial for carefully selected population through MDT process and should be available to centres for clinical use for non-research population that have existing neuromodulation commissioned services. With this wider access approach to therapy, we can maximise its use and benefits for genuinely indicated patient group without limiting them to just research club. All patients should be part of neuromodulation registry as outlined by GIRFT spinal pathway to facilitate robust outcome data collection.	
22	Consultee 17 NHS professional Specialised Pain Clinical Reference Group at NHS England	**1**	**Draft recommendations** We thank NICE for IPG draft on Neurostimulation of lumbar muscles for refractory non-specific chronic low back pain. We also thank for an opportunity to offer our feedback based on our experience of this technology for long term severe refractory mechanical low back pain cases with limited pain relief options.	Thank you for your comments.
23	Consultee 17 NHS professional Specialised Pain Clinical Reference Group at NHS England	**1.1**	**Evidence on its efficacy is inadequate in quantity and quality.** We have noted the published sham-controlled trial reviewed for this IPG. It is important to understand that published evidence and the fact that the decrease in pain intensity showed a clinically meaningful and statistically significant between-	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was

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			group difference at 120 days. Indeed, the committee note that: a. LBP-VAS was significantly in favour of the therapeutic stimulation treatment group (-3.3 compared with -2.4; difference of -0.9 cm; 95% CI -1.6 to -0.1 cm; p=0.032). b. The cumulative-proportion-of-responders analysis showed that therapeutic stimulation was superior to sham-control (p=0.0499). This warrants an interpretation of the totality of data, rather than the reliance on P values and the primary outcome at a single time point in assessing a rehabilitation-based therapy. This unfortunately has not been taken into account in the final treatment efficacy assessment. In contrast to an immediate treatment effect seen with palliative neurostimulation treatments such as Spinal Cord Stimulation (SCS), restorative neurostimulation follows a more gradual rehabilitative trajectory which varies by patient. Consequently, the lack of significance at 120 days should not be interpreted as lack of long-term effect since the treatment effect for most patients continued to increase after 120 days.	included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1.
24	Consultee 17 NHS professional Specialised Pain Clinical Reference Group at NHS England	**1.1**	**Evidence on its efficacy is inadequate in quantity and quality.** The secondary outcomes, including disability, quality of life and patient satisfaction, consistently showed a statistically significant and clinically meaningful difference at 120 days in favour of the treatment. This as well as well as the 1-year data supports the more gradual rehabilitative trajectory restorative	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.

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			effect hypothesis. This matches our experience as investigators studying this treatment with 4 years follow up (Mitchell B et al. Durability of the Therapeutic Effect of Restorative Neurostimulation for Refractory Chronic Low Back Pain. Neuromodulation 2021; E-pub ahead of print.DOI:10.1111/ner.13477) as well as the two 2 years follow up from the Reactiv8-B study data (Neurosurgery submitted June 2021). Both the above manuscripts add to the quantity of the evidence and confirm the durability of the response to the therapy. Quality of the evidence: a) We note that among neurostimulation devices reviewed by NICE for the treatment of pain (SCS, PNS etc..) this is the only device to undergo a comparison to an active sham in a powered rigorous parallel group double-blind design. Hence, we disagree with the committee's statement that the quality of the evidence is inadequate. We believe this to be the case especially by comparison to NICE recommended SCS devices were sham controlled studies are small size and report an overall mixed response as per NICE's assessment (https://www.nice.org.uk/guidance/mtg41) and the literature (Duarte RV.et al. Systematic review and meta-analysis of placebo/sham controlled randomised trials of spinal cord stimulation for neuropathic pain. Pain 2020;161(1):24-35.)	IPAC considered your comments, all the evidence and changed the recommendation in 1.1.

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			b) We note that the 4 years follow up (Mitchell et al 2021) is again unique in assessment of longevity of the response to therapy with the longest SCS RCT reporting a follow up of 2 years at most. Hence, we believe that on balance, and compared literature available for SCS, the literature for the Multifidus stimulator is appropriate for the consideration of routine use within MDT selection process.	
25	Consultee 17 NHS professional Specialised Pain Clinical Reference Group at NHS England	**General, 1**	Pain CRG members' experience clearly demonstrates that this therapy is safe and effective in the long term. Our view is that this treatment should be reserved for a small number of CLBP sufferers who: 1. demonstrate multifidus dysfunction on prone instability test and, 2. failed to respond to conservative treatments, 3. continue to be socially active and psychologically well-adjusted, 4. have undergone and an MDT assessment. It is our view that the therapy should be available to centres for clinical use for non-research population that have 1. existing neuromodulation commissioned services. All patients' outcomes should be reported on the national neuromodulation registry (NNR) as	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1. data collection via the National Neuromodulation Registry (NNR) was recommended in 1.2. 1.5 about further research was also slightly amended.

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			outlined by GIRFT spinal pathway to facilitate robust outcome data collection.	*committee comment* 3.7 has been amended and details about the quality of the randomised trial has been removed.
26	Consultee 1 Company Mainstay Medical	**Title & 1.1**	We submit that the guidance has not recognised that the patients being considered for this procedure are a distinct subset of patients with chronic low back pain[1,2]. We submit that the wording of the title and the guidance is potentially misleading. 'Non-specific chronic low back pain' includes a variety of aetiologies[1] and comprises a significant proportion of the population This is discussed in further detail below. We propose that the title of the guidance should be changed to 'Neurostimulation of lumbar muscles for severe disabling refractory chronic low back pain associated with multifidus dysfunction' and that the text of 1.1 be amended accordingly. All the patients entered into the RCT and patients treated outside the trials have this diagnosis. **References** 1. Freeman, M.D., M.A. Woodham, and A.W. Woodham, The role of the lumbar multifidus in chronic low back pain: a review. PM R, 2010. 2(2): p. 142-6; quiz 1 p following 167. 2. Russo, M., et al., Muscle Control and Non-specific Chronic Low Back Pain. Neuromodulation, 2018. 21(1): p. 1-9.	Thank you for your comments. IPAC considered your comments about the wording of the title but did not change the title.
27	Consultee 1 Company Mainstay Medical	**1.1**	We submit that the statement 'Evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research' is based on a misreading of the available evidence. Specifically, we submit that the	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-

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			committee has not taken account of an alternative pre-specified analysis of the primary endpoint which is statistically significant, and has therefore not given proper weight to the findings of the pivotal trial. We submit that the committee should also take into account secondary inputs (for a discussion of the issues see for example Pocock (2016)[3] and Freemantle (2001)[4]). Taken together with the secondary endpoints measured in that trial and set in the context of evidence from other studies and newly published papers, we submit that the evidence available to the committee (with the addition of new papers reporting 2-year and 4-year results) is sufficient to support comfortably a 'special arrangements recommendation'. In considering the appropriate recommendation, the committee should take appropriate account of the fact that the procedure is reversible, and as the draft guidance acknowledges, the adverse event profile of similar procedure spinal cord stimulation is well-understood (although the committee will note that no lead migrations were reported in Gilligan (2021) at the time of the 1-year visit). References: 3. Pocock, S.J. and G.W. Stone, The Primary Outcome Fails - What Next? N Engl J Med, 2016. 375(9): p. 861-70. 4. Freemantle, N., Interpreting the results of secondary end points and subgroup analyses in clinical trials: should we lock the crazy aunt in the	A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1. 2.5 was amended to state that the procedure is reversible

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			attic? BMJ (Clinical research ed), 2001. 322(7292): p. 989-991.	
28	Consultee 18 NHS professional on behalf of UK Reactiv8-A and Reactiv8-B study and PMCF investigators	**General, 1**	Our long experience as investigators of the MS therapy leads us to conclude that this therapy is safe and effective in the long term. We believe that MS therapy should be reserved for a small number of CLBP sufferers who: 1. demonstrate multifidus dysfunction on prone instability test and, 2. fail to respond to the conservative options as per NICE guidance CG59 3. continue to be socially active and psychologically well-adjusted, 4. have undergone a positive MDT assessment. It is our view that the therapy should be available to centres for clinical use for non-research population subject to the below conditions: 1. therapy access should be restricted to existing neuromodulation commissioned services. All patients implanted should have their outcomes reported on the National Neuromodulation registry (NNR) as recommended by NICE and GIRFT spinal pathway to facilitate robust outcome data collection.	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1. data collection via the National Neuromodulation Registry (NNR) was recommended in 1.2.
29	Consultee 18 NHS professional on behalf of UK Reactiv8-A and Reactiv8-B study	**1.1**	**Evidence on its efficacy is inadequate in quantity and quality.** We appreciate that the Gilligan 2021 study has returned a non-significant difference to active sham on the primary outcome at 120 days. However, we take	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK

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	and PMCF investigators		the view that the study results when analysed globally point to a different conclusion: Indeed, the committee note that: a. LBP-VAS was significantly in favour of the therapeutic stimulation treatment group (-3.3 compared with -2.4; difference of -0.9 cm; 95% CI -1.6 to -0.1 cm; p=0.032). b. The cumulative-proportion-of-responders analysis showed that therapeutic stimulation was superior to sham-control (p=0.0499). c. The secondary outcomes, including disability, quality of life and patient satisfaction, consistently showed a statistically significant and clinically meaningful difference at 120 days in favour of the treatment. The above data interpreted with our experience of the rehabilitative mechanism of action of the therapy where effects accrue over time, in our view points to a superiority of the treatment over sham, a view shared by the FDA in their analysis of the same data. It is our collective experience that contrary to the palliative neurostimulation therapies such Spinal Cord Stimulation (SCS) where maximal effects are almost immediate and fade over time, restorative multifidus neurostimulation follows a more gradual rehabilitative trajectory which varies by patient. Consequently, the lack of significance at 120 days should not be interpreted as lack of long-term effect since the treatment effect for most patients continued to increase after 120 days.	based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1.

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30	Consultee 19 NHS professional Consultant in pain medicine at Mid & South Essex University NHSFT (formerly Basildon & Thurrock University Hospitals NHSFT)	**1.1**	I am an investigator in the current Reactiv8 PMCF study. My patients have passed through the 3-year follow-up data collection point but the study will continue for 5 years. I have also commenced, following submission of a business case, a routine service, to select, implant and follow-up routine NHS patients treated with this device. The key to acceptance of the business case was not only due to the efficacy as described by Gilligan et al 2021 RCT versus sham data but also my local experience of patient outcomes from PMCF study and a cost modelling exercise from both a Trust and local CCG perspective. I have recently submitted the 2-year follow-up data of the UK PMCF study to “Pain and Therapy” July 2021. This collects the data from multiple sites involved with PMCF. **Efficacy results** 37/42 completed 2-year FU appointments - In the 37 patients completing 2 year follow up, Numerical Rating Scale (NRS) pain improved from 7.0 ± 0.2 to 3.5 ± 0.3 ($p<0.001$), Oswestry Disability Index Disability (ODI) improved from 46.2±2.2 to 29.2± 3.1 ($p<0.001$) Health related quality of Life (EQ5D) improved from 0.426±0.035 to 0.675±0.030 ($p<0.001$) Additionally, 57% of patients experienced a greater than 50% reduction in pain and 51% of patients benefited by greater than a 15-point reduction in ODI, both substantial improvements **Safety results**	Thank you for your comments and sharing your research and clinical experience. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1. Cost-effectiveness is not part of the remit of the IP Programme.

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			In this PMCF cohort of patients implanted with the Reactiv8 only 12 of the 42 patients (28.6%) experienced an adverse event. Of the 20 adverse events, 10 were stimulation related with seven of them resolving with simple re-programming. There were two lead fractures resulting in a revision procedure rate of 4.7% and four of the 42 (9.5%) patients had their device explanted due to lack of efficacy. The safety results compare very favourably with other neurostimulation therapies such as dorsal root ganglion and even spinal cord stimulation Multifidus nerve stimulation is a RESTORATIVE treatment. Some patient's recovery profile is more rapid than others, with some requiring 6 to 12 months before maximal benefit is achieved. In addition, it is my hope that it will be preventive of the future complications of developing further symptomatic spondylosis.	
31	Consultee 19 NHS professional Consultant in pain medicine at Mid & South Essex University NHSFT (formerly Basildon & Thurrock University Hospitals NHSFT)	**1.1**	**Evidence of efficacy is inadequate in quantity and quality** I disagree with the NICE committee upon its conclusion about the quality of the evidence. I am co-author of the following manuscript Katz N; Dworkin RH; North R; Thomson S; Eldabe S; Hayek S; Kopell B; Markman J; Rezai A; Taylor RS; Turk D; Buchser E; Fields H; Fiore G; Ferguson McK; Gewandter J; Hilker C; Jain R; Leitner A; Loeser J; McNicol E; Nurmikko T; Shipley J; Singh R; Trescot A; van Dongen R; Venkatesan L. Research design considerations for randomized controlled	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.

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			trials of spinal cord stimulation for pain: July 2021 - Volume 162 - Issue 7 - p 1935-1956 Many of the recommendations from the above, albeit for SCS, were included in the design of Reactiv8-B study. This was the first sham controlled neurostimulation randomised controlled trial. The issue is that the primary end point was a composite (30% responder rate with unchanged opioid) and at 120 days it just failed to reach statistical significance despite every other measure as recommended by IMMPACT doing so. Most of the "changed" opioid in the treatment arm of the study was either reduction or for acute pain NOT associated with back pain. VASPI change on its own showed both statistical and clinically useful superiority at 120 days along with ODI, EQ5D-5L etc. In addition, there are 4-year follow-up data (Mitchell et al 2021) and now 2-year follow up data from UK multisite real world PMCF (Thomson et al 2021). My conclusion is that Multifidus nerve stimulation using Reactiv8 by Mainstay Medical is both efficacious and safe in this small group of well selected long term chronic back pain sufferers. This treatment should be available to NHS patients via neuromodulation centres as a routine. All patients and devices should be included in the National Neuromodulation Registry. I will present a composite of narrative data from my patients later in this commentary.	IPAC considered your comments, all the evidence and changed the recommendation in 1.1. data collection via the National Neuromodulation Registry (NNR) was recommended in 1.2.

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32	Consultee 18 NHS professional on behalf of UK Reactiv8-A and Reactiv8-B study and PMCF investigators	**1.1**	**Evidence on its efficacy is inadequate in quantity and quality.** This as well as well as the 1-year data supports the more gradual rehabilitative trajectory restorative effect hypothesis. The longevity of the therapeutic effect of multifidus stimulation is confirmed in the publication of our experience of the 4 year follow up of the Reactiv8-A study cohort (Mitchell B et al. Durability of the Therapeutic Effect of Restorative Neurostimulation for Refractory Chronic Low Back Pain. Neuromodulation 2021; E-pub ahead of print.DOI:10.1111/ner.13477) as well as the recently submitted UK data from post marketing follow up study (Thomson et al Pain and Therapy submitted July 2021) as well as the two 2 year follow up from the Reactiv8-B study data (Neurosurgery submitted June 2021). Both the above manuscripts add to the quantity of the evidence and confirm the durability of the response to the therapy. Quality of the evidence: c) The Gilligan et al 2021 study is to our knowledge the only study to compare a neurostimulation therapy to an active sham in a rigorous parallel group rigorous double-blind design. Hence, we suggest that the study is of higher quality than most neurostimulation studies. We believe this to be the case especially by comparison to NICE recommended SCS devices were sham controlled studies are of small size and report an overall mixed response as confirmed by NICE's own assessment	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1.

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			(https://www.nice.org.uk/guidance/mtg41) and the literature (Duarte RV.et al.. Systematic review and meta-analysis of placebo/sham controlled randomised trials of spinal cord stimulation for neuropathic pain. Pain 2020;161(1):24-35.) d) We note a 4 year follow up (Mitchell et al 2021) is unique in assessment of longevity of the response to a neurostimulation therapy with the longest SCS study reporting a follow up of 2 years at most. Hence, based on our experience and our reading of the literature of neurostimulation therapies we conclude that evidence for Multifidus Stimulation not only appropriate but superior to other neurostimulation therapies recommended by NICE at the same stage.	
33	Consultee 1 Company	**1.1**	We understand that NICE has to provide an overview of all the evidence in the public domain but we also think it is important to properly distinguish between the earlier studies carried out with standard electrodes designed for spinal cord stimulation and a lateral surgical approach, and the current version of the device and surgical technique that uses electrodes specifically designed for restorative neurostimulation and a midline surgical approach. In the evidence review, in the section on "what the procedure involves" it is incorrectly stated that the device can be inserted by either a lateral or midline approach. Whilst the lateral approach was used in the past only the midline approach is now used. The results achieved with the electrodes designed for	Thank you for your comments. Procedure description in section 2.3 has been amended to state that a 'mid-line' approach is used. Reference to lateral surgical approach is removed. The committee did not compare the evidence for safety for this procedure with that for spinal cord stimulation. Also, the IP programme does not assess the efficacy and safety of comparator interventions. Therefore the statement about safety cannot be amended as suggested by the consultee.

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			restorative neurostimulation and midline approach and reported in the ReActiv8-B pivotal trial (Gilligan et al. 2021) and PMCF trial (Thomson et al. 2021) show device related complication rates in these studies in line with those reported for spinal cord stimulators which are in routine use in the NHS (Eldabe et al.2016, Hayek et al. 2015). We therefore think that this opening sentence on safety should be redrafted to make it clear that restorative neurostimulation has a similar safety profile to spinal cord stimulation. Eldabe, et al., (2016). Complications of Spinal Cord Stimulation and Peripheral Nerve Stimulation Techniques: A Review of the Literature. Pain Medicine, 17, 325-336 Hayek et al. (2015). Treatment-Limiting Complications of Percutaneous SCS Implants: A Review of Eight Years of Experience From an Academic Center Database. Neuromodulation 18(7), 603-8. Gilligan C, Volschenk W, Russo M et al. (2021) Long-Term Outcomes of Restorative Neurostimulation in Patients with Refractory 2 Chronic Low Back Pain Secondary to Multifidus Dysfunction: 2-Year Results of the 3 ReActiv8-B Pivotal Trial. Accepted for publication in Neuromodulation: Technology at the Neural Interface. https://doi.org/10.1016/j.neurom.2021.10.011 Thomson S, Chawla R, Love-Jones S et al. Restorative Neurostimulation for Chronic Mechanical Low Back Pain: Results from a Prospective Multi-	The committee has considered the ReActiv8-B pivotal trial (Gilligan 2021), and PMCF trial (Thomson 2021) that have been included in the overview of evidence.

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			centre Longitudinal Cohort. Pain Therapy. 2021 Dec; 10(2): 1451–1465.	
34	Consultee 1 Company	**1.1**	Whilst we understand that this is a new procedure and therefore evidence of safety and efficacy is limited we think it is important to draw attention to the evidence base. In the public domain there are four peer reviewed publications that report on the results of three clinical trials and a total of 325 patients, of which 204 were enrolled in the sham-controlled RCT. Evidence on the duration of the effectiveness of restorative neuromodulation is available for up to four years, and 2 years in the RCT.	Thank you for your comments. Evidence on safety and efficacy from 4 peer reviewed publications has been considered in the overview of evidence.
35	Consultee 2 NHS professional ReActiv8-PMCF investigator	**1.1**	"My comments relate to the draft recommendations document: 1.Section 1.1 Safety Evidence on the safety of neurostimulation of lumbar muscles for refractory non-specific chronic low back pain shows well-recognised complications. While the statement is a general one it is in a sense unfair as it fails to distinguish between earlier studies where spinal stimulation leads where used resulting in a much higher rate of migration and later studies (Gilligan et al 2021, Thomson et al 2021) where midline approach and tined self-anchoring leads have shown an overall much lower rate of lead migration (1%) than all other neuromodulation studies.	Thank you for your comments. IPAC considered your comments and amended the wording in section 1.1.

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			2.Section 1.1. Efficacy “Evidence on its efficacy is limited in quantity and quality.” This statement is again a generalisation that takes no account of the context of neurmodulation devices where in many instances a single RCT/ prospective series leads to market access and NICE submission (please see NICE Senza assessment MTG41). In this case four peer reviewed publications report on the results of three clinical trials and a total of 325 patients, of which 204 were enrolled in the sham-controlled RCT. This, in the context of neuromodulation studies, is the highest level of evidence submitted for a device adoption hitherto.	
36	Consultee 3 NHS professional ReActiv8-PMCF investigator	**1.1**	1.1. Safety - The NICE committee did not distinguish between the early "proof of concept" work using equipment designed for spinal cord stimulation and secondly using present day equipment but with a lateral approach. Neither of these are done in the RCT (Gilligan et al) and in the long term cohort (Thomson et al) where complications are low and compare favourably to those seen in spinal cord stimulation Could this be re-phrased?	Thank you for your comments. IPAC considered your comments and amended the wording in section 1.1.
37	Consultee 4 Recativ8 investigator	**1.1**	The results achieved with the proprietary electrodes and midline approach are reported in the ReActiv8-B pivotal trial (Gilligan et al. 2021) and the PMCF (Thomson et al. 2021). Overall device related complication rates in these studies are in line with those reported for spinal cord stimulators which are in routine use in the NHS (Eldabe et al.2016, Hayek et al. 2015). We would therefore like to see the	Thank you for your comments. The committee has considered the ReActiv8-B pivotal trial (Gilligan 2021), and PMCF trial (Thomson 2021) that have been included in the overview of evidence. The committee did not compare the evidence for safety for this procedure with that for spinal cord

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			sentence on safety removed from the document or redrafted to make it clear that restorative neurostimulation has a similar safety profile to spinal cord stimulation.	stimulation. Also, the IP programme does not assess the efficacy and safety of comparator interventions. Therefore the statement about safety cannot not be amended as suggested by the consultee.
38	Consultee 5 The British Orthopaedic Association	**1**	The BOA supports the guidance written by BASS/UKSSB.	Thank you for your comments.
39	Consultee 6 NHS professional University Hospital Southampton	**1.2**	These patients are assessed in a multidisciplinary setting. The multi-disciplinary team would involve a neurosurgeon (Implanter), pain physician, pain psychologist and pain neuromodulation specialist nurses/ physiotherapists. There is no need for a spinal orthopaedic or spinal neurosurgeon in the MDT team. These patients would have seen spinal surgeon through the muscular skeletal team pathway. The spinal surgeon would have established that there is no spinal surgical intervention planned for these patients. The aim of the multidisciplinary team assessment is to ensure that patient have mechanical back pain and that they have tried all the reasonable conservative options such as physiotherapy, pain medication, pain management program etc. Once the team feels that patient is suitable for multifidus stimulator they are placed on the waiting list. It is important to emphasize that these patient have not undergone any operations and are not candidates for	Thank you for your comments. IPAC considered your comments and amended the wording in 1.4 slightly to state that MDT should include those with experience in pain management and of neuromodulation stimulation procedures.

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			spinal fusion. In my set up, I am hoping to see about 10-12 patient a year who would be suitable candidate for multifidus stimulator.	
40	Consultee 7 Genesis Research Services	**1.2**	Having implanted 14 patients in the ReActiv8 B study, our MDT consisted of a Clinical Pain Nurse, Pain Specialist, and Clinical Psychologist. A neurosurgical review was not required as the cohort had no underlying indications for neurosurgical intervention such as decompression or fusion for instability. This should therefore not be a prerequisite.	Thank you for your comments. In section 1.4 in the guidance, IPAC recommended patient assessment through an MDT. IPAC considered your comments and amended the wording in 1.4 slightly to state that MDT should include those with experience in pain management and of neuromodulation stimulation procedures.
41	Consultee 8 on behalf of The British Pain Society	1.2	"1.2 The BPS, as a multidisciplinary society, is in agreement that a multidisciplinary team should be involved in patient selection but the multidisciplinary team should include a neurosurgeon or a specialist in pain management; a pain nurse and a clinical psychologist, as this is aligned with how the majority of national implantation centres are set up."	Thank you for your comments. IPAC considered your comments and amended the wording in 1.4 slightly to state that MDT should include those with experience in pain management and of neuromodulation stimulation procedures.
42	Consultee 10 NHS professional NHS - Royal Brompton & Harefield hospitals	1.2	Agree - this is how we run all neuromodulation patient selection	Thank you for your comments. Consultee agrees with section 1.2 in the guidance.
43	Consultee 11 NHS professional	**1.2**	**1.2 Patient selection should be done by a multidisciplinary team including a neurosurgeon, a specialist in pain management, a pain nurse and a clinical psychologist.**	Thank you for your comments and agreeing with section 1.2 in the guidance. Section 1.3 in NICE TA159 (guidance on SCS for chronic pain of neuropathic or ischemic origin) states that *'spinal cord stimulation should*

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			Response: I agree with the committee's recommendation that patient selection should be done by an MDT team, this is consistent with the recommendation of an MDT assessment for spinal cord stimulation (SCS) devices. However, we consider that the specific recommendation of a neurosurgeon is neither justified nor is it rationale given that a) The device implant is extraspinal and NICE do not specify a neurosurgeon presence for the intraspinal implant of SCS devices where neural damage is much more likely. b) Neurosurgeons do not routinely see Non-Specific Low Back Pain (NSLBP) patients all of whom will have been screened by an MSK service and absence of a surgical target confirmed prior to referral for consideration for Multifidus Stimulation (MS). The recommendation of a physiotherapist on the MDT team would in my view be more relevant to therapy than that of a neurosurgeon.	*be provided only after an assessment by a multidisciplinary team experienced in chronic pain assessment and management of people with spinal cord stimulation devices, including experience in the provision of ongoing monitoring and support of the person assessed'.* This recommendation is quite broad and do not give specific details of who should be part of MDT. IPAC considered your comments and amended the wording in 1.4 slightly to state that MDT should include those with experience in pain management and of neuromodulation stimulation procedures.
44	Consultee 13 NHS professional Consultant in Pain Medicine and Neuromodulation The Walton Centre NHS FT, Liverpool	**1.2**	I agree that patient selection by a multidisciplinary team is essential but I do not think the presence of a neurosurgeon should be mandated.	Thank you for your commentsand agreeing with section 1.4 in the guidance. IPAC considered your comments and amended the wording in 1.4 slightly to state that MDT should include those with experience in pain management and of neuromodulation stimulation procedures.
45	Consultee 14 NHS professional President on behalf	**1.2**	**Patient selection should be done by a multidisciplinary team including a neurosurgeon,**	Thank you for your comments and agreeing with section 1.4 in the guidance.

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	of the Neuromodulation Society of UK & Ireland and board members		**a specialist in pain management, a pain nurse and a clinical psychologist.** As per NICE TA159 guidance, in the UK institutions, patient assessment and selection for spial cord stimulation is routinely conducted by a multidisciplinary team. However, we consider that the specific recommendation of a patient selection done by a multidisciplinary team including a neurosurgeon, is neither justified nor rationale given that: a) Neurosurgeons do not routinely see Non-Specific Low Back Pain (NSLBP) patients all of whom will have been screened by an MSK service and absence of a surgical target confirmed prior to referral for consideration for Multifidus Stimulation (MS). b) The device implant is extraspinal c) In TA159 guidance, NICE do not specify a neurosurgeon presence for the intraspinal implant of SCS devices where neural damage is much more likely. d) The presence of a physiotherapist on the MDT team would be more relevant than a neurosurgeon. In a UK based Post Marketing Clinical Follow up study (Thomson et al 2021 Pain and Therapy	Section 1.3 in NICE TA159 (guidance on SCS for chronic pain of neuropathic or ischemic origin) states that *'spinal cord stimulation should be provided only after an assessment by a multidisciplinary team experienced in chronic pain assessment and management of people with spinal cord stimulation devices, including experience in the provision of ongoing monitoring and support of the person assessed'.* This recommendation is quite broad and do not give specific details of who should be part of MDT. IPAC considered your comments and amended the wording in 1.4 slightly to state that MDT should include those with experience in pain management and of neuromodulation stimulation procedures. The UK based PMCF study (Thomson 2021) was added to the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1.

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			submitted July 2021), patients selected for the therapy suffered with years of low back pain and have undergone all options on the therapeutic pathway for low back pain management outlined by NICE NG59. All patients were assessed and surgical options excluded prior to their referral to a neurmodulation specialist centre. Patients in the post-marketing clinical follow up study were psychologically well adjusted and seeking to maintain their active role in society.	
46	Consultee 15 NHS professional Consultant in Anaesthesia and Pain Medicine Leeds Teaching Hospitals NHS Trust	**1.2**	**Patient selection should be done by a multidisciplinary team including a neurosurgeon, a specialist in pain management, a pain nurse and a clinical psychologist.** These patients are normally seen by the Musculoskeletal team and might have some input from spinal surgeons. We don't see any definitive role of Neurosurgeons and this should be reviewed. Multidisciplinary team would include the implanter (Pain Specialist, Neurosurgeons or the Spinal Surgeons) along with physiotherapist, nurses and psychologist.	Thank you for your comments and agreeing with section 1.3 in the guidance. IPAC considered your comments and amended the wording in 1.4 slightly to state that MDT should include those with experience in pain management and of neuromodulation stimulation procedures.
47	Consultee 18 NHS professional on behalf of UK Reactiv8-A and Reactiv8-B study and PMCF investigators	**1.2**	**Patient selection should be done by a multidisciplinary team including a neurosurgeon, a specialist in pain management, a pain nurse and a clinical psychologist.** In our experience of the less restrictive Post Marketing Clinical Follow up study (Thomson et al 2021) patients selected for the therapy suffered with years of low back pain and have undergone all options on the	Thank you for your comments and agreeing with section 1.4 in the guidance. IPAC considered your comments and amended the wording in 1.4 slightly to state that MDT should include those with experience in pain management and of neuromodulation stimulation procedures.

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			therapeutic pathway for low back pain management outlined by NICE NG59. All patients have been assessed and surgical options excluded prior to their referral to a neurmodulation specialist centre. Furthermore, our patients were psychologically well adjusted and seeking to maintain their active role in society. We agree with the committee and confirm that in our institutions, patient selection is routinely conducted by multidisciplinary team, this is consistent with the recommendation of an MDT assessment for spinal cord stimulation (SCS) devices. However, we consider that the specific recommendation of a neurosurgeon is neither justified nor is it rationale given that a) The device implant is extraspinal and NICE do not specify a neurosurgeon presence for the intraspinal implant of SCS devices where neural damage is much more likely. b) Neurosurgeons do not routinely see Non-Specific Low Back Pain (NSLBP) patients all of whom will have been screened by an MSK service and absence of a surgical target confirmed prior to referral for consideration for Multifidus Stimulation (MS). We therefore consider the presence of a physiotherapist on the MDT team more relevant than that of a neurosurgeon.	
48	Consultee 17 NHS professional Specialised Pain Clinical Reference	**1.2**	**Patient selection should be done by a multidisciplinary team including a neurosurgeon, a specialist in pain management, a pain nurse and a clinical psychologist.**	Thank you for your comments and agreeing withwith section 1.4 in the guidance. IPAC considered your comments and amended the wording in 1.4 slightly to state that MDT

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	Group at NHS England		A typical patient will have a mechanical low back pain and would have undergone physical therapy and therapeutic low back pain management pathway outlined by NICE NG59. The typical patient is keen to go back to work and ready to engage with the therapy. The MRI and surgical assessment will confirm the non-suitability of any surgical procedure. Patient selection is routinely conducted with a multidisciplinary team including a specialist in pain management, a pain nurse, physiotherapist and clinical psychologist. These cases will have already been assessed by neurosurgical/ orthopaedic spinal services with MRI scans to consider other spine surgery treatments. Thus, we are unsure of the additional requirement for neurosurgical input to the rigorous MDT selection process. The patients are thus screened through a very rigorous methodology within MDT described as above. Less than 5% of patients reviewed in MDT are deemed suitable for this therapy in our experience.	should include those with experience in pain management and of neuromodulation stimulation procedures.
49	Consultee 19 NHS professional Consultant in pain medicine at Mid & South Essex University NHSFT (formerly Basildon & Thurrock University Hospitals NHSFT)	**1.2**	**Patient selection should be done by a multidisciplinary team including a neurosurgeon, a specialist in pain management, a pain nurse and a clinical psychologist** All neuromodulation centres in UK have access to a multidisciplinary team (MDT). The exact composition of the MDT is not specified. The NICE committee recommendation that a neurosurgeon should be specifically part of the team is not rationale nor justifiable.	Thank you for your comments and agreeingwith section 1.4 in the guidance. IPAC considered your comments and amended the wording in 1.4 slightly to state that MDT should include those with experience in pain management and of neuromodulation stimulation procedures.

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			Neurosurgeons are not involved in the management of non-specific low back pain. None of my patients were screened by a neurosurgeon. All of my patients may have been considered at some stage in their 15 year back pain history by an orthopaedic spine surgeon. All of my patients were under the active management of the chronic pain service, supported by the MDT. Our MDT includes pain specialists, physiotherapists, pain nurse specialists (all involved in holistic pain management, psychologist not included during PMCF recruitment). I have interdisciplinary access to orthopaedic spine, rheumatology, neurology etc. The surgical technique is extra-spinal. SCS is intra-spinal – a neurosurgeon is not NICE mandated (nor should it be).	
50	Consultee 7 Genesis Research Services	**1.3**	"Consideration of an implant of a restorative Multifidus Peripheral Nerve Stimulator is based on the criteria of selected patients with CLBP with associated significant disability as defined by the Oswestry Disability index. Our pain clinic is using this device commercially. In my clinic's cohort, this has been a paradigm shift away from destructive procedures to restoring normal function in the selected patient. The patients had a variety of underlying pathological conditions broadly	Thank you for your comments and sharing information about your clinical experience. The NICE IP programme manual states that efficacy outcomes from unpublished studies are not normally presented to the Committee. When substantial new evidence is published NICE will review the guidance.

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			categorized by severe discogenic disease, associated Modic changes, and facet joint arthropathy, with no neurosurgical indication for decompressive surgery. All patients implanted had multifidus muscle dysfunction as defined by objective prone instability testing and in addition had significant multifidus loss on MRI due to fatty infiltration. All of the patients in our cohort had received pain management for an average of 14 years of current best practice. They all failed this utterly. This therapy is not aimed at replacing current best practice, but is for those that fail the current best practice guidelines. In the suitable cohort, the therapy achieves remission in the majority of patients, for which standard of care, as defined by the NICE guidelines, could not attain. In my practice, only a small number would qualify for this therapy as defined by the current inclusion criteria, which, in the busy practice, would equate to approximately 20 patients in a year and we expect this therapy to be incorporated into the standard of care in future. This would benefit any health care system by decreasing the resource burden attributed to difficult to treat patients with chronic nonspecific mechanical lower back pain. Our outcomes have demonstrated remitter status in the vast majority patients with a very early decrease in their disability. In my experience, their self efficacy, kinesiophobia and catastrophising improved. Analgesic consumption and primary care visits decreased. Our patient satisfaction was high.	Cost-effectiveness is not part of the remit of the IP Programme.

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			The cohort on average had multiple physical therapy sessions. This did not include other health care access which was extremely high considering 37% were on opioids and thus would have repeated general practice visits. In addition, more than half failed interventional procedures. Taking only this into consideration and not counting the economic loss through employment, I believe that this therapy would be cost effective."	
51	Consultee 8 on behalf of The British Pain Society	1.3	"1.3 As stated in previous comments further research will be available very soon and should be allowed to be assessed during this review to prevent detriment to patients by significantly delaying their exposure to this treatment."	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1.
52	Consultee 10 NHS professional NHS - Royal Brompton & Harefield hospitals	1.3	There is already a good RCT. Why deny UK patients an effective treatment? All patients data will be kept in the National Neuromodulation Registry, so further research will deny a proven effective treatment to selected patients. This is a small cohort of patients who have failed to improve with other standard back pain treatments and is specifically for patients with	Thank you for your comments. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.

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			mechanical low back pain and multifidus muscle atrophy.	IPAC considered your comments, all the evidence and changed the recommendation in 1.1. Data submission to the national neuromodulation registry was recommended in 1.2.
53	Consultee 11 NHS professional	**1.3**	**1.3. Further research should be randomised controlled trials comparing the procedure with current best practice. It should report details of patient selection and long-term outcomes.** Response: In my experience patients selected for MS device implantation have suffered with CLBP of an average of >10 years and thus have exhausted all NHS standard care treatment options including many rounds of physiotherapy and analgesia. My experience from conducting studies comparing active implantable devices to standard care in low back pain is that these attract patients who have exhausted standard care and would thus join the study in order to access the implantable device with predictable bias against standard care. I therefore, believe that the comparison to standard care while desirable is clinically unrealistic.	Thank you for your comments. Section 1.5 wording was amended.
54	Consultee 13 NHS professional Consultant in Pain Medicine and Neuromodulation	**1.3**	The recommendation to undertake randomised controlled trials comparing the procedure with current best practice may cause unnecessary delays to patient receiving a therapy. Firstly a well designed RCT has already been carried out which shows that the benefit of the procedure develops over time and is sustained, and secondly,	Thank you for your comments.

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	The Walton Centre NHS FT, Liverpool		the patients that I would consider for this procedure have already failed current best practice.	Reactiv8 B randomised controlled trial (-Gilligan 2021) included in the overview compared the procedure with sham stimulation. Section 1.5 wording was amended.
55	Consultee 14 NHS professional President on behalf of the Neuromodulation Society of UK & Ireland and board members	**1.3**	**Further research should be randomised controlled trials comparing the procedure with current best practice. It should report details of patient selection and long-term outcomes.** An implantable restorative-neurostimulator for refractory mechanical chronic low back pain: a randomized sham-controlled clinical trial (Gilligan 2021) is the only study to compare a neurostimulation therapy to an active sham in a rigorous parallel group rigorous double-blind design. Whilst the NSUKI is always supportive of more research, we do not feel further research would add anything that would change the clinical practice. NSUKI had developed National Neuromodulation Registry (NNR) that has been adapted by most of the centres currently commissioned for Neuromodulation. Enrolling all the patients implanted with this therapy in the NNR as recommended by NICE and GIRFT spinal pathway would produce robust, long-term real life outcomes for this therapy.	Thank you for your comments. Section 1.5 wording was amended that research should be suitably powered randomised controlled trials comparing the procedure with current best practice with appropriate duration.
56	Consultee 15 NHS professional Consultant in	**1.3**	**Further research should be randomised controlled trials comparing the procedure with**	Thank you for your comments.

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	Anaesthesia and Pain Medicine Leeds Teaching Hospitals NHS Trust		**current best practice. It should report details of patient selection and long-term outcomes.** Gilligan et al is the only study to compare a neurostimulator for refractory mechanical low back pain to an active sham arm. With the above argument, reconsideration could be given to this therapies access to very hard to treat selected back pain patients. Real world data should be collected through the National Neuromodulation Registry (NNR) to provide a long term real life data.	Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1. Data submission to the national neuromodulation registry was recommended in 1.2. Section 1.5 wording was amended that research should be suitably powered randomised controlled trials comparing the procedure with current best practice with appropriate duration.
57	Consultee 1 Company Mainstay Medical	**1.3, 2.2**	The draft guidance recommends that research studies should be RCTs comparing this procedure with current best practice. The patients for which restorative neurostimulation is proposed have already failed best current practice. As the draft guidance and NG59 acknowledge there are a range of treatment options used in different combinations, different techniques, at different time points etc. If this remains in the guidance, we suggest that the text be amended to include a clear statement of what NICE has in mind. To illustrate the difficulty, the patients for whom neurostimulation is proposed have failed the range of non-invasive treatments described	Thank you for your comments. Section 1.5 wording was amended that research should be suitably powered randomised controlled trials comparing the procedure with current best practice with appropriate duration.

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			in NG59, have positive signs of multifidus dysfunction, and have no signs of an alternative treatable cause for their LBP. NG59 includes no treatment option for patients who are refractory to non-invasive treatments and those with multifidus dysfunction with which the present guidance is concerned. In short, there is no current treatment option for these patients.	
58	Consultee 19 NHS professional Consultant in pain medicine at Mid & South Essex University NHSFT (formerly Basildon & Thurrock University Hospitals NHSFT)	**1.3**	**Further research** Like with any commercially available technology, future research to better understand mechanism of action, range of indication, clinical and cost effectiveness will occur. But there is sufficient research to satisfy the questions of efficacy and safety. This committee could assist by providing their well thought through recommendations for research so that future clinical researchers, such as myself with other colleagues, can explore the benefits of this and other technologies. This can assist us being successful with NIHR applications.	Thank you for your comments. Section 1.5 wording was amended that research should be suitably powered randomised controlled trials comparing the procedure with current best practice with appropriate duration.
59	Consultee 2 NHS professional ReActiv8-PMCF investigator	**1.5**	3. Section 1.5 Further Research "Suitably powered randomised controlled trials comparing the procedure with sham and current best practice with appropriate duration". I have a few concerns particularly regarding the first recommendation: 1. An RCT of the device against sham has already been conducted, thus a re-run of the same design is unlikely to produce different results unless the	Thank you for your comments. IPAC considered your comments and amended the wording in section 1.5.

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			primary outcome collection time point is extended beyond 3 months. Such a study may prove to be difficult to recruit to given the reported positive long-term impact of the therapy on participants enrolled in open label studies. Furthermore, studies have largely demonstrated that multifidus stimulation therapy efficacy benefits accrue over time thus necessitating a randomisation of participants to a sham intervention for an extended time period would be difficult at best and unethical at worst. 2. Trial of the device against current best practice in UK: While this is a more feasible study design there remains the concern that since the therapy is only recommended following the failure of conservative treatment, it follows that participants randomised to the best practice group are highly likely to receive treatments they have already experienced firstly enhancing an already existing nocebo effect and second making drop out much more likely in the best practice group of such a study."	
60	Consultee 1 Company	**1.5**	Whilst we agree that additional studies comparing restorative neurostimulation to current best practice are desirable we do not think a further sham controlled RCT is appropriate. In addition to the ethical issues of recruiting patients to a sham arm against a treatment with proven efficacy we feel it would be very difficult to enrol patients into and manage a clinical trial with a sham procedure when the active procedure is clinically available and publicised. At this stage in the development of the treatment technology we have been advised by	Thank you for your comments. IPAC considered your comments and amended the wording in section 1.5.

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			clinicians that it is important to collect real-world data to support treatment decisions in daily practice. We would therefore like to see this recommendation amended so that the reference to sham procedures is removed and replaced with a reference to suitably powered trials comparing the procedure with current best practice with appropriate duration.	
61	Consultee 3 NHS professional ReActiv8-PMCF investigator	**1.5**	I agree that with different populations using this procedure, further research with sham control is required. However now we need to emphasise that the appropriate comparator in this population is current best practice.	Thank you for your comments. IPAC considered your comments and amended the wording in section 1.5.
62	Consultee 4 Recativ8 investigator	**1.5**	Whilst we agree that additional studies comparing restorative neurostimulation to current best practice are desirable, we do not think a further sham controlled RCT is appropriate. We believe that there may be ethical issues recruiting patients to a sham controlled study against a treatment with proven efficacy. Moreover, we feel it would be very difficult to enrol patients into and manage a clinical trial with a sham procedure when the active procedure is clinically available. It is important to collect real-world data to support in making treatment decisions in daily practice.	Thank you for your comment. IPAC considered your comments and amended the wording in section 1.5.
63	Consultee 4 Recativ8 investigator	**1.1, 1.5**	"I would encourage the committee to look at the results of the ReActiv8-B trial published in the journal PAIN and Simon Thomson's PMCF trial when evaluating the safety of the device and procedure. Those trials reflect the current surgical technique and demonstrate a safety profile comparable to spinal cord stimulators.	Thank you for your comments. The committee has considered the ReActiv8-B pivotal trial (Gilligan 2021), and PMCF trial (Thomson 2021) that have been included in the overview of evidence. The committee did not compare the evidence for safety for this procedure with that for spinal cord

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			I agree with the committee's suggestion that further trials should be conducted, but believe that they should be comparisons to best practice and optimized medical management rather than additional sham-controlled trials. I think that ethical and practical concerns preclude further sham-controlled trials for this therapy; the therapy delivers durable, excellent outcomes for many patients and it would be very straightforward for clinical trial subjects to detect the difference between sham stimulation and therapeutic stimulation now that the device is in widespread use around the world."	stimulation. Also, the IP programme does not assess the efficacy and safety of comparator interventions. IPAC considered your comments about further research and amended the wording in section 1.5.
64	Consultee 13 NHS professional Consultant in Pain Medicine and Neuromodulation The Walton Centre NHS FT, Liverpool	**2.1**	Whilst I agree that non-specific chronic low back pain (NSCLBP) can present in various ways I think the wording of this section does not recognise the specific nature of the back pain for which this procedure is intended. These are patients with very long-term chronic pain, who have failed all current treatments and in whom multifidus dysfunction has been demonstrated.	Thank you for your comments. Section 2.1 wording was amended to state the specific nature of the back pain for which this procedure is not intended.
65	Consultee 1 Company Mainstay Medical	**2.1/2.5**	The wording of 2.1 defines NSCLBP widely. The wording of the last sentence ('NSCLBP is a common condition with several recognisable contributing or causative factors. These include [our emphasis] functional instability of the spine caused by dysfunction of the lumbar multifidus (large muscles that support the lower back) and arthrogenic muscle inhibition') does not state or imply that the guidance is restricted to the subgroup of patients suffering from NSCLBP for which restorative neurostimulation is proposed. More generally, the guidance does not clearly distinguish two different treatment paradigms:	Thank you for your comments. Section 2.1 wording was amended to state the specific nature of the back pain for which this procedure is not intended. IPAC considered your comments in 2.5 about 'restorative neurostimulation' but decided not to amend.

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			(i) restorative (i.e.,rehabilitative) neurostimulation of muscles with the aim of reducing spinal instability and thereby relieving pain and improving function from (ii) conventional analgesic neurostimulation of spinal cord pain fibres to interrupt neural transmission of pain messages. While there are similarities in the procedure for implanting ReActiv8 and those for implanting spinal cord stimulators, the target population (aetiology) and the therapeutic intention (mechanism of action) are different. The description of the condition in 2.1 should be amended accordingly to state clearly that the guidance applies (only) to the target population for the procedure. 2.5 should be incorporated in the redrafted 2.1. The committee should note that the box describing the condition on page 1 of the overview similarly fails to distinguish between aetiologies and implies (erroneously) that the overview applies to the full spectrum of NSCLBP.	
66	Consultee 1 Company	**2.1**	We do not think this is how non-specific chronic low back pain (NSCLBP) is usually described. It typically presents as predominantly nociceptive mechanical pain (associated with mechanical injury to tissues surrounding the spine joints, including muscles, fascia, and ligaments).	Thank you for your comments. Section 2.1 states the specific nature of the back pain for which this procedure is intended. **IPAC considered your comments and added a sentence in2.1 to state that** *'"This treatment is not intended for neuropathic pain".*

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67	Consultee 3 NHS professional ReActiv8-PMCF investigator	**Indications and treatment** **2.1, 2.2**	Non-specific chronic low back pain is a broad population. But multifidus nerve stimulation for non-specific chronic low back pain (NSCLBP) typically presenting as predominantly nociceptive mechanical pain (associated with mechanical injury to tissues surrounding the spine joints, including muscles, fascia, and ligaments). That is, NOT neuropathic - should this be made clearer? Furthermore, you are aware of the ICD-11 project where terms are being suggested. How will the current NICE terminology of NSCLBP change? This treatment is for Chronic secondary MSK pain (MG30.3) or Chronic secondary MSK pain associated with structural changes (MG30.31) in distinction to chronic neuropathic pain (MG30.5). For example	Thank you for your comments. Section 2.1 states the specific nature of the back pain for which this procedure is intended. IPAC considered your comments and added a sentence in2.1 to state that *'"This treatment is not intended for neuropathic pain".*
68	Consultee 11 NHS professional	**General, 2.2**	This report misses that this is resorative therapy in a chronically debilitated population who have failed all current NICE recommendations (NG59). It is therefore not unsuprising that there no statistical improvement within three months, and recently submitted evidence is that this becomes a statistically significant improvement beyond this time.	Thank you for your comments. IPAC considered your comments in 2.5 about 'restorative neurostimulation' but decided not to amend. *Evidence from recent publications -the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.*

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				IPAC considered your comments, all the evidence and changed the recommendation in 1.1. Section 1.5 of the guidance recommends *'further research and* when substantial new evidence is published NICE will review the guidance.
69	Consultee 6 NHS professional University Hospital Southampton	**2.2**	"Low back pain is extremely common condition. However, subsets of the low back pain patients have evidence of multifidus dysfunction. This is typically seen on the MRI scan when they have varying degrees of atrophy of the multifidus muscle. One could consider a physical test to assess the multifidus dysfunction. Clinically these patients have low back pain which is of mechanical in nature. The pain is chronic and intractable despite all conservative management. They are not candidates for any spinal surgical procedures such as fusion. Hence, for these patients there is currently no treatment. These are the patient that can be considered for multifidus stimulator. It is important to emphasise that currently, there is no treatment for these patients at all.	Thank you for your comments. IPAC considered your comments but decided not to amend.
70	Consultee 9 International Neuromodulation Society	**2.2, 2.5**	Several compelling reasons exist for the rapid adoption of this novel approach: 1.These patients have no other treatment alternatives and there is high quality evidence supporting the efficacy and safety of multifidus	Thank you for your comments. IPAC considered your comments in 2.2 and 2.5 about 'restorative neurostimulation' but decided not to amend.

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			muscle stimulation for chronic mechanical low back pain. While chronic neuropathic back pain, including failed back surgery syndrome (FBSS) has been successfully treated for years using spinal cord stimulation (SCS), chronic mechanical low back pain is nociceptive in nature; SCS is not indicated for nociceptive pain. After physical therapy, pharmacotherapy and injection therapy there are NO existing treatments for patients with chronic mechanical low back pain. Such patients are often treated with chronic opioids which are minimally effective with significant long term complications; patients are unlikely to return to work and are destined to suffer. Neurostimulation of the lumbar muscles, branded ReActiv8 (Mainstay Medical Limited, Dublin, Ireland), is intended only for the treatment of chronic low back pain where dysfunction of the lumbar multifidus has been demonstrated. Patients in the now published peer reviewed studies represent those with severe chronic low back pain as eligibility criteria required pain intensity of at least 6 on a 10 point visual analogue scale (VAS) or numeric rating scale (NRS) and a score of at least 21 on the Oswestry disability index (ODI). In fact, at baseline, patients in the ReActiv8-B randomized controlled trial (RCT) had an average VAS of greater than 7, almost 40 on the ODI, and an average of 14 years of chronic back pain. This is a group of severely impacted patients which have a significant need which is currently unmet. Published studies consistently report that	*Evidence from recent publications -the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.* *IPAC considered your comments, all the evidence and changed the recommendation in 1.1.* Section 1.5 of the guidance recommends *'further research and* when substantial new evidence is published NICE will review the guidance

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			these patients rarely experience spontaneous, substantial improvements in their pain and disability. The nature of multifidus muscle stimulation therapy is different to other treatments; it is a rehabilitative rather than palliative therapy. For neuropathic back pain, SCS is a palliative therapy that does nothing to address the cause of the pain but rather suppresses pain transmission to the brain. It usually has its greatest effect in the short term and either stabilizes or deteriorates over time. On the other hand, as a restorative therapy, multifidus muscle stimulation therapy aims to reactivate and strengthen the multifidus muscles and thus treat the root cause of chronic mechanical low back pain. The effect of this stimulation grows over time as would be expected for a rehabilitative therapy.	
71	Consultee 10 NHS professional NHS - Royal Brompton & Harefield hospitals	2.2	Multifidus stimulation is a last resort treatment for those patients that have not responded to other treatments	Thank you for your comments. IPAC considered your comments but decided not to amend.
72	Consultee 13 NHS professional Consultant in Pain Medicine and Neuromodulation The Walton Centre NHS FT, Liverpool	**2.2**	The current NICE guidance for low back pain does not offer treatments for the carefully selected group of patients for whom this procedure is intended.	Thank you for your comments. IPAC considered your comments but decided not to amend.

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73	Consultee 1 Company Mainstay Medical	**2.2**	We submit that the description of treatments is misleading in that it describes the range of treatments for low back pain in general and does not recognise that the procedure being considered is intended for the treatment of CLBP associated multifidus dysfunction and not for CLBP of other aetiologies. The procedure performed in the pivotal trial was 'bilateral stimulation of the L2 medial branch of the dorsal ramus as it crosses the transverse process at L3 as an aid in the management of intractable chronic low back pain associated with multifidus muscle dysfunction, as evidenced by imaging or physiological testing in adults who have failed therapy including pain medications and physical therapy and are not candidates for spine surgery.' Treatment options for this group of patients are largely ineffective and patients for whom the procedure would be considered are significantly disabled by their symptoms. The patients in the pivotal RCT had (mean ± SD) 14.2±10.6 years of pain since onset, reported 97% of days over the last year with LBP, reported an average pain intensive of 7.3±0.7 on VAS 7-day recall and an average disability that was borderline 'severe' (39±10% on ODI). This pain and disability profile persisted despite all having attempted physical therapy with an average of 31 ± 52 prior physical therapy sessions, and nearly half (49%) of the patients had at least one injection. On average patients had missed 20.2 ± 66.9 days of work due to back pain in the previous year. Although this is in part referred to in passing in the overview (page 14) the degree of morbidity in the	Thank you for your comments. IPAC considered your comments but decided not to amend.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			target population is not apparent from the text of the guidance.	
74	Consultee 1 Company Mainstay Medical	**2.2**	The guidance should specifically refer to the need to establish multifidus dysfunction as a clinical eligibility criterion for this procedure. In the ReActiv8-B pivotal study this was done using the Prone Instability Test (PIT) which is reliable[8], predicts success with a stabilisation exercise programme for subjects with LBNP that included exercises designed to reactivate the multifidus[9], and has satisfactory inter-rater reliability[10,11]. The text does not make clear that the treatment options available to the target population are of limited efficacy: the committee may not have been clear that the refractory, severely impacted patients for whom the procedure is intended (see earlier comment on morbidity in the relevant population) have a significant need which is currently unmet. Patients in the included studies represent those with 'severe chronic low back pain' as eligibility criteria required pain intensity of at least 6/10 on VAS or NRS and at least a disability impact of 21 on the ODI. In the ReActiv8-B pivotal study candidates were required to have had pain on more than half the days in the prior year. In the trial, only 3 participants had a pain duration less than one year. References: 8. Hicks, G.E., et al., Interrater reliability of clinical examination measures for identification of lumbar segmental instability. Arch Phys Med Rehabil, 2003. 84(12): p. 1858-64. 9. Hebert, J.J., et al., The relationship of transversus abdominis and lumbar multifidus activation and	Thank you for your comments. IPAC considered your comments but decided not to amend.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			prognostic factors for clinical success with a stabilization exercise program: a cross-sectional study. Arch Phys Med Rehabil, 2010. 91(1): p. 78-85. 10. May, S. and R. Johnson, Stabilisation exercises for low back pain: a systematic review. Physiotherapy, 2008. 94: p. 179-189. 11. Denteneer, L., et al., Inter- and Intrarater Reliability of Clinical Tests Associated With Functional Lumbar Segmental Instability and Motor Control Impairment in Patients With Low Back Pain: A Systematic Review. Arch Phys Med Rehabil, 2017. 98(1): p. 151-164 e6.	
75	Consultee 1 Company Mainstay Medical	**2.2**	The committee should note that no reference is made in NG59 to the group of patients for whom this procedure is intended.	Thank you for your comments. IPAC considered your comments but decided not to amend.
76	Consultee 19 NHS professional Consultant in pain medicine at Mid & South Essex University NHSFT (formerly Basildon & Thurrock University Hospitals NHSFT)	**2.2**	**Current treatments** NICE NG59 has rationalised and limited the available treatment to chronic back pain patients. There is an unmet need. For example, some of my patients do well with lumbar medial branch radiofrequency neurolysis, but not all get relief for more than 1 year. These are some of the patients who do well with multifidus nerve stimulation. Indeed, it was this cohort of patients that would have required repeat MBBRF that when incorporated into my business case cost modelling exercise made the use of multifidus nerve stimulation dominant over a 5-year time horizon from hospital and drug costs alone. Let alone the societal costs, that in this group are profound.	Thank you for your comments. IPAC considered your comments but decided not to amend. Cost-effectiveness is not part of the remit of the IP Programme.

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77	Consultee 9 International Neuromodulation Society	**2.3**	6. The extra-spinal placement of leads greatly reduces surgical risk and improves safety. Unlike SCS, where the leads are placed in the intraspinal epidural space overlying the dura, multifidus muscle stimulation leads are placed through the muscle and to the transverse spinous process. Thus, the risk of neurologic complications of spinal cord injury, intraspinal nerve root injury or cerebrospinal fluid leak is eliminated. The extra-spinal leads are secured by the flexible tines on the distal end of the lead which bracket the L2/L3 inter-tranversarius muscle.	Thank you for your comment. The procedure description (in section 2.3) has been amended.
78	Consultee 10 NHS professional NHS - Royal Brompton & Harefield hospitals	**2.3**	The procedure is safe and straightforward in the hands of experienced neuromodulators (pain physicians and neurosurgeons).	Thank you for your comments. section 1.4 in the guidance states MDT involvement in patient selection.
79	Consultee 14 NHS professional President on behalf of the Neuromodulation Society of UK & Ireland and board members	**2.3**	**The distal end of each lead has 2 stimulating electrodes**. The distal end of each lead has 4 stimulating electrodes.	Thank you for your comments. wording in section 2.3 about the number of stimulating electrodes was amended.
80	Consultee 15 NHS professional Consultant in	**2.3**	**The distal end of each lead has 2 stimulating electrodes.** These electrodes contain 4 active contacts.	Thank you for your comments. wording in section 2.3 about the number of stimulating electrodes was amended.

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	Anaesthesia and Pain Medicine Leeds Teaching Hospitals NHS Trust			
81	Consultee 1 Company Mainstay Medical	**2.3**	We suggest the following rewording 'The procedure is done under general anaesthesia, or local anaesthesia with sedation. A pulse generator (neurostimulator) is implanted in a subcutaneous pocket created in the upper buttock. Under fluoroscopic guidance through a 'midline' approach, 2 stimulation leads are inserted. The distal end of each lead has 4 stimulation electrodes...'. See Decker (2015) for establishing that the midline approach was preferable to the lateral approach (only the midline approach is allowed in current labelling).	Thank you for your comments. wording in section 2.3 about the number of stimulating electrodes was amended.
82	Consultee 1 Company	**2.3**	'and secured in place' Rather than say the leads are secured in place it would be more accurate to state that the leads are fixated to the L2/3 intertransversarii using flexible tines	Thank you for your comments. The procedure description in 2.3 is intended to be a simple summary. IPAC considered your comments and amended text in 2.3.
83	Consultee 4 Recativ8 investigator	**2.3**	In this procedure, a cut is made in the low back and two wires are placed on the nerves that control the muscles either side of the spine (lumbar muscles). The wires are then connected to a small battery-powered device (neurostimulator), which is typically implanted in upper buttock.	Thank you for your comments. IPAC considered your comments and amended text in 2.3.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
84	Consultee 4 Recativ8 investigator	**2.3**	The pulse generator is implanted in the upper buttock. The leads are inserted via midline approach. The lateral approach is abandoned due to high complication rates. The leads are not secured- the tines act as the anchors. Under fluoroscopy guidance through a midline approach, 2 stimulating leads are inserted percutaneously. The distal ends of each lead have 4 stimulating electrodes. They are positioned next to the spinal column, near the medial branch of the L2 motor nerve supply (dorsal ramus Nerve) to the multifidus muscles. The leads are tunnelled internally, then the proximal ends are connected to the pulse generator, which is implanted in the upper buttock subcutaneously.	Thank you for your comments. IPAC considered your comments and amended text in 2.3.
85	Consultee 1 Company Mainstay Medical	**2.4**	We suggest rewording the first sentence as follows: 'Fourteen days after the implantation procedure, the patient can start to use the device to initiate the process of rehabilitating the multifidus muscles which supports the spine...' Note that there should be a similar change to the text on p4 of the overview.	Thank you for your comments. IPAC considered your comments and slightly amended 2.4.
86	Consultee 1 Company	**2.4**	It would be more accurate to say approximately fourteen days after the implantation procedure.	Thank you for your comments. IPAC considered your comments and amended text in 2.4.
87	Consultee 8 on behalf of The British Pain Society	**2.5**	The mode of action is aimed at rehabilitation of the multifidus muscle and would therefore understandably be a time-dependent process.	Thank you for your comments.

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			It is noted within the available studies that patient improvement continues beyond the 120 day mark and that new long term data is due to be available which is expected to show continued long term improvement and supporting the treatment as an efficacious procedure which should be supported by NICE. When reviewing the ReActiv8B treatment group the published data at 1 year shows both primary and secondary outcomes are significantly improved.	IPAC considered your comments in 2.5 about 'restorative neurostimulation' but decided not to amend. *Evidence from recent publications -the randomised controlled trial (Reactiv8 B trial- Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.* *IPAC considered your comments, all the evidence and changed the recommendation in 1.1.*
88	Consultee 1 Company Mainstay Medical	**2.5**	We suggest rewording as follows: 'A restorative neurostimulator is not a pain management device. Unlike a spinal cord stimulator or peripheral nerve stimulator which have an immediate analgesic effect in patients with neuropathic LBP, a restorative neurostimulator is intended to achieve longer-term rehabilitation of multifidus muscle function thereby stabilising the spinal column.	Thank you for your comments. IPAC considered your comments in 2.5 about 'restorative neurostimulation' but decided not to amend.
89	Consultee 6 NHS professional	**3.1**	I have now done about 10 implants as a part of PMCF study- a research trial. The stimulator is completely extra-spinal and has an extremely good	Thank you for your comments and sharing your experience with this procedure.

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	University Hospital Southampton		safety profile. In fact the safety profile of this stimulator is compatible with any neuromodulation device and may be even less than the standard spinal cord stimulators because the electrodes do not enter the spinal canal. The new multifidus stimulator electrodes have tynes, which mitigate the risk of lead migration. The experience from the trial has been extremely positive. My patients have had marked improvement in their low back pain as well as disability scores. Some of the patients have prescribed this as miracle. It is important to understand that the multifidus stimulator unlike spinal cord stimulator does not give pain relief immediately. It takes anything more than 3-6 months for the stimulator effect to kick in, as the mechanism is restorative rather than via gait mechanism like spinal cord stimulator. The randomised controlled trial (Reactiv8 B trial) has shown statistically significant improvement in all aspects although the primary end point was not met with at 120 days. This is not surprising given the restorative mechanism of the multifidus stimulator. 120 days is not sufficient for the stimulator effect to kick in and hence, there was no significant difference in the pain scores between the Sham stimulation and the actual stimulation group at 120 days. The 1 year, 2 year and 4 year outcome data has shown sustained statistically significant and clinically meaningful improvements.	The post marketing clinical follow-up [PMCF] study NCT01985230 (**ReActiv8-A continuation study**) is an ongoing study that will complete in December 2024 and has been noted in our overview. Section 1.1 of the guidance states that '*Evidence on the safety of neurostimulation of lumbar muscles for refractory non-specific chronic low back pain shows well-recognised complications'.* *Evidence from recent publications -the randomised controlled trial (Reactiv8 B trial- Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.* *IPAC considered your comments, all the evidence and changed the recommendation in 1.1.*
90	Consultee 8 of behalf of The British Pain Society	3.1	As previously commented the evidence base is due to be significantly expanded with new data currently undergoing peer-review prior to publication. As this data is precipitant the BPS would ask the committee	Thank you for your comments. *Evidence from recent publications -the randomised controlled trial (Reactiv8 B trial-*

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			to withhold a final decision on outcomes until it has had chance to review the newer evidence. This would avoid unnecessary patient distress for those who would otherwise have been eligible for this treatment. The use of a research context decision has already been enacted by the Pain establishment and the new data would hopefully allow a more supportive response from NICE.	*Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.* *IPAC considered your comments, all the evidence and changed the recommendation in 1.1.*
91	Consultee 9 International Neuromodulation Society	**3.1**	"As the President and Executive Board Members of the International Neuromodulation Society, we feel compelled to provide commentary on the recent NICE guidance concerning the neurostimulation of lumbar muscles for refractory, non-specific chronic low back pain. Since the time of your review earlier this year, results of the long term prospective randomized trial have undergone peer review and provide Level I evidence supporting this new therapy. References Gilligan C, Volschenk W, Russo M, et al. An implantable restorative-neurostimulator for refractory mechanical chronic low back pain. Pain 2021; Publish Ah. doi:10.1097/j.pain.0000000000002258. Mitchell, B., Deckers, K., De Smedt, K., Russo, M., Georgius, P., Green, M., Gulve, A., van Buyten, J.-P., Smet, I., Mehta, V., Baranidharan, G., Rathmell, J., Gilligan, C., Goss, B. and Eldabe, S. (2021), Durability of the Therapeutic Effect of Restorative	Thank you for your comments. *Evidence from recent publications -the randomised controlled trial (Reactiv8 B trial- Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.* *IPAC considered your comments, all the evidence and changed the recommendation in 1.1.*

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			Neurostimulation for Refractory Chronic Low Back Pain. Neuromodulation: Technology at the Neural Interface. https://doi.org/10.1111/ner.13477"	
92	Consultee 9 International Neuromodulation Society	**3.1**	2.Clinical results are clinically significant and improve over time. The data from the ReActiv8 RCT strongly support the suggested nature of this therapy. The primary endpoint is only one of many clinically-relevant data points from the study. The prespecified cumulative-proportion-of-responders ITT analysis, which has greater statistical power than the dichotomised primary outcome and was based on primary outcome data, showed a significant difference between the treatment and control groups at 120 days. Furthermore, the improvement in pain intensity (VAS) showed a clinically meaningful and statistically significant between-group difference at 120 days. This warrants interpretation of the totality of data rather than a single data point. The secondary outcomes, including disability, quality of life and patient satisfaction, consistently showed a statistically significant and clinically meaningful difference at 120 days in favour of the treatment. The one-year improvements compared to baseline are clinically substantial, and highly statistically significant for all outcome measures and 'responder' proportions, P<0.0001 (Gilligan, 2021)	Thank you for your comments. *Evidence from recent publications -the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.* *IPAC considered your comments, all the evidence and changed the recommendation in 1.1.*
93	Consultee 9 International Neuromodulation Society	**3.1**	3. Safety and efficacy data for neurostimulation of the lumbar muscles for the treatment of chronic mechanical low back pain has been generated in high quality clinical trials.	Thank you for your comments. *Evidence from recent publications -the randomised controlled trial (Reactiv8 B trial-*

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			ReActiv8-B was first of its kind sham-controlled triple-blinded RCT. It was a multi-centre international study with its protocol approved by the FDA under the IDE process. The patients were refractory to best current practice with on average 14 years of CLBP. It is the first sham-controlled, double-blinded trial (N=204; Level 1 RCT) of an implantable neurostimulator for CLBP that is consistent with the rigor described in the IMMPACT emerging quality standards for neuromodulation trials. Data from this study was the basis for device approval in the USA (FDA Premarket Approval) and Australia (Registry of Therapeutic Goods Australia). The multifidus muscle stimulation system is the only implantable neuromodulation device to be compared against a sham device in a rigorous double blinded design. Such a design has not been applied on such a scale in a parallel design for pain devices recommended by NICE.	*Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.* *IPAC considered your comments, all the evidence and changed the recommendation in 1.1.*
94	Consultee 9 International Neuromodulation Society	**3.1**	4. As clinicians, we believe that the long term data is compelling and is compelling to the international membership of health care providers who provide neuromodulation The four-year results from the ReActiv8-A study have been accepted for publication and the accepted manuscript is available online (Mitchell B et al. Durability of the therapeutic effective of restorative neurostimulation for refractory chronic low back pain. Neuromodulation. DOI: 10.1111/ner.13477). The comprehensive report of the ReActiv8-B RCT has been accepted in the journal PAIN and its full text is available online (Gilligan, C et al. 2021) An	Thank you for your comments. *Evidence from recent publications -the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.* *IPAC considered your comments, all the evidence and changed the recommendation in 1.1.*

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			implantable restorative neurostimulator for refractory mechanical chronic low back pain: a randomized sham-controlled clinical trial. PAIN Publish Ahead of Print DOI: 10.1097/j.pain. 0000000000002258). A second paper first authored by Gilligan has been submitted for peer review since the NICE review; results demonstrate continuing improvement in outcomes in the second year following the procedure, thus suggesting long-term effectiveness of the procedure in disabling CLBP secondary to multifidus muscle dysfunction. The Mitchell et al. paper reporting four-year follow-up results of the ReActiv8-A trial show a similar pattern with rapid improvement in outcomes in the first year, followed by stable or improving outcomes out to four years.	
95	Consultee 9 International Neuromodulation Society	**3.1**	5. The stability and rigor of the device used for multifidus muscle stimulation is better than comparable devices used in neurostimulation procedures. Lead migration is the most common reason for SCS revision; the lead migration rate in the ReActiv8-B study is zero. The absence of lead migrations using the current commercial leads (8145/65) and using a mid-line surgical approach a compelling demonstration of the rigor of the device and procedure. The rate of lead fractures was 2.5% in the ReActiv8-B study, comparing favorably with published SCS safety data of 9-12% and 11.1% by Eldabe (2016) and Hayek (2015), respectively. No lead migrations were reported in the in the ReActiv8-	Thank you for your comments. *Evidence from recent publications -the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.* *IPAC considered your comments, all the evidence and changed the recommendation in 1.1.*

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			B study (N=204). Ranges reported by Eldabe and Hayek for SCS are 2-27% and 8.5%, respectively. References Gilligan C, Volschenk W, Russo M et al. An implantable restorative-neurostimulator for refractory mechanical chronic low back pain. Pain 2021; Publish Ah. doi:10.1097/j.pain.0000000000002258. Eldabe S, Buchser E, Duarte RV. Complications of Spinal Cord Stimulation and Peripheral Nerve Stimulation Techniques: A Review of the Literature. Pain Med. 2016 Feb;17(2):325-36. doi: 10.1093/pm/pnv025. PMID: 26814260. Hayek, S.M., Veizi, E. and Hanes, M. (2015), Spinal Cord Stimulator Complications. Neuromodulation: Technology at the Neural Interface, 18: 603-609. https://doi.org/10.1111/ner.12312	The committee did not compare the evidence for safety for this procedure with that for spinal cord stimulation. Also, the IP programme does not assess the efficacy and safety of comparator interventions.
96	Consultee 11 NHS professional	**1, 3.1**	"The committee may wish to consider the complications within the continuum of research necessary to develop and perfect an implantable device. a) The Deckers 2015 study used commercially available SCS devices designed for implantation into the epidural space as opposed to the medial branch location where muscular forces were shown to cause a high rate of migration. Experience from this study led to the design of the first purpose made lead for Multifidus Stimulation (MS) device. Hence the high	Thank you for your comments. IPAC considered evidence on safety from study 1 (Gilligan 2021) and study 2 (Deckers 2018, 2015). *Evidence from recent publications the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in*

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			rate of lead complications observed in Deckers 2015 is inapplicable to the current CE marked MS device. b) Data from the Deckers 2018 study is a heterogenous mix of an initial cohort and a late cohort with different lead design and surgical approach leading to a improvement in AE rate. c) Therefore, a realistic assessment of potential for device and procedure complications should include only the patients who underwent a midline approach implant using the current version of the MS device lead in the Decker 2018 study and the full cohort of the Gilligan 2021 study. d). We note that the committee considers that that the safety shows well recognised complications. It is our opinion that when the clinically relevant safety data from up to date lead and implantation approach are considered for the commercially available version of the MS device and lead, the MS procedure related complications are lower or comparable to SCS devices recommended by NICE for the treatment of low back pain for example the infection rate of 2.9% compares well with the SCS literature quoted rates mean 6.15% lead replacement rate for MS 2.9% compares favourably with mean SCS rates of 6.3% (Eldabe S, et al. Complications of Spinal Cord Stimulation and Peripheral Nerve Stimulation Techniques: A Review of the Literature. Pain Med. 2016;17(2):325-36). Most importantly the overall device explant rates of MS 9.3% compare favourably with the removal of SCS devices recommended by NICE MTG 41 for treatment of Low back pain with explant rates of 11.1-22.2% reported at 12 and 24	*the summary of evidence in the overview and considered by IPAC.* *IPAC considered your comments, all the evidence and changed the recommendation in 1.1.* The committee did not compare the evidence for safety for this procedure with that for spinal cord stimulation. Only evidence on efficacy and safety for neurostimulation of lumbar muscles for refractory non-specific chronic low back pain was assessed in this guidance.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			months. (Wang VC, et al. Explantation Rates of High Frequency Spinal Cord Stimulation in Two Outpatient Clinics. Neuromodulation 2020;05:05.	
97	Consultee 1 Company Mainstay Medical	**3.1 Efficacy summary, p5 overview**	We submit that the statement '…the proportion of 'responders' in the intention to treat analysis (that is, more than 30% relief on the low back pain visual-analog-scale [VAS] without analgesics increase) at 120-day follow up were not significantly different in the therapeutic stimulation group than in the low-level sham stimulation control group (57% compared with 47%; difference of 10%; 95% confidence interval [CI], -3.3% to 24.1%, p=0.138)' is incomplete and misleading. The Statistical Analysis Plan [SAP] for the ReActiv8-B pivotal study [available on request] proposed that 'individual components of the primary efficacy endpoint (VAS and medications) will be analyzed and presented separately. Cumulative proportion of responder analysis will also be used as a way of presenting the data.' The Cumulative Proportion of Responders Analysis (CPRA) is a method of evaluating patient responses over a full range of response levels, utilizing exactly the same composite data as the primary endpoint. Rather than relying on one cut-point for evaluation, the CPRA provides a more comprehensive summary of the data[16-19]. The CPRA, which was prespecified in the Clinical Investigation Protocol and SAP, using the same data as used for the primary endpoint analysis, demonstrated a significant difference between the Treatment group and the Control group (p=0.0499). Using the ITT CPRA analysis of the primary	Thank you for your comments. *Evidence from recent publications -the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.* *IPAC considered your comments, all the evidence and changed the recommendation in 1.1.*

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			endpoint, the Treatment group showed a higher percentage of responders across all threshold levels. This analysis was accepted by the US Food and Drugs Administration: see Summary of Safety and Effectiveness Data (SSED)[2]. We submit that this review, being in the published domain and subject to a thorough formal peer-review process should be given at least the same weight as a paper published in a peer-reviewed journal. This analysis is referred to in passing in the efficacy summary but is not given the evidential status that it merits. To someone not familiar with the detail, the presentation in the overview is likely to have been misleading. Moreover, the primary endpoint definition of a responder included no increase in pain medications. Nine patients in both the treatment and control group had increases in pain medications for any reason within the two-week window prior to the 120-day visit, all of which were counted as treatment failures for the primary effectiveness endpoint. Of the 18 patients who increased medications, 6—all in the treatment group—had increases in medications unrelated to either LBP or the procedure (broken ankle, tooth extraction, URTI, anal abscess, knee injury and renal stone). Had these medications been excluded from the analysis of the primary efficacy endpoint, the difference between the number of respondents in the two groups would have been statistically significant (p=0.048)20. These data are not mentioned in the overview. The SAP stated that 'Rescue medications taken on an exceptional basis for acute pain conditions other than back pain will	

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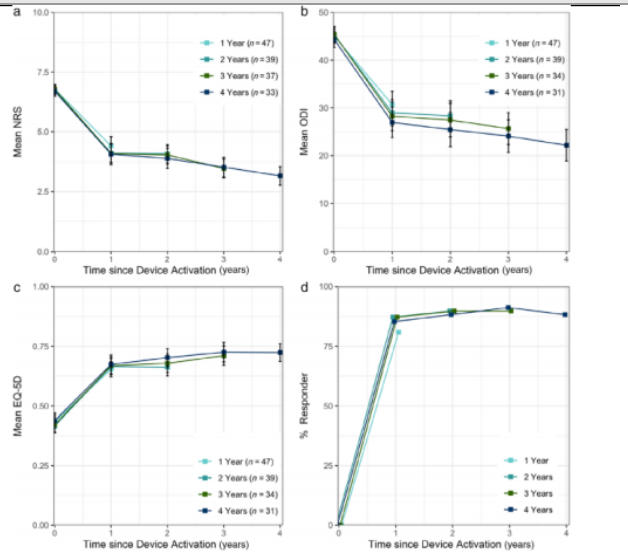
			also be documented and their possible effect examined as part of sensitivity analyses.' We believe that these data are material to the interpretation of the ReActiv8-B pivotal study results as a whole and should not have been omitted by the committee. **References** 16. Farrar, J.T., R.H. Dworkin, and M.B. Max, Use of the cumulative proportion of responders analysis graph to present pain data over a range of cut-off points: making clinical trial data more understandable. J Pain Symptom Manage, 2006. 31(4): p. 369-77. 17. Fedorov, V., F. Mannino, and R. Zhang, Consequences of dichotomization. Pharm Stat, 2009. 8(1): p. 50-61. 18. Senn, S. and S. Julious, Measurement in clinical trials: a neglected issue for statisticians? Stat Med, 2009. 28(26): p. 3189-209. 19. Capppelleri, J.C., et al., Patient-Reported Outcomes, Measurement, Implementation and Interpretation. 2014: CRC press. 20. Mainstay Medical, ReActiv8®. Implantable Electrical Stimulation System. Implant and Programming Manual. 2021, Mainstay Medical Limited: Dublin, Ireland	
98	Consultee 1 Company Mainstay Medical	**3.1 Analysis [of ReActiv8-B pivotal study],**	We submit that the overview is defective in its assessment of the evidence base and should re-evaluate the Gilligan (2021) paper. We submit that the committee has not considered the evidence from the pivotal RCT in its totality. Since a pre-specified analysis of the primary efficacy endpoint was	Thank you for your comments. *Evidence from recent publications -the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based*

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
		overview, p13	statistically significant, the committee should take into account clinically meaningful improvements in secondary outcomes. In the ReActiv8-B pivotal study, results for most secondary endpoints at 120 days favoured treatment. Since the purpose of the procedure is restorative, results are likely to be cumulative and outcomes should therefore be looked at over a longer timeframe: Gilligan reported that for participants who completed the 1-year follow-up (176/204, 86.3%) efficacy outcomes showed consistently significant and clinically meaningful improvements compared to baseline. In the Gilligan paper reporting 2-year results (submitted to a peer review journal since the overview was prepared) show continuing improvement in outcomes in Year 2 following the procedure suggesting long-term effectiveness of the procedure in disabling CLBP secondary to multifidus muscle dysfunction. In the Mitchell et al. paper 5 reporting the 4-year follow-up results of the ReActiv8-A trial show a similar pattern: rapid improvement in outcomes in the first year, following by stable or improving figures out to 4 years. We invite the committee to take note of the FDA Summary of Safety Effectiveness Data[2] conclusion about the ReActiv8-B pivotal study results at one year that: '[t]he totality of efficacy outcome data demonstrated the effectiveness of the ReActiv8 system. Specifically, considering the cumulative proportion of responders at all levels of response the treatment group outperforms the control group at all	*PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.* *IPAC considered your comments, all the evidence and changed the recommendation in 1.1.*

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			levels of response. The benefits observed during the blinded study phase, continued to increase through 1 year. Across all pre-specified endpoints, the 1-year data demonstrated that patients have reduced pain, decreased disability improved quality of life, positive subject and clinician impression of change, and high overall treatment satisfaction'.	
99	Consultee 1 Company Mainstay Medical	**1, 3.1**	The draft guidance recommends that researchers report on long-term outcomes. The committee should be advised that the 4-year results from the ReActiv8-A study have recently been published[5]. In summary, the paper shows that the results of neurostimulation are stable between years 1 and 4 (Figure 1). The graphs show, for example, the mean change in NRS at one year from baseline for the one-year completed cohort (n = 47), the two-year completed cohort (n = 39), the three-year completed cohort (n = 37), and the four-year completed cohort (n = 33) and the standard deviation of those four means. **(Image on original document)** Figure 1: Mean ± SEM (a) NRS, (b) ODI, and (c) EQ-5D, and (d) proportion of participants benefiting by more than one minimally clinically important change	Thank you for your comments. *Evidence from recent publications -the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC.* *IPAC considered your comments, all the evidence and changed the recommendation in 1.1.* The conference abstract by Ardreshiri et al will also be considered for safety issues but not for efficacy as it is not peer reviewed. The NICE IP programme manual states that efficacy outcomes from unpublished studies are not normally presented to the Committee. When substantial new evidence is published NICE will review the guidance.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			 The committee should also be advised that a paper reporting the 2-year results of the pivotal trial has been submitted to a peer-reviewed journal and is under review: acceptance is anticipated very shortly. This open-label follow-up of 204 patients found that at 2 years (n=156), the proportion of participants with ≥50% CLBP relief was 71% and 65% reported CLBP resolution (VAS≤2.5cm); 61% had a reduction in ODI of ≥20points; 76% had improvements of ≥50% in VAS and/or ≥20points in ODI, and 56% had substantial improvements in both VAS and ODI. Eighty-seven percent of participants had continued device use during the second year for a median of 43% of the maximum duration, and 60% (34/57) had	

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			voluntarily discontinued (39%) or reduced (21%) opioid intake. Key efficacy outcomes progressively improved over time and changes from baseline were statistically significant and clinically meaningful at all follow-ups ($p<0.001$) (Table 1 and Figure 2 through Figure 7). **(Image on original document)** Table 1: Outcomes reported for completers and all participants with stratified imputation for missing data VAS = Visual Analog Scale; ODI = Oswestry Disability Index; SGIC = Subject Global Impression of Change; TSQ = Treatment Satisfaction Questionnaire; CGI = Clinician Global Impression. Continuous outcome estimates from mixed model repeated measures regression models adjusted for baseline, all other binary outcomes analysed with Multiple Imputation for missing data. *For continuous outcomes $p<0.0001$ for two-sided t-test if change from baseline differs from 0. Statistics are % (n/N) for binary outcomes and N, mean (standard error) for continuous.	

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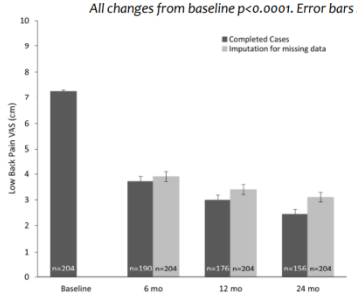
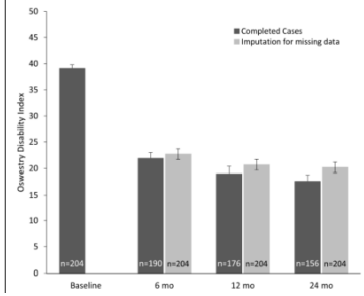
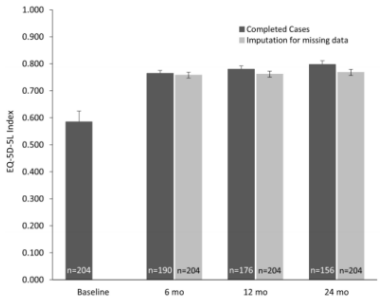
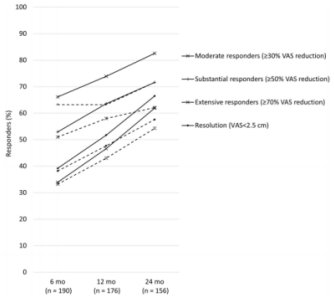
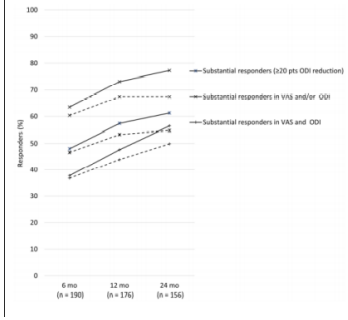
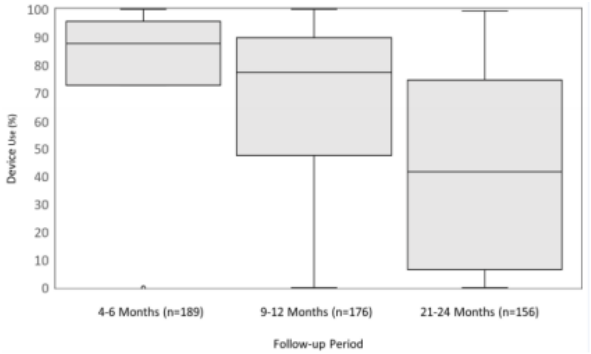
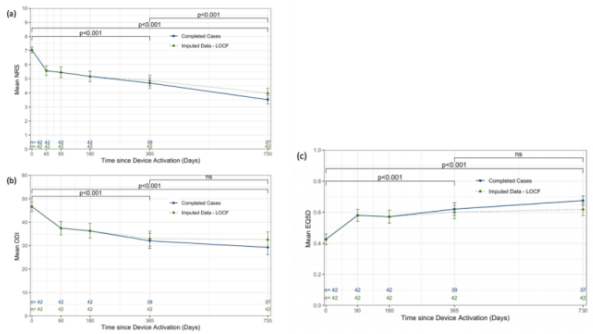
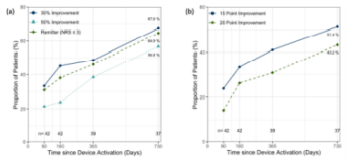
Analysis	Baseline	6-months		1-year		2-year	
	Mean±SD	Mean±SD or %(n/N) (95% CI)*		Mean±SD or %(n/N) (95% CI)*		Mean±SD or %(n/N) (95% CI)*	
	N=204	N=190	N=204	N=176	N=204	N=156	N=204
LBP VAS (cm)	7.3 ± 0.7	3.7 (0.2)	3.9 (0.2)	3.0 (0.2)	3.4 (0.2)	2.4 (0.2)	3.1 (0.2)
Change in VAS (cm)		-3.6 (0.2) (-3.9, -3.3)	-3.4 (0.2) (-3.8, -3.1)	-4.3 (0.2) (-4.7, -3.9)	-3.9 (0.2) (-4.3, -3.6)	-4.8 (0.2) (-5.2, -4.5)	-4.2 (0.2) (-4.6, -3.8)
Change in VAS (%)		-48.6 (2.7) (-53.9, -43.3)	-47.1 (2.6) (-52.3, -41.9)	-58.9 (2.6) (-64.1, -53.6)	-54.3 (2.7) (-59.5, -49.0)	-66.7 (2.6) (-71.7, -61.6)	-58.1 (2.7) (-63.4, -52.8)
≥30% improvement in VAS		66.1 (125/189) (59.4, 72.9)	63.2 (3.5) (56.5, 70.0)	73.9 (130/176) (67.4, 80.4)	66.9 (3.4) (60.3, 73.6)	82.6 (128/155) (76.6, 88.6)	71.6 (3.3) (65.1, 78.1)
≥50% improvement in VAS		52.9 (100/189) (45.8, 60.0)	51.0 (3.6) (44.0, 58.0)	63.6 (112/176) (56.5, 70.7)	58.0 (3.5) (51.1, 65.0)	71.6 (111/155) (64.5, 78.7)	62.1 (3.5) (55.1, 69.0)
≥70% improvement in VAS		33.9 (64/189) (27.1, 40.6)	33.2 (3.4) (26.5, 39.9)	46.6 (82/176) (39.2, 54.0)	43.0 (3.6) (36.1, 50.0)	61.9 (96/155) (54.3, 69.6)	54.3 (3.7) (47.1, 61.5)
LBP resolution (VAS ≤ 2.5 cm)		39.2 (74/189) (32.2, 46.1)	38.3 (3.5) (31.4, 45.1)	51.7 (91/176) (44.3, 59.1)	47.7 (3.5) (40.7, 54.6)	66.5 (103/155) (59.0, 73.9)	57.6 (3.6) (50.5, 64.7)
ODI	39.1 ± 10.3	21.9 (1.1)	22.7 (1.0)	19.0 (1.4)	20.7 (1.0)	17.6 (1.2)	20.2 (1.0)
Change in ODI		-17.0 (1.1) (-19.2, -14.8)	-16.4 (1.0) (-18.4, -14.4)	-19.9 (1.2) (-22.3, -17.6)	-18.4 (1.0) (-20.4, -16.4)	-21.4 (1.3) (-24.0, -18.7)	-18.9 (1.0) (-21.0, -16.8)
Change in ODI (%)		-43.0 (2.8) (-48.5, -37.4)	-41.5 (2.7) (-46.8, -36.1)	-50.5 (2.9) (-56.3, -44.8)	-46.4 (2.8) (-51.8, -41.0)	-54.3 (3.2) (-60.6, -48.0)	-47.5 (2.8) (-53.0, -42.0)
≥20 Pt. improvement in ODI		48.1 (91/189) (41.0, 55.3)	46.7 (3.5) (39.8, 53.7)	57.4 (101/176) (50.1, 64.7)	53.4 (3.5) (46.5, 60.3)	61.3 (95/155) (53.6, 69.0)	54.8 (3.6) (47.7, 61.9)
Composite of VAS and ODI							
≥50% improvement in VAS and/or ≥20 Pt. ODI		63.5 (120/189) (56.6, 70.4)	60.4 (3.5) (53.6, 67.2)	73.3 (129/176) (66.8, 79.8)	67.4 (3.4) (60.8, 74.0)	77.3 (119/154) (70.7, 83.9)	67.4 (3.5) (60.4, 74.3)
≥50% improvement in VAS and ≥20 Pt. ODI		37.8 (71/188) (30.8, 44.7)	36.8 (3.4) (30.0, 43.5)	47.7 (84/176) (40.3, 55.1)	44.0 (3.6) (37.0, 51.1)	56.5 (87/154) (48.7, 64.3)	49.9 (3.6) (42.8, 57.1)
EQ-5D-5L index	0.585 ± 0.174	0.765 (0.010)	0.758 (0.011)	0.780 (0.012)	0.762 (0.011)	0.798 (0.013)	0.768 (0.011)
Change in EQ-5D-5L index		0.180 (0.014) (0.153, 0.207)	0.173 (0.011) (0.151, 0.194)	0.198 (0.016) (0.167, 0.229)	0.177 (0.011) (0.156, 0.199)	0.218 (0.017) (0.184, 0.253)	0.183 (0.011) (0.161, 0.205)
PPR (%)		55.0 (2.5) (50.1, 59.9)	53.3 (2.5) (48.4, 58.2)	65.7 (2.4) (60.9, 70.5)	60.7 (2.5) (55.8, 65.6)	72.1 (2.4) (67.3, 77.0)	62.3 (2.5) (57.3, 67.3)
SGIC "Better" or "Much better"		57.4 (109/190) (50.3, 64.4)	55.1 (3.5) (48.2, 62.0)	71.6 (126/176) (64.9, 78.3)	65.9 (3.4) (59.3, 72.5)	78.6 (121/154) (72.1, 85.1)	68.6 (3.4) (61.9, 75.2)
TSQ "Definitely satisfied"		64.7 (123/190) (57.9, 71.5)	62.8 (3.4) (56.0, 69.5)	78.2 (136/174) (72.0, 84.3)	71.8 (3.2) (65.5, 78.1)	80.0 (124/155) (73.7, 86.3)	68.3 (3.4) (61.6, 75.1)
CGI "Much better"		56.8 (108/190) (49.8, 63.9)	55.0 (3.6) (48.0, 62.0)	73.3 (129/176) (66.8, 79.8)	67.5 (3.4) (60.8, 74.1)	77.6 (118/152) (71.7, 84.3)	66.6 (3.6) (59.6, 73.7)

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			Figure 2: Mean ratings over time for Low Back Pain VAS *All changes from baseline p<0.0001. Error bars represent the standard error of the mean.*  Figure 3: Mean ratings over time for Oswestry Disability Index *All changes from baseline p<0.0001. Error bars represent the standard error of the mean.*  Figure 4 mean ratings overtime for EQ-5D-5L index	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			All changes from baseline p<0.0001. Error bars represent the standard error of the mean.  Figure 5: Response rates at common clinical importance thresholds for VAS (Reduction ≥50% and 70%, and absolute VAS≤2.5 cm). *Solid lines represent completed cases, dashed lines represent imputation for missing data (N=204).*  	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			Figure 6: Response rates at common clinical importance thresholds for ODI (≥20 points) and composites of VAS and ODI (≥50% and/or 20 points, ≥50% and/or 20 points). *Solid lines represent completed cases, dashed lines represent imputation for missing data (N=204).*  Figure 7: Interquartile ranges of device use as a percentage of the maximum cumulative duration permitted.  A paper reporting the 2-year data from an open label five-year prospective follow-up of 42 patients with intractable CLBP treated with restorative neurostimulation at 5 sites in the United Kingdom has been submitted for publication[6]. 37 patients	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			completed 2-year followup. In these patients, NRS improved from 7.0±0.2 to 3.5±0.3 (p<0.001), ODI improved from 46.2±2.2 to 29.2± 3.1 (p<0.001) and EQ5D improved from 0.426±0.035 to 0.675±0.030 (p<0.001) (Figure 8). There was a statistically significant improvement in mean NRS between 1 and 2 years. 57% of patients experienced >50% reduction in pain, 51% of patients benefited by >15-point reduction in ODI, and 65% were reporting mild to negligible pain (NRS ≤ 3) (Figure 9). In a real-world sample of patients, these results show that restorative neurostimulation provides substantial and durable benefit to a cohort of patients for whom, as described earlier, there appear to be no effective treatment options. **(Image on original document)** Figure 8: Mean±SEM patient reported outcomes (a) NRS (b) ODI (c) EQ-5D-5L *Statistically significant improvements over baseline at all time points.* *Missing data was imputed using last observation carried forward.* 	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			Figure 9: The proportion of patients reaching clinically meaningful thresholds in (a) Pain NRS and (b) ODI  We submit that the committee should include all these data in an updated overview and redrafted guidance. The submitted manuscripts are provided with this response and we will advise NICE when the manuscripts are accepted for publication. The committee may wish to note a report in a conference abstract by Ardreshiri et al.[7] reporting the results of a prospective registry of cases in Germany. Patients enrolled into the registry were on average 53 years old, with a history of back pain for an average of 8 years. All had failed conservative management, including a combination of physiotherapy, medication, injections and/or radio frequency ablations. At baseline the mean (±SEM) NRS, ODI and EQ-5D were 7.3±0.2, 42.4±1.8 and 0.508±0.03 respectively. At the time of submission 59, 39 and 16 patients have reached 6, 12 and 24 months since implantation. At one year follow-up, 56.4% of patients experienced a reduction >50 in pain and 69.3% of patients experienced either a 50% reduction in pain or a 15-point reduction in ODI. This magnitude of response appears to be maintained (68.8%) of the current sample of patients with two years follow-up. A copy of the abstract is provided with this response.	

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			Patients recruited into all these studies will continue to be followed-up (5 years for ReActiv8-A and PMCF, 7 years for ReActiv8-B pivotal study). **References** 5. Mitchell, B., et al., Durability of the Therapeutic Effect of Restorative Neurostimulation for Refractory Chronic Low Back Pain. Neuromodulation, 2021. 6. Thomson, S., et al., Restorative Neurostimulation for chronic mechanical low back pain – results from a prospective multi-centre longitudinal cohort. [Submitted manuscript]. 2021. 7. Ardreshiri, A., et al., Multi-Centre Prospective Cohort of Intractable Chronic Low Back Pain Patients Treated with Restorative Neurostimulation - Interim Analysis of the ReActiv8-C Registry., in DWG - Deutschen Wirbelsäulengesellschaft – The German Spine Society. 2021.	
100	Consultee 1 Company	**General introduction**	In order to guide the reader through the evidence that has been reviewed we think it would be helpful to provide a table with the main study parameters as part of the introduction with the surgical technique, lead type, type of study and patient numbers. We would be happy to provide NICE with such a table. the studies are: Gilligan published 2021, started 2016 RCT ReActiv8 vs sham control ReActiv8 leads, Current Midline 204 patients Thomson published 2021 started 2017 PMCF Open label ReActiv8 leads midline 42 patients Mitchell published 2021 started 2014 CE mark study Open label approach lateral Mainly original leads 53	Thank you for your comments. Please see the summary of key evidence section in the IP overview which provides details of the 4 studies (Gilligan 2021, Thomson 2021, Mitchell 2021, Deckers 2015) listed.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			patients Deckers published 2015 started 2011 Proof of concept Open label SCS product approach lateral SCS leads 26 patients	
101	Consultee 1 Company	**Efficacy summary**	We think it would help the reader understand the RCT data if it was stated that that the control group crossed over to active stimulation after the 120 day visit.	Thank you for your comments. The text in the overview for study 1 table (Gilligan 2021) has been amended to reflect this.
102	Consultee 1 Company	**Efficacy summary**	'A prospective case series of 42 patients' We think it would be helpful to point out here that this was the open label study	Thank you for your comments. Study 3 (Thomson 2021) is a post-market clinical follow-up study. Text in the overview has been amended to state that this is an open label study.
103	Consultee 1 Company	**Efficacy summary**	'A prospective case series of 42 patients with chronic mechanical low back pain (CMLBP), implanted with a neurostimulator for contraction of the lumbar multifidus, reported a reduction in mean ODI for complete cases from 46.2±2.2 at baseline to 29.2±3.1 (difference of 17.0, p<0.0001) after 2 years'. The p value in this sentence should be p<0.001	Thank you for your comments. The text in the overview (in page 7, Thomson 2021) has been amended.
104	Consultee 1 Company	**Efficacy summary**	'In the RCT' We think it would be helpful to add here at the 120-day follow-up	Thank you for your comments. The text in the overview (on page 5, Gilligan 2021) has been amended.
105	Consultee 1 Company	**Efficacy summary**	'95% CI -4.7 to -3.8' This should be 3.9 not 3.8	Thank you for your comments. The text in the overview (in page 5, Gilligan 2021) has been amended.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
106	Consultee 1 Company	**Efficacy summary**	'95% CI -53.6 to -64.1%; p<0.0001' This should be 95% CI -64.1% to -53.6%; p<0.0001)	Thank you for your comments. The text in the overview (in page 5, Gilligan 2021) has been amended.
107	Consultee 1 Company	**Efficacy summary**	'-4.6 to -3.8' This should be -5.24 to -4.5	Thank you for your comments. The text in the overview (in page 5, Gilligan 2021) has been amended.
108	Consultee 1 Company	**Efficacy summary**	'A prospective case series of 53 patients' We think it would be helpful to point out here that this is the the initial open-label study	Thank you for your comments. Study 2 (Deckers 2018, Mitchell 2021) is a described as prospective case series. The text has been amended.
109	Consultee 1 Company	**Efficacy summary**	'The responder rate (defined as patients with 2-point reduction in the mean NRS pain score from baseline to 90 days post-stimulation without a clinically meaningful increase in LBP medications) was 58% (30/52)'. We think it would be more accurate to revise this sentence to The responder rate (defined as patients with at least a 2-point reduction in the mean 7-day average NRS pain score from baseline to 90 days post-stimulation without a clinically meaningful increase in LBP medications) was 58% (30/52).	Thank you for your comments. This sentence in the overview (in page 6, Mtichell 2021) has been amended.
110	Consultee 1 Company	**Efficacy summary**	'A prospective case series of 42 patients with chronic mechanical low back pain (CMLBP), implanted with a neurostimulator for contraction of the lumbar multifidus, reported that the mean NRS improved from 7.0±0.2 at baseline to 3.5 ± 0.3 (p<0.0001) after 2-year follow up for complete cases'. The p value should be p<0.001	Thank you for your comments. The text in the overview (in page 6, Thomson 2021) has been amended.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
111	Consultee 1 Company	**Efficacy summary**	A case series of 28 patients with continuing chronic low back pain (CLBP) despite physical therapy and medical treatment and no prior surgery, implanted with pulse generators and leads, We think it would be helpful to point out that this was the initial feasibility study. There were 26 patients not 28 and the pulse generators and leads implanted were commercially available and designed for spinal cord stimulation as this was prior to the development of the pulse generator and leads designed for restorative neurostimulation.	Thank you for your comments. The text has been amended in study 4 (Deckers 2015) in the overview. Study 4 in summary of evidence table clearly states that neurostimulation devices are used in this study.
112	Consultee 1 Company	**Efficacy summary**	'At 1-year follow up, in the overall combined cohort (n=176), ODI scores improved by -19.9±15.8 points from baseline (95% CI -2.3 to -17.6; p<0.0001) or 50.5±38.7% (95% CI -44.8 to -56.3; p<0.0001). At 2-year follow up, a reduction in mean ODI from 39.1±10.3 at baseline to 17.6±1.2 for completed cases was reported (difference of -21.5, 95% CI -24.0 to -18.7 or % difference of -54.3%±3.2 (-95% CI -60.6% to -48.0%, p<0.0001). 61.3% (95/155) of patients experienced a ≥20 point improvement in ODI (95% CI 53.6% to 69.0%) (Gilligan 2021)'. For accuracy this text should read: At 1-year follow up, in the overall combined cohort (n=176), ODI scores improved by -19.9±1.2 points from baseline (95% CI -22.3 to -17.6; p<0.0001) or -50.5±38.7% (95% CI -56.3 to -44.8; p<0.0001). At 2-year follow up, a reduction in mean ODI from 39.1±10.3 at baseline to 17.6±1.2 for completed cases was	Thank you for your comments. The text on page 6, 7 (in study Giliigan 2021) in the overview has been amended.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			reported (difference of -21.4, 95% CI -24.0 to -18.7 or % difference of -54.3%±3.2 (-95% CI -60.6% to -48.0%, p<0.0001). 61.3% (95/155) of patients experienced a ≥20- point improvement in ODI (95% CI 53.6% to 69.0%) (Gilligan 2021).	
113	Consultee 1 Company	**Efficacy summary**	The case series of 28 patients reported that disability scores (measured using the 100-point ODI scale) We think it would be helpful to point out here that this was the initial feasibility study, there were 26 patients (not 28) and patients were implanted with SCS devices.	Thank you for your comments. The text on page 7 (in Deckers 2015) in the overview has been amended.
114	Consultee 1 Company	**Efficacy summary**	*'At 1-year follow up, in the overall combined cohort (n=176), the EQ-5D-5L index improved by 0.198±0.207 (95% CI 0.167 to 0.229; p<0.0001)'.* At one year follow up the improvement in EQ-5D was 0.198±0.016 and not 0.198±0.207 *'At 2 year follow up, an increase in EQ-5D from 0.585±0.174 at baseline to 0.798±0.013 in complete cases was reported (difference of 0.213±0.017, 95% CI 0.184 to 0.253, p<0.0001) (Gilligan 2021)'.* At 2 year follow up the difference was 0.218±0.017 and not 0.213±0.017.	Thank you for your comment. This text on page 8 (Gilligan 2021) in the overview has been amended.
115	Consultee 1 Company	**Efficacy summary**	'The case series of 28 patients reported that quality of life'	Thank you for your comments. Study 4 (Deckers 2015) describes that the study used neurostimulator leads. Text about the

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			As commented previously this was 26 patients, the initial feasibility study and commercially available spinal cord simulators. We think it would be helpful for readers of the evidence review to understand the evolution of the technology and the surgical technique and that the four studies referenced use different devices and surgical techniques. In particular the initial feasibility study used devices designed for spinal cord stimulation and not devices designed specifically for restorative neurostimulation. The learning from this study drove the device design that is used today.	number of patients has been amended in the overview. In response to the comments about evolution of the technology, section 3.5 in the guidance has been amended as follows: 'The committee was informed that there have been changes in the leads used in the device and in the surgical technique used to implant them, which have reduced the risk of lead fractures'. The majority of the adverse events came from earlier devices.
116	Consultee 1 Company	**Efficacy summary**	'In the open label follow up of the RCT of 204 patients with chronic mechanical low back pain (CMLBP), 80% (124/155) of patients answered 'definitely satisfied' on the treatment satisfaction questionnaire (95% CI 73.7% to 86.3%) (Gilligan 2021)'. We think it is confusing to include this statement here. It should be included after the next paragraph on the RCT as the open label phase followed the RCT.	Thank you for your comments. Text on page 8 (in Gilligan 2021) in the overview has been amended.
117	Consultee 1 Company	**Safety summary**	*'A total of 76 adverse events were reported in 66% (35/53) of patients in the case series of 53 patients'.* We think it would be helpful to point out here that this was a different lead and a different surgical approach to those currently approved.	Thank you for your comments. Text on page 9 (Deckers 2018) in the overview has been amended.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
118	Consultee 1 Company	**Safety summary**	*'A prospective case series of 42 patients with chronic mechanical low back pain (CMLBP), implanted with a neurostimulator for contraction of the lumbar multifidus, reported 20 adverse advents related to the procedure, the device, or stimulation across 28.6% (12/42) of patients, 15 of which were resolved. The biggest proportion of events were stimulation related (Thomson 2021)'.* We think it would be fair to point out that the stimulation related events were resolved with reprogramming in most cases	Thank you for your comment. Text on page 9 (Thomson 2021) in the overview has been amended.
119	Consultee 1 Company	**Safety summary**	*'A total of 97 adverse events were reported in the case series of 28 patients. Of these, 60 were related to the device, the procedure or both (27 device related,13 procedure related and 20 both device and procedure related) and happened in 74% (20/27) of patients (Deckers 2015)'.* *'13 procedure related adverse events (pain [3 events], abnormal healing [1 event], nausea or vomiting related to anaesthesia [1 event], nervous system injury [2 events], musculoskeletal stiffness [2 events], infection [2 events], seroma [1 event], and risk associated with surgery [1 event]) were reported in the case series of 28 patients (Deckers 2015)'.* *'20 surgical revisions were done in 63% (17/27) of patients in the case series of 28 patients. These were for repositioning 12 lead migrations in 10 patients, high impedance in 2, implanted pulse generator migration in 2, discomfort because of lead*	Thank you for your comments. Study 4 (Deckers 2015) describes that the study used neurostimulator leads. In response to the comment about evolution of technology, section 3.5 in the guidance has been amended as follows: 'The committee was informed that there have been changes in the leads used in the device and in the surgical technique used to implant them, which have reduced the risk of lead fractures'. The majority of the adverse events came from earlier devices.

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			anchor in 2, pulse generator failure in 1 and device explantation in 1 patient (Decker 2015)'. *'Pain (5 events), tissue injury and fever in 1 patient each, were reported in the case series of 28 patients (Deckers 2015)'.* *'Over stimulation of tissue was reported in 11% (3/27) of patients (5 events) in the case series of 28 patients (Decker 2015)'.* Again **we think it would be helpful to point out that the 26 patient feasibility study used earlier versions of the device and surgical technique that are no longer in use.**	
120	Consultee 1 Company	**Safety summary**	*'Lead fractures and inadequate stimulation'* This is an important section and we think it is important to highlight here the changes that have been made to the devices and the leads over the time in which the data were collected. The problems of lead fracture and migration related to earlier versions of the leads and surgical technique that are no longer used. To put these data in context they should be compared to the data from the RCT and PMCF where the new leads and surgical technique were used. We can provide a summary table of these data. In the RCT and PMCF studies the lead conductor fracture rate was 4% and lead migration <1%.	Thank you for your comments. The text on page 10 (study 4 Deckers 2015) in the overview has been amended to reflect that the devices and leads used were earlier versions and the surgical technique (lateral approach) is no longer used. In response to the comments about evolution of the technology, section 3.5 in the guidance has been amended.

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121	Consultee 1 Company	**Safety summary**	Lead migration We think this section should include a reference to the 2 year RCT data. The publication states that " no lead migrations were observed in this trial". In the RCT the current versions of the technology and surgical technique were used so this observation of no lead migrations provides important context for the lead migrations reported in earlier studies.	The text on page 11 (in Gilligan 2021) in the overview has been amended. In response to the comments about evolution of the technology, section 3.5 in the guidance has been amended.
122	Consultee 1 Company	**Safety summary**	Device explantation We think it would be helpful to point out that the 26 patient feasibility study and 53 patient case series used earlier versions of the device technology that are no longer used and an earlier version of the surgical technique that is no longer recommended.	Thank you for your comments. In response to the comments about evolution of the technology, section 3.5 in the guidance has been amended.
123	Consultee 1 Company	**Rapid review of literature**	Inclusion criteria for identification of relevant studies We suggest adding to this introduction the product type used in each of the studies. Thus for the RCT the product is the ReActiv8 System 75% of patients current lead, 25% old lead no longer used. For the 53 patient case series described in two publications mostly the old lead design was used and implantation was through the lateral approach which is no longer used. The two smaller case series are very different. One was the initial feasibility study using spinal cord simulator technology and the lateral approach whereas the other (PMCF) used the current ReActiv8 device and the midline approach.	Thank you for your comments. The device/product type and surgical approaches used are described under each study in the summary of evidence in the overview.

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			We think the changes in technology and surgical technique are helpful to interpret the safety and efficacy data that are reported.	
124	Consultee 1 Company	**Overview**	Study 4 Deckers K 2015 We suggest making it clear that this was a proof of concept study. Also include in the table the product used which was SCS commercially available systems	Thank you for your comments. Text for study 4 (Deckers 2015) in the table has been amended to make it clear.
125	Consultee 1 Company	**Overview**	Study 1 Gilligan C (2021) Suggest adding to the table the product used. For the RCT the product is the ReActiv8 System 75% of patients current lead, 25% old lead no longer used	Thank you for your comments. Text for study 1 (Gilligan 2021) in the table has been amended to make it clear.
126	Consultee 1 Company	**Overview**	Study 2 Deckers K (2018), Mitchell B (2021) Suggest product details added to the table for clarity. In this study product is ReActiv8 with original lead design, no longer used and old lateral surgical approach that is no longer used	Thank you for your comments. Text for study 2 (Deckers 2018, Mitchell 2021) in the table has been amended to make it clear.
127	Consultee 1 Company	**Overview**	Study 3 Thomson S (2021 Suggest add product details to the table at the start of this section. The product is current ReActiv8 System.	Thank you for your comments. Text for study (Thomson 2021) in the table has been amended to make it clear.
128	Consultee 1 Company	**Overview**	Key efficacy findings There were 26 not 28 patients	Thank you for your comments.

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				Text (in Deckers 2015) in the overview has been amended to make it clear.
129	Consultee 4 Recativ8 investigator	**Overall**	Restorative neurostimulation has a similar safety profile to spinal cord stimulation. The current proprietary tined electrodes inserted via a midline approach has very low risk of migration and fractures. The previous model of the electrodes inserted via lateral approach has now been abandoned	Thank you for your comments. In response to the comments about evolution of the technology, section 3.5 in the guidance has been amended.
130	Consultee 8 on behalf of The British Pain Society	3.2	It must be noted that all secondary outcomes looking at patient functionality, disability and well-being showed significant improvement with evidence to support continuing improvement beyond the 120 day mark. Whilst we understand that there was no significant difference in VAS pain scoring between the treatment and sham groups it must be noted that VAS changes is notoriously difficult to assess within a research protocol due to its subjective nature and the more overarching validated scoring systems assessing function, disability and well-being should hold more strength when assessing this treatment than simple VAS scoring.	Thank you for your comments. IPAC amended 3.2 key efficacy outcomes.
131	Consultee 10 NHS professional NHS - Royal Brompton & Harefield hospitals	**3.3**	The procedure has a favourable safety profile compared to other neuromodulation procedures.	Thank you for your comments.
132	Consultee 1 Company Mainstay Medical	**3.3**	We suggest that ‘lead migration’ be added to the list of key safety outcomes, because it is the most	Thank you for your comments. IPAC amended 3.3 key safety outcomes.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			common complication and reason for revision with other types of implanted neurostimulators.	
133	Consultee 8 on behalf of The British Pain Society	**3.4**	The BPS would hope that further patient input has been sought and indeed must be sought prior to any final decision being concluded.	Thank you for your comments. NICE sent the patient survey link onto the clinicians who have not previously received the survey and asked for patient input. we received 22 responses. This patient commentary was summarised and presented to the committee for consideration. Section 3.4 has been amended to reflect this.
134	Consultee 14 NHS professional President on behalf of the Neuromodulation Society of UK & Ireland and board members	**3.4**	**Patient commentary was sought but none was received.** We are unaware that NSUKI was contacted to seek patients for giving feedback. The society feels that patient input must be taken into consideration before a final decision about this therapy.	Thank you for your comments. NICE sent the patient survey link onto the clinicians who have not previously received the survey and asked for patient input. we have received 22 responses. This patient commentary was summarised and presented to the committee for consideration. Section 3.4 has been amended to reflect this.
135	Consultee 15 NHS professional Consultant in Anaesthesia and Pain Medicine Leeds Teaching Hospitals NHS Trust	**3.4**	**Patient commentary was sought but none was received**. Patient input must be taken into consideration before a final decision about this therapy. I had the invitation to send, but the patients involved in the trial are excluded. This will give very little to no feedback as we in United Kingdom have done this as a part of research before being use commercially and to get NICE recognition in doing so. The feedback should	Thank you for your comments. NICE sent the patient survey link onto the clinicians who have not previously received the survey and asked for patient input. we have received 22 responses. This patient commentary was summarised and presented to the committee for consideration. Section 3.4 has been amended to reflect this.

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			also expand to anyone with the therapy experience to get a true reflection of this therapy in UK.	
136	Consultee 17 NHS professional Specialised Pain Clinical Reference Group at NHS England	**3.4**	**Patient commentary was sought but none was received.** Patient reported outcomes are important and we aim to have this information collected. We cannot comment why patient commentaries were not received. Our experience of long term follow up (over 2 years) suggests significant, life changing improvement in quality of life. We are hopeful that some of the recipients of this treatment will respond to this consultation.	Thank you for your comments. NICE sent the patient survey link onto the clinicians who have not previously received the survey and asked for patient input. we have received 22 responses. This patient commentary was summarised and presented to the committee for consideration. Section 3.4 has been amended.
137	Consultee 1 Company Mainstay Medical	**3.4**	We were surprised to read that 'Patient commentary was sought but none was received.' To the best of our knowledge, patients were not asked to comment. We understand that there were also been problems inviting patient participation in the consultation, which have now been addressed by extending the deadline for patients to submit comments. We are confident that there will be a substantial patient response and request that the committee review the wording of this section when approving final guidance. The present wording is unnecessarily and inaccurately negative.	Thank you for your comments. NICE sent the patient survey link onto the clinicians who have not previously received the survey and asked for patient input. we have received 22 responses. This patient commentary was summarised and presented to the committee for consideration. Section 3.4 has been amended.
138	Consultee 18 NHS professional on behalf of UK Reactiv8-A and Reactiv8-B study and PMCF investigators	**3.4**	**Patient commentary was sought but none was received.** We are unaware that any of our patients have been contacted to offer feedback. We will however aim to encourage patients who have received the therapy to engage with NICE and provide the user experience.	Thank you for your comments. NICE sent the patient survey link onto the clinicians who have not previously received the survey and asked for patient input. we have received 22 responses. This patient commentary was summarised and presented to the committee for consideration. Section 3.4 has been amended.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
139	Consultee 19 NHS professional Consultant in pain medicine at Mid & South Essex University NHSFT (formerly Basildon & Thurrock University Hospitals NHSFT)	**3.4**	**Patient commentary** None of my patients were requested to supply feedback about their treatment. I have made contact and some have volunteered (within this short time frame) their responses below **Patient Experience Questionnaires Collated Responses** **From July 2021** **Patient 1,2,3,5,6 had implant 3 years ago; patient 4 had implant 3 months ago** **Restorative Neuromodulation with ReActiv8 for Back Pain** 1. *What was it like living with back pain prior to the operation?* "I would rather have given birth to a baby every day at least the pain would go eventually" Patient 1 "Devastating. The years prior to the implant are a bit of a blur now, I was taking so many prescription and non-prescription drugs that those few years seem very hazy. Daily I would be taking large amounts of codeine, tramadol, ibuprofen and Valium. There wasn't that many days when I wouldn't be taking so many meds that I would be in a constant light headed, drowsy state. My daily life was hell". Patient 2 "Extremely debilitating, and depressing, causing not only physical pain but anxiety and stress around what the future holds". Patient 3	Thank you for your comments. NICE appreciates your effort to secure patient commentary which is helpful for the committee. NICE also sent the patient survey link onto the clinicians who have not previously received the survey and asked for patient input. we have received 22 responses. This patient commentary along with your patients' responses was summarised and presented to the committee for consideration. Section 3.4 has been amended.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			"I was uncomfortable, irritable and depressed. I had restricted movement and felt pain at all times and struggled to do everyday tasks". Patient 4 "My back pain was terrible. I had been hospitalised four times. On regular occasions I could not attend work and my day to day life was heavily affected by the pain I was in. Patient 4 Very hard to get around with everything. Patient 6 2. *Please can you compare life before and after the procedure?* "Life prior to the procedure was about almost constant pain and dark thoughts regarding what the future held for me, this was interspersed by the use of pain killers and the odd pain injection. After the procedure I feel that I am able to control the pain with much more confidence and not having to take excessive oral medication. Able to enjoy physical exercise on a regular basis". Patient 1 "Like night and day. The complete opposite to before, I hardly ever take any medication now. There is nothing I feel I could not physically do now whereas before the simplest of daily tasks like showering, brushing my teeth, etc were agony". Patient 2 "Prior to the procedure it was very difficult to carry out routine tasks without pain, or without concern for causing greater pain. Following the	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			procedure, day to day tasks can be completed without worry or pain". Patient 3 "Too soon to give any comparison". Patient 4 "After the procedure my back [pain] is reduced a great deal. I'm able to walk 5 miles, swim between 50 and 64 lengths of the pool. I have only been hospitalised once in three and half years which I believe was due to Covid lockdown. I only take paracetamol and rest if I have a flare up". Patient 5 Life before was very painful. Since operation perfect/lovely Patient 6 *3. Please describe any side effects of the procedure?* "No specific adverse side effects". Patient 1 "I have lost a substantial amount of weight since I had the procedure. I now find the implant quite uncomfortable at times in certain positions. Sitting, driving, lying down it feels like I am pushing against the implant and it can be uncomfortable". Patient 2 "Slight discomfort at the site area caused by the implant". Patient 3 "A little discomfort at site of unit in lower back" Patient 4	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			"The shape of the box with corners can sometimes get caught on chairs which is painful. A much smaller round battery would be so much better. Patient 5 No side effect Patient 6 4. *Can you describe how your back pain and ability to undertake everyday activities was progressing before you had the procedure and how this changed after the procedure?* "Prior to the procedure I felt that I was beginning to be controlled by the usage of pain killers to get through day. I wanted to be able to control the pain and not the pain controlling me. I was not able to carry out a number of everyday chores, standing still for any length of time, sleep pattern disturbed, at sometimes not feeling comfortable with driving. The greatest thing is the confidence the procedure has given me regarding getting on with my life, walking, sitting comfortably, reduction in pain, which has in part helped me greatly in the reduction of taking oral medication for pain" Patient 1 "Every day activities were getting harder before. Washing, showering, teeth brushing, walking was a painful horrible experience. Since the procedure I have been pretty much able to do every activity without inhibition". Patient 2	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			"Sitting was very uncomfortable, as was short sharp movements, both are now relatively pain free". Patient 3 "Before the procedure, there was no real relief of back spasms/pain even after physiotherapy. It's too soon to see if the procedure has made a difference" Patient 4 "I had a lot of limitations i.e. walking, swimming driving, not being able to sit for longer than 30 minutes without moving. Now, as above, I can sit, walk and swim for at least one hour. Migraines have reduced significantly" Patient 5. Before: I could not engage with activities at all because of pain Now: I can perform all the activities without any problem Patient 6 5. *What outcome do you value most now that you have had the procedure?* "Being able to stand. The pain is now greatly reduced in severity, though remains there constantly, but now manageable. Able to stand for a longer length of time and I do not have to resort to the excessive use of pain killers or pain management injections" Patient 1 "Getting my life back" Patient 2 "The ability to not worry about completing any task" Patient 3	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			"Hopefully a relaxed back no spasms and to a degree pain free". Patient 4 "Freedom to live a more normal life and to exercise without pain. Greater mobility. The fear of ending up back in hospital is greatly reduced". Patient 5 I can play with my grandchildren and contribute more at my work. I am building engines and must lift heavy objects Patient 6 6. *What difference has the procedure made to:* a. *Your physical wellbeing; you may want to think about symptoms, pain, mobility and disability* "Mobility greatly improved, pain remains though greatly reduced, feel more confident in getting about any doing my daily business". Patient 1 "It has allowed to be much more physically active. Regularly working out in the gym, boxing, walking, all of these elements I could not really do before" Patient 2	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			"Much improved from a mental health aspect. Much more mobile, and much less pain". Patient 3 "Still early days". Patient 4 "The pain is greatly reduced. My mobility is much better as I can now walk for 5 miles, swim 50 lengths of the pool. Although I have retired from a heavy manual job I am now able to focus on my branch security duties i.e. meeting, travel and supporting my members. Symptom wise I rarely get migraines and am usually able to be mobile" Patient 5 100% physical ability - Patient 6 *b. Your lifestyles and the choices that you make; you may want to think about impact on daily activities, work, hobbies, social life and relationships* "Confidence has risen regarding my thoughts of being in control of my own body, able to participate in my pastime of walking". Patient 1 "There is nothing I have to think about whether I can do it or not now, before every activity I had to think and usually decide against doing it" Patient 2	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			"Less stress and worry, so relationships are improved with loved ones". Patient 3 "Still early days" Patient 4 "I am now able to attend football matches which I used to find hard sitting down so also theatres, cinemas and shows. I can now drive for at least one hour without needing to stop hence I am able to go on more holidays. I am enjoying my swimming again". Patient 5 Everything is fine. I feel I am engaging 100% after the procedure. Before 30% - Patient 6 *c. Your psychological health: you may want to think about mood, anxiety, distress* "I worry about the future and what will happen to me if the trial is discontinued and I have to revert back to relying on taking pills and injections, which as far as I am concerned can never be a long-term solution". Patient 1 "I still have struggles with this area, I believe the implant and quality of life improvements have made a drastic change to this but this is still an area that challenges me at times". Patient 2 "Less stress and worry, so relationships are improved with loved ones". Patient 3	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			“Still early days, but a bit more positive”. Patient 4 “Before the procedure I was always living in fear that I would end up back in hospital in terrible pain. Obviously that fear will never completely go but the device has helped me recognise that I can get on with a normal life (almost). Much less nervous”. Patient 5 Much better in every aspect, as with previous question. – Patient 6 *d. Other treatments that you have for your back pain.* “None”. Patient 1 “I have still required 2 procedures with Dr Thompson since the implant for cortisone injections” Patient 2 “Not applicable”. Patient 3 “Still early days”. Patient 4 “My use of strong pain killer which I always used to worry about i.e. Naproxen is very low. Only taken July 2020 when hospitalised. I occasionally take Zapain and Paracetamol to work though pain”. Patient 5	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			No medication for my back pain apart the 30 min twice a day. Previously medication and injections were not effective – Patient 6 7. *What was your experience of having the operation itself?* "Pain free experience" Patient 1 "Have very little memory of the procedure itself, sore for a couple of weeks afterwards but 3 weeks after it I went on a business trip in India and a 2 week holiday long haul with no adverse reaction". Patient 2 "Quick and easy. Sore recovery initially". Patient 3 "Staff were friendly and caring. Everything seemed to go ok. No issues". Patient 4 "Very positive. I felt that the team communicated well what the procedure would be, the recovery period and the first activation one week later. Due to Covid the regular checks have not all been happening but I do like the idea of two checks each year to reset the clock to BST and to communicate any worries or fears. Overall, I am very happy and willing to talk about the device/symptoms if this helps for fitting more devices". Patient 5	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			Everything was fine. No complain at all – Patient 6	
140	Consultee 8 on behalf of The British Pain Society	**3.5**	The BPS are pleased that lead changes have been noted to reduce lead fractures. The degree of complications noted with this treatment is no more than those seen within the delivery of Spinal Cord Stimulation, which is supported by NICE, and therefore should not be seen as a detriment.	Thank you for your comments. The committee did not compare the evidence for safety for this procedure with that for spinal cord stimulation. Also, the IP programme does not assess the efficacy and safety of comparator interventions.
141	Consultee 13 NHS professional, Consultant in Pain Medicine and Neuromodulation The Walton Centre NHS FT, Liverpool	**3.5**	I understand that changes have been made in the leads and surgical technique over time. My experience has been very positive with the latest version of the commercially available leads and with the mid-line surgical approach and I have not experienced problems with lead fracture or migration.	Thank you for your comments. Section 3.5 has been amended.
142	Consultee 14 NHS professional President on behalf of the Neuromodulation Society of UK & Ireland and board members	**3.5**	**There have been changes in the leads used in the device and in the surgical technique used to implant them, which have reduced the risk of lead fractures.** The committee need to consider the complications reported in the overview document within the continuum of research necessary to develop and perfect an implantable device. Initial studies by Deckers 2015 involved using the commercially available SCS devices designed for implantation into the epidural space as opposed to the medial branch location where muscular forces were shown to cause a high rate of migration. Hence the high rate of lead complications observed in Deckers 2015 is not applicable to the current	Thank you for your comments. Section 3.5 has been amended. evidence on safety from study 1 (Gilligan 2021) and study 2 (Deckers 2018) was considered as this reflects safety profile of CE marked device and current implantation approach. committee noted that the concept study (Deckers 2015) used off-label devices and reported high complications.

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			Multifidus Muscle Stimulation device. The same is applicable to the interpretation of the data from the Deckers 2018 study where the learning from the safety data of the initial cohort led to the redesign of the lead as well as revision of the surgical approach. We therefore believe that a realistic up to date assessment of potential for device and procedure complications should include only the patients who underwent a midline approach implant in the Decker 2018 study and the full cohort of the Gilligan 2021 study. In our experience neurostimulation implanted therapies share a number of common complications, such as lead migration, lead fracture, infection and discomfort over the battery site and explant due to lack of efficacy. Using purpose made and new standardised midline surgical approach, in the Gilligan study the incidence of lead migration / fracture is much lower for this therapy than other SCS devices recommended by NICE HTA TAG 159. Other complications are very much in line with those reported following the implant of SCS devices.	
143	Consultee 15 NHS professional Consultant in Anaesthesia and Pain Medicine Leeds Teaching Hospitals NHS Trust	**3.5**	**There have been changes in the leads used in the device and in the surgical technique used to implant them, which have reduced the risk of lead fractures.** United Kingdom Neuromodulation units had a significant contribution to the development of the device and the technique involved in the pivotal study (including our unit). The concept of multifidus	Thank you for your comments. Section 3.5 has been amended. evidence on safety from study 1 (Gilligan 2021) and study 2 (Deckers 2018) was considered as this reflects safety profile of CE marked device and current implantation approach. committee noted that the concept study (Deckers 2015)

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			rehabilitation was first tested using off label use of current SCS devices (Deckers 2015). The therapy worked, but needed specific design to keep the electrodes in place. The next CE mark study had higher complications with newer electrodes when implanted from a lateral angle as we went through the muscle which was then subjected to contraction leading to complications (Deckers 2018). This led to a change in angle of approach to the target half way through the study(more medial and less through the contracting muscles) leading on to reduced complications. This was then incorporated into the Gilligan et al study. Taking the complications from the first 2 studies, where both the electrodes and the approach are entirely different and the nature of those studies is more to test the concept and improve the hardware is not an appropriate intepretation. In conclusion, the true reflection on complication will be the Deckers 2018 with specified midline approach and the Gilligan 2021 study. The complications as compared to the SCS as per NICE TA159 are either equal or slightly less when the above is taken into account.	used off-label devices and reported high complications.
144	Consultee 17 NHS professional Specialised Pain Clinical Reference Group at NHS England	**3.5**	**There have been changes in the leads used in the device and in the surgical technique used to implant them, which have reduced the risk of lead fractures.** We agree that there has been improvement in hardware to reduce technical issues with lead fracture and migration as expected with any such technology. We believe that a realistic up to date assessment of potential for device and procedure	Thank you for your comments. Section 3.5 has been amended. evidence on safety from study 1 (Gilligan 2021) and study 2 (Deckers 2018) was considered as this reflects safety profile of CE marked device and current implantation approach. The committee noted that the concept study

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			complications includes only the patients who underwent a midline approach implant in the Decker 2018 study and the full cohort of the Gilligan 2021 study since this groups mirrors the safety profile of the current commercially available Reactiv8 device. The safety profile of which is now in line with data originally published for multicentre PROCESS Trial in 2007 for spinal cord stimulation HTA TAG 159. We estimate further reduction in such complication with improved hardware and understanding of implantation technique. The procedure in our opinion and experience has overall a favourable safety profile compared to other neuromodulation procedures.	(Deckers 2015) used off-label devices and reported high complications.
145	Consultee 18 NHS professional on behalf of UK Reactiv8-A and Reactiv8-B study and PMCF investigators	**3.5**	**There have been changes in the leads used in the device and in the surgical technique used to implant them, which have reduced the risk of lead fractures.** We agree the committee need to consider the complications reported in the overview document within the continuum of research necessary to develop and perfect an implantable device. a) We believe that in considering the Deckers 2015 study the committee should be mindful of the fact that the devices used in this cohort were commercially available SCS devices designed for implantation into the epidural space as opposed to the medial branch location where muscular forces were shown to cause a high rate of migration. Hence the high rate of lead complications observed in Deckers 2015 is inapplicable to the	Thank you for your comments. Section 3.5 has been amended. evidence on safety from study 1 (Gilligan 2021) and study 2 (Deckers 2018) was considered as this reflects safety profile of CE marked device and current implantation approach. The committee noted that the concept study (Deckers 2015) used off-label devices and reported high complications.

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			current Multifidus Stimulation (MS) device. b) The same is applicable to the interpretation of the data from the Deckers 2018 study where the learning from the safety data of the initial cohort led to the redesign of the lead as well as revision of the surgical approach. c) We therefore believe that a realistic up to date assessment of potential for device and procedure complications should include only the patients who underwent a midline approach implant in the Decker 2018 study and the full cohort of the Gilligan 2021 study. In our experience neurostimulation implanted therapies share a number of common complications, such as lead migration, lead fracture, infection and discomfort over the battery site and explant due to lack of efficacy. It is our experience that the incidence of lead migration much lower for MS therapy than other SCS devices recommended by NICE HTA TAG 159. Other complications are in our experience very much in line with those reported following the implant of SCS devices.	
146	Consultee 19 NHS professional Consultant in pain medicine at Mid & South Essex University NHSFT (formerly Basildon &	**3.5**	**There have been changes in the leads used in the device and in the surgical technique used to implant them, which have reduced the risk of lead fractures** It is important to understand that some of the data that you have considered was first proof of concept (Deckers et al 2015) using SCS equipment and	Thank you for your comments. Section 3.5 has been amended. evidence on safety from study 1 (Gilligan 2021) and study 2 (Deckers 2018) was considered as this reflects safety profile of CE marked device

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
	Thurrock University Hospitals NHSFT)		second where some were treated a lateral surgical implant technique that was abandoned following the learning from this study (Deckers et al 2018) There is relevant information on safety from Gilligan et al 2021 and Thomson et al 2021 In my personal series of 14 patients, I have not had one high impedance contact, migrated or fractured lead, nor implant infection.	and current implantation approach. The committee noted that the concept study (Deckers 2015) used off-label devices and reported high complications. IPAC also considered safety data from Thomson et al 2021 and Gilligan 2021 RCT (included in the summary of evidence in the overview).
147	Consultee 8 on behalf of The British Pain Society	**3.6**	Most SCS systems are MRI-conditional and no system is MRI compatible. There is already a well trodden path with regards implantation of neuromodulation devices and MRI requirement consideration and this has been transferred to the implantation of these devices by the experienced implantation centres so this should not be viewed as a detriment.	Thank you for your comments. IPAC amended wording in 3.6 to state that devices are incompatible with MRI
148	Consultee 11 NHS professional	**3.6**	**3.6 The devices are considered incompatible with MRI, although research into that is ongoing.** Response: This is indeed a limitation of the current version of the device. However, this is not unique to the MS device and many commercially available SCS devices remain non MR compatible while some have been adopted into MR compatibility.	Thank you for your comment. IPAC amended wording in 3.6 to state that devices are incompatible with MRI.
149	Consultee 14 NHS professional President on behalf of the Neuromodulation Society of UK & Ireland and board members	**3.6**	**The devices are considered incompatible with MRI, although research into that is ongoing.** All the neuromodulation devices on the market are MRI-conditional and no system is MRI compatible. We accept this to be an issue that may impact acceptance of the therapy. However, many neuromodulation devices that have been implanted as non-MRI conditional have now	Thank you for your comments. IPAC amended wording in 3.6 to state that devices are incompatible with MRI .

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			been retrospectively adopted as MRI conditional through manufacturer research. This device should not be an exception to this rule. Moreover, we consider the hurdles to MRI conditionality be significantly lower in an extraspinal device.	
150	Consultee 15 NHS professional Consultant in Anaesthesia and Pain Medicine Leeds Teaching Hospitals NHS Trust	**3.6**	**The devices are considered incompatible with MRI, although research into that is ongoing.** No implantable devices are compatible for MRI. They are currently conditional with restriction on MRI parameters and lead position ect. The key concern would be the heating of the electrodes and in this case the electrode is next to the Lumbar Medial Branches, which are normally denervated for back pain treatment as per NICE TA59. Most new companies in the market initially launch the product and then get the MRI conditionality and this will not be an exception. During consent process, the patients are warned about this as a routine clinical practice.	Thank you for your comments. IPAC amended wording in 3.6 to state that devices are incompatible with MRI .
151	Consultee 17 NHS professional Specialised Pain Clinical Reference Group at NHS England	**3.6**	**The devices are considered incompatible with MRI, although research into that is ongoing.** We accept this to be an issue that may impact acceptance of the therapy. However, our experience is that many SCS devices that have been sold and implanted as non-MR compatible have now been retrospectively adopted as MR compatible through manufacturer research. We do not see this device as an exception to this rule. Moreover, we consider the hurdles to MR compatibility be significantly lower in an extraspinal device.	Thank you for your comments. IPAC amended wording in 3.6 to state that devices are incompatible with MRI.
152	Consultee 18	**3.6**	**The devices are considered incompatible with MRI, although research into that is ongoing.**	Thank you for your comments.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
	NHS professional on behalf of UK Reactiv8-A and Reactiv8-B study and PMCF investigators		We accept this to be an issue that may impact acceptance of the therapy. However, our experience is that many neurostimulation devices that have been implanted as non-MR compatible have now been retrospectively adopted as MR compatible through manufacturer research. We do not see this device as an exception to this rule. Moreover, we consider the hurdles to MR compatibility be significantly lower in an extraspinal device.	IPAC amended wording in 3.6 to state that devices are incompatible with MRI.
153	Consultee 19 NHS professional Consultant in pain medicine at Mid & South Essex University NHSFT (formerly Basildon & Thurrock University Hospitals NHSFT)	**3.6.**	**The devices are considered incompatible with MRI, although research into that is ongoing** MRI safety is stratified. At present the Reactiv8 device is classified as “incompatible” but in the near future it is likely to be re-classified as conditional. The potential danger to patient is less than with SCS as it is extra-spinal	Thank you for your comments. IPAC amended wording in 3.6 to state that devices are incompatible with MRI.
154	Consultee 8 on behalf of The British Pain Society	**3.7**	"It is noted that the treatment is aimed at a very specific sub-population of all those that suffer from low back pain. There has been developed over previous years a robust patient selection process to identify that sub-population and this would also respond to the committee comment with regards point 3.7 as to the non-typical sub-population who would have enhanced outcomes with this treatment as opposed to following other treatments within NICE Guideline on Low Back Pain and Sciatica in over 16’s.	Thank you for your comments and sharing the patient screening process/criteria for neurostimulation of lumbar muscles for refractory non-specific long term chronic low back pain. The randomised sham-controlled trial (ReActiv8-B Study Gilligan 2021) and 2 other case series followed the screening process. *Committee comment* 3.7 has been amended and details about the quality of the randomised trial has been removed.

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			Patient screening for the ReActiv8 System for Chronic Low Back Pain (CLBP): (this was a table which I have pasted the text from here) STEP 1 INCLUDE IF… □ Primary diagnosis ■ M54.5 – Low Back Pain □ Treatment history - Guideline recommended treatments for CLBP including at least: □ Medication □ Physical therapy □ Multi-modal treatment [DRG I42A or I42B] □ Severe CLBP ■ VAS or NRS score ≥6 (≤9) □ CLBP related Disability ■ ODI score ≥21 (≤60) □ Motivation ■ Patient is committed to long term therapy compliance. STEP 2 EXCLUDE IF… -Indications for spine surgery - Any indication which normally would indicate spine surgery including:	

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			□ MRI reveals pathology indicating a surgical intervention □ Neurological deficits or radiculopathy extending below the knee -Prior lumbar spine surgery - Any surgical procedures involving trauma to the multifidus, its innervation or joint structures including: □ Hardware implants (cages, discs, screws, rods…) □ Resection of posterior bony anatomy (facets, lamina…) - Radiculopathy - Even if surgery is not indicated, symptoms including one or more of: □ Radiating below the knee □ Evidence of neuropathy □ Neurological deficits such as muscle weakening, etc. □ Pain in leg worse than pain in lower back - Predominantly neuropathic CLBP E.g. diagnosed by: □ Pain DETECT >18 - Sacroiliac joint pain - Also excluded if this is a comorbid pain condition to CLBP.	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			STEP 3 ACCEPTABLE IF… □ Comorbidity ■Patient is otherwise relatively healthy. ■Comorbidity is NOT linked to CLBP (e.g. hip problems) □Prior rhizotomy ■ Time since procedure is >12 months □ Obesity ■ BMI<35 and after consideration of psychological issues, causality between obesity and pain and surgical risks. □ Depression ■ Mild or moderate and likely to be related to back pain. □ Prior percutaneous discectomy ■No trauma to the multifidus and its innervation and ■ Time since procedure is >12 months □ Disc degeneration ■ Not an indication for surgery.	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			□ Spondylo- or Retrolisthesis ■ Grade 0 or 1 and ■ Not an indication for surgery □ Scoliosis ■ Cobb angle < 25° □ History of cancer ■ Need for future MRI imaging has been considered."	
155	Consultee 8 on behalf of The British Pain Society	**3.7**	It is noted that the treatment is aimed at a very specific sub-population of all those that suffer from low back pain. There has been developed over previous years a robust patient selection process to identify that sub-population and this would also respond to the committee comment with regards point 3.7 as to the non-typical sub-population who would have enhanced outcomes with this treatment as opposed to following other treatments within NICE Guideline on Low Back Pain and Sciatics in over 16's.	Thank you for your comments about patient screening process/criteria for neurostimulation of lumbar muscles for refractory non-specific chronic low back pain. The randomised sham-controlled trial (ReActiv8-B Study NCT02577354) and 2 other case series followed the patient screening process. *committee comment* 3.7 has been amended and details about the quality of the randomised trial has been removed.
156	Consultee 10 NHS professional NHS - Royal Brompton & Harefield hospitals	**3.7**	"The primary endpoint was set prior to the study at 3 months which is the usual for spinal cord stimulation devices that have an immediate response. The primary endpoint was not met in this study as 3 months was too soon to see the best response to this therapy. This is a long term restorative treatment and we are seeing excellent results at the 1 and 2 year point (in our centre 3 year results continue to improve). The long term effects were not considered	Thank you for your comments. *committee comment* 3.7 has been amended and details about the quality of the randomised trial has been removed.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			by the committee and I feel they should consider these long term good results so as not to disadvantage selected patients. The improvement in pain intensity (VAS) showed a clinically meaningful and statistically significant between-group difference at 120 days. This warrants interpretation of the totality of data. The secondary outcomes, including disability, quality of life and patient satisfaction, consistently showed a statistically significant and clinically meaningful difference at 120 days in favour of the treatment The one-year improvements are clinically substantial, and statistically significant for all outcome measures. (Gilligan 2021) The treatment is durable as the one-year improvements found in the RCT are sustained through two years (submitted and under peer-review), and data from the ReActiv8-A study demonstrate 4-year durability (accepted for publication in Neuromodulation)."	
157	Consultee 11 NHS professional	**3.7**	**3.7 There has been a well-conducted randomised controlled trial comparing the procedure against low-level sham stimulation, which did not show efficacy for the primary endpoint. But the patient selection for the trial was highly selective and not typical of patients with this condition, because it included young patients with a low BMI.**	Thank you for your comments. *committee comment* 3.7 has been amended and details about the quality of the randomised trial has been removed.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			Response: I have now worked on selecting patients for the MS device for over a decade, indeed the average candidate presenting for an MS device implant is different from the profile of a chronic pain clinic patient presenting for SCS for example as the majority were more active and had better function as reflected by the higher baseline EQ-5D than the average pain population. I therefore suggest that the selection criteria for the study are taken forward into clinical practice."	
158	Consultee 13 NHS professional Consultant in Pain Medicine and Neuromodulation The Walton Centre NHS FT, Liverpool	**3.7**	As very well recognised pain is not only a VAS number and in my view of the outcome of the RCT is that the totality of the evidence taking into account both the primary and secondary outcomes demonstrated both safety and efficacy. I am particularly pleased with the two-year results from the RCT which show that the pain relief is sustained, as maintaining a long term effect in Chronic pain patients is difficult to achieve with other pain relief modalities. The same two-year benefit has been shown in the PMCF study in which I have participated. I am also aware of data from the original study of the procedure where the pain relief has been shown to be maintained for four years. I think this is an excellent outcome in this group of patients that are very hard to treat.	Thank you for your comments. *Committee comment* 3.7 has been amended and details about the quality of the randomised trial has been removed.Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1.
159	Consultee 13 NHS professional, Consultant in Pain Medicine and Neuromodulation	**3.7**	I did not participate in the RCT but I can confirm that for the PMCF study (in which I participated) the patients recruited were typical of the population of NSCLBP patients for whom this procedure is intended.	Thank you for your comments. The UK based PMCF study (Thomson 2021) was added to the summary of evidence in the overview and considered by IPAC.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
	The Walton Centre NHS FT, Liverpool			*Committee comment* 3.7 has been amended and details about the quality of the randomised trial has been removed.
160	Consultee 14 NHS professional President on behalf of the Neuromodulation Society of UK & Ireland and board members	**3.7**	**There has been a well-conducted randomised controlled trial comparing the procedure against low-level sham stimulation, which did not show efficacy for the primary endpoint. But the patient selection for the trial was highly selective and not typical of patients with this condition, because it included young patients with a low BMI.** Indeed, this therapy is not for every patient suffering from non-specific chronic low back pain. It should be aimed at a very specific sub-population experiencing moderate to severe low back pain who: 1. demonstrate multifidus dysfunction on prone instability test 2. fail to respond to the conservative options as per NICE guidance CG59 3. fail to respond to specific physiotherapy targeting multifidus muscles 4. have no radicular symptoms or any indication for surgery 5. continue to be socially active and have no significant psychological issues 6. are considered suitable for implant at aa MDT assessment. The therapy should be available to centres for clinical use for non-research population subject to the below conditions: 5. therapy access should be restricted to	Thank you for your comments. *committee comment* 3.7 has been amended and details about the quality of the randomised trial has been removed. Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1. Data submission to a registry was recommended in 1.2. wording in section 1.5 about further research was also amended.

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			existing neuromodulation commissioned services. All patients implanted should have their outcomes reported on the National Neuromodulation registry (NNR) as recommended by NICE and GIRFT spinal pathway to facilitate robust outcome data collection. This would provide long-term real life outcomes for this therapy.	
161	Consultee 10 NHS professional Consultant in Anaesthesia and Pain Medicine Leeds Teaching Hospitals NHS Trust	**3.7**	**There has been a well-conducted randomised controlled trial comparing the procedure against low-level sham stimulation, which did not show efficacy for the primary endpoint. But the patient selection for the trial was highly selective and not typical of patients with this condition, because it included young patients with a low BMI.** The patient selection is clear and based on various inclusion criteria such as failure to NICE CG59 guidance, specific physical therapy aimed at Multifidus muscle, no radicular symptoms and have done the appropriate management such as weight loss, smoking cessation and be active. They are assessed by a Multidisciplinary team well experienced in SCS therapy and offer after confirming that there is some Multifidus dysfunction refractory to physical therapy. I hope the therapy could be available for use by the current experienced Neuromodulation service for this much selected group of patients without any restrictions as the current SCS practice. Being involved in the therapy from inception and seeing	Thank you for your comments. *Committee comment* 3.7 has been amended and details about the quality of the randomised trial has been removed.Evidence from the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			how well all my patients have done, It will be a disappointment not to be able to offer this therapy to a highly selected group of young and active patients.	
162	Consultee 1 Company Mainstay Medical	**3.7**	The wording of 3.7 'There has been a well-conducted randomised controlled trial comparing the procedure against low-level sham stimulation, which did not show efficacy for the primary endpoint' is incomplete and misleading. As we argue in the following row, an alternative pre-specified analysis of the primary efficacy endpoint reports a statistically significant result which should be noted and given the proper weight.	Thank you for your comments. *Committee comment* 3.7 has been amended and details about the quality of the randomised trial has been removed. Evidence from recent publications- the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1.
163	Consultee 1 Company Mainstay Medical	**3.7**	The wording of the second sentence in 3.7 'But the patient selection for the trial was highly selective and not typical of patients with this condition, because it included young patients with a low BMI' should also be changed. As per our comments above, the guidance has grouped together disparate aetiologies of LBP and we suggest that the committee is not therefore in a position to support this statement without further definition. In respect of age, a systematic review of the prevalence of low back pain in 54 countries found a peak in prevalence between the ages of 40 and 49[12]	Thank you for your comments. IPAC noted that these patients are a subset of patients with non-specific chronic low back pain who are refractory to conservative pain management and not suitable for interventional or surgical procedures and currently there is no treatment available. *committee comment* 3.7 has been amended and details about the quality of the randomised trial has been removed.

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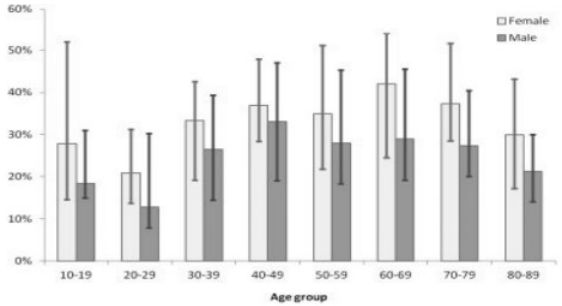
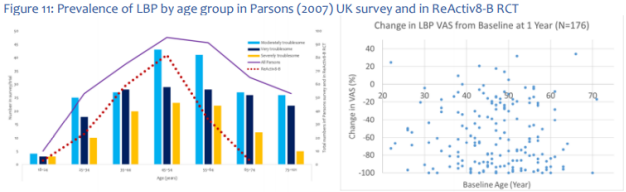
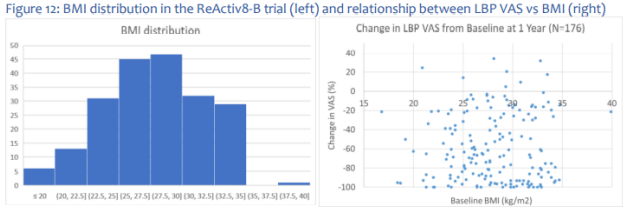
			(Figure 10): the age of the treatment group in the pivotal trial was 46±10 years (48±9 in the control group). Age inclusion criterion for the trial was ≥22 ≤75 years. **(Image on original document)** Figure 10: Median prevalence of low back pain, with IQR, according to sex and midpoint of age group  Figure 11 (right) shows that age is in any case not a predictor of response to changes in LBP VAS: the average VAS improvement for 14/176 patients aged >60 years is 60.6% vs 58.9% for the total population. **(Image on original document)**	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			A comparison between the results of a large survey carried out in 16 MRC GP Research Framework practices in 2001-2003[13] and the age distribution in the ReActiv8-B RCT is shown in Figure 11 (left). Figure 11 (right) shows that age is in any case not a predictor of response to changes in LBP VAS: the average VAS improvement for 14/176 patients aged >60 years is 60.6% vs 58.9% for the total population. Figure 11: Prevalence of LBP by age group in Parsons (2007) UK survey and in ReActiv8-B RCT  In respect of BMI, average BMI in the ReActive8-B pivotal study population was 27.9±4.0 kg/m2 which is very close to the age matched average BMI of the 'MRC National Survey of Health and Development' sample included in analysis of the above referenced study. In England 28% of people have a BMI>30 kg/m2 and 3% have a BMI>40 kg/m^2 [14]. In the, 57/176 (32%) had BMI >30 kg/m2 (Figure 12). The graph on the right shows that high BMI is not a predictor of poor response (Figure 12): the average VAS improvement for 57/176 obese patients was 59.4% and for the total population it was 58.9%. **(Image on original document)** Figure 12: BMI distribution in the ReActiv8-B trial (left) and relationship between LBP VAS vs BMI (right)  Frilander et al. found that being overweight or obese in early adulthood and later increased the risk of	

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			radiating but not NSLBP among men[15]. BMI was 28±4 in the ReActiv8-B pivotal study: in comparison, a long-term follow-up of n=978 male participants from the Geelong Osteoporosis Study reported that those (n=124) with high pain intensity and/or disability had a mean BMI of 28.6±4.5. The wording of the second sentence in 3.7 suggests that the findings of the ReActiv8-B pivotal study should be discounted as lacking external validity, which we submit is incorrect and should be deleted unless it can be properly referenced to relevant data in the final guidance. **References** 12. Hoy, D., et al., A systematic review of the global prevalence of low back pain. Arthritis Rheum, 2012. 64(6): p. 2028-37. 13. Parsons, S., et al., Prevalence and comparative troublesomeness by age of musculoskeletal pain in different body locations. Fam Pract, 2007. 24(4): p. 308-16. 14. Muthuri, S., et al., Do the associations of body mass index and waist circumference with back pain change as people age? 32 years of follow-up in a British birth cohort. BMJ Open, 2020. 10(12): p. e039197. 15. Frilander, H., et al., Role of overweight and obesity in low back disorders among men: a longitudinal study with a life course approach.BMJ Open, 2015. 5(8): p. e007805.	
164	Consultee 19 NHS professional Consultant in pain	**3.7.**	**But the patient selection for the trial was highly selective and not typical of patients with this condition, because it included young patients with a low BMI**	Thank you for your comments. IPAC noted that these are a subset of patients with non-specific chronic low back pain who are

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	medicine at Mid & South Essex University NHSFT (formerly Basildon & Thurrock University Hospitals NHSFT)		There is a small group of patients within the chronic pain service who fit the agreed criteria for multifidus nerve stimulation. This is not a treatment for ALL back pain. It fits within the NICE CG59 recommendations as part of interventional treatment options including medial branch radiofrequency neurolysis (MBBRF) and epidural. It will prevent repeat MBBRF and unnecessary spinal fusion surgery. This committee could mandate that all patients treated with this device should be included in the National Neuromodulation Registry to facilitate robust long-term clinical outcome data.	refractory to conservative pain management and not suitable for interventional or surgical procedures and currently there is no treatment available. In section 1.2 IPAC recommended that all patients should be entered into the National Neuromodulation Registry. *committee comment* 3.7 has been amended and details about the quality of the randomised trial has been removed.
165	Consultee 10 NHS professional NHS - Royal Brompton & Harefield hospitals	**General**	I am a pain physician who took part in the PMCF study in UK with 9 patients who are all benefiting from the therapy at 3 years now. There is not an instant response to the therapy (like there is in spinal cord stimulation therapy), there is a restorative effect which at one year onwards provides good pain, relief, improved mobility and funciton	Thank you for your comments and sharing your clinical experience.
166	Consultee 18 NHS professional on behalf of investigators involved in the studies of the Multifidus stimulator device in the UK-UK Reactiv8-A (Deckers et al 2018) and Reactiv8-B	**General**	We thank NICE for IPG draft on Neurostimulation of lumbar muscles for refractory non-specific chronic low back pain. Our feedback reflects our collective experience of this technology in patients with refractory low back pain during our work on the Reactiv8-A study (Deckers et al 2018) and Reactiv8-B study (Gilligan et al 2021) as well as the recently submitted UK Post marketing clinical follow up study (PMCF) (Thomson et al submitted to Pain and Therapy July 2021).	Thank you for your comments. Reactiv8-A study (Deckers et al 2018) and Reactiv8-B study (Gilligan et al 2021) are included in the summary of evidence. Evidence from recent publications- the randomised controlled trial (Reactiv8 B trial-Gilligan 2021) with 1 and 2 year follow-up, the 4-year results from the ReActiv8-A study (Mitchel 2021), and data from the UK based PMCF study (Thomson 2021) was included in

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	study (Gilligan et al 2021) and PMCF study (submitted July 2021).			the summary of evidence in the overview and considered by IPAC. IPAC considered your comments, all the evidence and changed the recommendation in 1.1.

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