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ORIGINAL ARTICLE

An international Delphi survey and consensus meeting to define the core outcome set for trigeminal neuralgia clinical trials

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Abstract

Background: Trigeminal neuralgia (TN) is an excruciating unilateral facial pain, which negatively affects patient's quality of life. Historically, it has been difficult to compare treatment efficacy due to the lack of standardized outcomes. In addition, patients' perspective has seldomly been acknowledged. The aim of this study was to reach consensus on what outcomes of treatment are important to different TN stakeholders (patients, clinicians and researchers), to identify the TN Core Outcome Set (TRINCOS).

Methods: A list of outcomes identified through a systematic review and focus group work was used to develop the survey questionnaire. A three-round Delphi was conducted. Participants were asked to score the outcomes on scale from 1 to 9 (1–3 not important;4–6 important but not critical;7–9 critical). Outcomes scored as critical by ≥70% and not important by <15% were retained, and those for which no consensus was reached were discussed at a consensus meeting.

Results: Of the 70 participants who completed the Delphi, 26 were patients, 38 were clinicians and six were researchers. Of the 40 outcomes presented, 17 were scored as critical and no consensus was met for 23 outcomes. Agreement was reached during a consensus meeting on 10 outcomes across six domains (pain, side effects, social impact, quality of life, global improvement, and satisfaction with treatment).

Conclusion: Implementation of TRINCOS in future clinical trials will improve homogeneity of studies' results, reduce the redundancy in the outcome assessment and effectively allow comparison of different treatments to better inform researchers, clinicians and most importantly patients, about the efficacy of the different treatments.

Significance: Implementation of a 10-item core outcome set in trigeminal neuralgia will improve comparability between studies allowing patients to have faster access to better treatments.

1 | INTRODUCTION

Trigeminal neuralgia (TN) is a 'recurrent unilateral brief electric shock like pain, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli'. It can be classified into classic, when there is evidence on imaging of a neurovascular compression, secondary, when there is an underlying disease, e.g., multiple sclerosis or a tumour in the cerebellopontine angle, and finally, idiopathic, in the absence of abnormalities on imaging. Patients might present with purely paroxysmal pain or paroxysmal pain and continuous or near continuous background pain (ICOP, 2020).

Although a rare condition with a prevalence ranging from 0.03% to 0.3% (De Toledo et al., 2016), it is a devastating disease, which can lead to suicide (Petrosky et al., 2018).

TN is a unique type of pain for which pharmacological and surgical options are available. The first-line treatments are carbamazepine and oxcarbazepine; other adjuvant options are available (gabapentin, pregabalin, lamotrigine and baclofen) but these recommendations are based on weak evidence (Bendtsen et al., 2019). When medication alone is either not effective or it causes intolerable side effects, a surgical option must be considered. The treatment of choice for those who have neurovascular compression and are fit enough is microvascular decompression. For the remaining patients, ablative techniques can be used (Bendtsen et al., 2019). Despite these options, no consensus exists yet as to what is the optimal treatment. The lack of randomized controlled trials, comparing the different drugs, drugs and surgery and the different surgical procedures, partly explains the lack of a clear ranking when it comes to treatment. Additionally, the lack of standardized outcomes and outcome measures used contributes to the heterogeneity of data and the growing inability to compare study results. The need for more standardized outcomes and for the assessment of end points other than those related to alleviation of TN pain has been highlighted over the years, e.g. neurology guidelines (Bendtsen et al., 2019; Cruccu et al., 2008). In the wider chronic pain field, the IMMPACT group (Initiative on Methods, Measurement and Pain Assessment in Clinical Trials) has provided recommendations on what outcomes should be measured in chronic pain clinical trials and these include four outcome domains besides pain, namely, the emotional and physical impact of the condition, satisfaction with treatment and adverse events (Turk et al., 2003).

The lack of information on outcomes fails to provide patients with adequate answers about the prognosis of the treatment options available and just adds to the misuse of research results. These research challenges could be improved if the wider research community assessed the same outcomes in a standardized way.

A core outcome set (COS) is defined by the Core Outcome Measures in Effectiveness Trials (COMET, n) Initiative as 'an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care' (Williamson et al., 2017). The aim of this study was to develop the COS to be used in all future TN clinical trials (medical or surgical), to improve combination and contrasting of results and improve patient care.

2 | METHODS

2.1 | Study overview

The TRINCOS study was designed to develop the COS to be used in clinical trials (medical or surgical) of adult patients with TN, as defined by the International Classification of Orofacial Pain. Methodological guidance was sought from the COMET Initiative (Williamson et al., 2017). The study was divided into five stages—see Figure 1 for details. Consensus methods are described in the present paper (stages 3 and 4); stages 1 and 2 have been described separately (Venda Nova et al., 2020; Venda Nova et al., 2021).

The reporting of this study followed guidance from the Core Outcome Set–STAndards for Reporting COS-STAR Statement (Kirkham et al., 2016). A registry entry was prospectively created for this study on the COMET Initiative website—https://www.comet-initiative.org/Studies/Details/1123.

Throughout the paper the term 'outcome domain' refers to the overarching classification, whereas 'outcome' refers to a dimension of that domain: for example, PAIN is an outcome domain, and PAIN INTENSITY an outcome or outcome dimension (Turk et al., 2003).

2.2 | Study design

Consensus methods were used to achieve the present study's aim. The Delphi method was developed by RAND Corporation in the 1950s. (Okoli & Pawlowski, 2004). It has specific features, which distinguish it from a traditional survey, for example, it must have at least two rounds to allow for feedback between rounds (Williamson et al., 2017), there is an assessment of the responses, participants can modify their responses between rounds, and it is an anonymous process. The advantage of this survey is that responses are more independent and not influenced by participants'

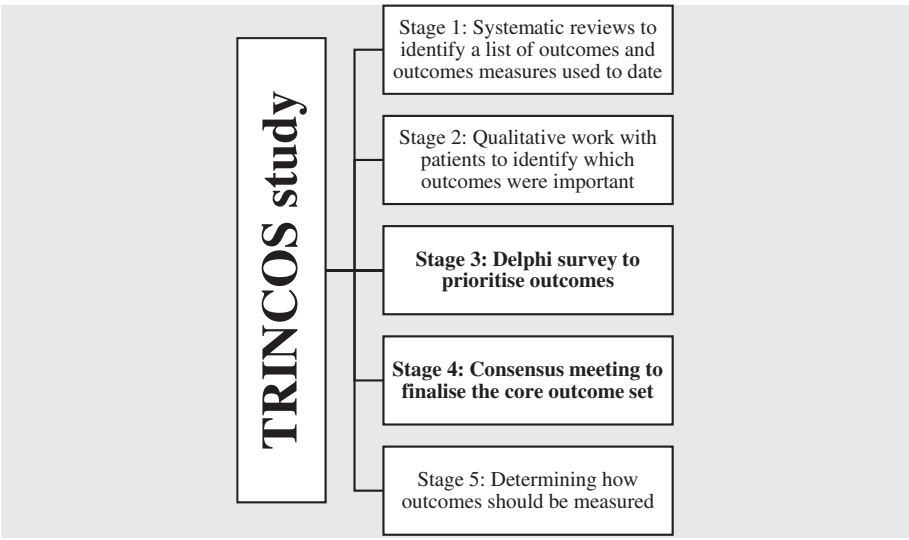

FIGURE 1 TRINCOS study stages.

status or perceived knowledge or expertise (Okoli & Pawlowski, 2004).

A consensus meeting is a process by which a group of people, usually experts on a given subject, meet face to face (or online) to debate, discuss and generate agreement on a given issue. By the end of the meeting, the group should reach a consensus, which differs from unanimity. Not all participants are unanimous in terms of the preferences, but there is a shared agreement by all. There is no specific guidance on how to run these meetings for a COS development study. In view of the recent need to shift to online meetings, guidance was sought from COMET on how to best prepare for the format change (Gorst et al., 2021).

2.3 | Participants

The sample size for a Delphi survey does not rely on statistical power, as opposed to a traditional survey, where it is expected that the results are generalizable to a larger population; nevertheless, the recommended panel size is between 10 and 18 participants (Okoli & Pawlowski, 2004). The focus of recruiting for a Delphi survey is on the expertise of the participants in a given field (Skulmoski et al., 2007). In the case of TN, clinicians, researchers and patients were the stakeholder groups identified with the right expertise to contribute to the consensus processes.

Patients were recruited from a patient organization, the TNA UK (Trigeminal Neuralgia Association). The study was advertised on the TNA website and newsletter. Patients contacted the study team if they wished to be included in the study. European and international patient association representatives were contacted via the email addresses available on their webpage.

Healthcare professionals and researchers, including industry representatives, were initially selected via http://expertscape.com, a website that features the researchers with the greatest output in a given area, and later contacted via email. Some of these researchers are also healthcare professionals. Those contacted were asked to forward the survey link to colleagues and contacts (snowball sampling). Healthcare professionals known to the research team were contacted directly. The members of the research team did not participate in the survey.

Email invitations with details of the study (background, aims and relevance and future implications of the project), contact details of the research team and the survey link, were sent to prospective participants.

Healthcare professionals and researchers who completed the three rounds of the Delphi were randomly selected and invited to participate in the consensus meeting. To increase generalizability of results, a new cohort of patients was recruited from a Facial Pain clinic at a London Teaching Hospital.

The aim was to recruit between 15 and 18 participants to allow for small group discussion, with a balanced number of participants per stakeholder group. Those attending received a voucher for their time and contribution.

2.4 | Information sources

The content design of the Delphi survey was informed by a qualitative focus group study conducted with TN patients in the latter part of 2020 (Venda Nova et al., in press). It was also based on the results of a systematic review summarizing the outcomes and outcomes measures used to date in TN intervention studies (Venda Nova

et al., 2020). For completeness ClinicalTrials.gov website was consulted for information on outcomes planned in newly registered trials.

The final list of outcomes was reviewed by the research team and outcomes were combined in several domains using the IMMPACT taxonomy for clinical trials in chronic pain as a guide (Turk et al., 2003); however, domains were not restricted to those recommended in the guidance and others were included.

Prior to the start of the Delphi, the survey questionnaire was piloted with three patients and three clinicians and feedback was sought on clarity of the questions and terminology, definitions of the outcomes and time taken to complete the survey. Their suggestions were considered before the survey was finalized. The final list of outcome domains and outcomes is in the appendix (Table S1, pp 2–3).

2.5 | Consensus processes

2.5.1 | Delphi survey

Patients, clinicians and researchers were invited to participate in a three-round Delphi survey. Each round was open for 4 weeks. The Delphi Manager software developed by the COMET Initiative was used to set up and run the online survey (COMET).

In round 1, the outcomes were listed in random order. Participants were asked to score each outcome to reflect 'how important' they felt they were on a Likert scale from 1 to 9, with 1–3 labelled 'not important', 4–6 labelled 'important but not critical' and 7–9 labelled 'critical'. If they could not score an item, an option 'unable to rate' was available. At the end of round 1, participants were able to suggest additional outcomes that they thought should be considered but had not been featured in the survey. Those who did not complete round 1 were not invited for the next round. In round 2, the distribution of scores awarded for each outcome during round 1 was summarized and divided by stakeholder group. The summary of scores per stakeholder group was visible to participants, and they were asked to re-score each outcome for importance considering their own group scores. This method has been shown to increase consensus (Brookes et al., 2016).

Similarly to round 1, only those completing round 2 were invited for the next round. In round 3 the distribution of scores was summarized and sent to participants. They were again asked to re-score the outcomes as described above. By repeating the process in three rounds, using group score feedback, can encourage convergence of ideas. No outcomes were excluded (either having reached cut off for inclusion in or exclusion from the COS) to give each outcome an equal change of highest level of consensus (Keeney et al., 2010). Although summaries of scores were visible to participants, anonymity of participants' personal details was maintained throughout the process.

The criteria for determining which outcomes should be included (consensus in) and which should be excluded (consensus out) were specified a priori. An outcome was considered 'in' if 70% or more scored it as a 7–9 and fewer than 15% scored it as 1–3, in all stakeholder groups. An outcome was considered 'out' if 50% or less scored it 7–9 in all stakeholder groups. Outcomes for which a consensus was not reached (no consensus), were taken forward for further discussion at the online consensus meeting. According to the COMET Handbook, there is no strict requirement for what criteria is adopted but is important that authors justify their choice (Williamson et al., 2017). The criteria adopted in this study is the same as described by Williamson et al. (Williamson et al., 2012) and the rationale is that the majority identify an outcome to be crucial and a small percentage considers it not important.

2.6 | Statistical analyses

Descriptive statistics were used to summarize the data set (number and percentage of those scoring each outcome, by stakeholder group). Overall attrition rate was calculated and mean scores of those completing round 1 alone were compared with those completing round 1 and 2, and mean scores of those completing round 1 and 2 only, where compared to those completing the three rounds. A t-test was used to assess if the differences in means were statistically significant ($p < 0.05$).

2.7 | Online consensus meeting

A meeting package was designed with the help of a patient who did not take part in the consensus process and sent via email to those who accepted the invitation. Guidance was sought from the COMET website for plain language summaries and their video explaining what a COS consist of was sent along with all the meeting package documents (consent form, glossary of terms, a list of outcomes which had reached consensus at the Delphi, the list of outcomes to be discussed at the meeting, the meeting agenda).

A 3-h online consensus meeting was held using an online platform (Zoom Video Communications, Inc.). The aim of this meeting was to discuss the outcomes which did not reach consensus during the Delphi survey followed by a new anonymous vote using the same criteria as that of the Delphi survey and, to hold a final majority vote (i.e., >50%) if the provisional COS included an extensive list of outcomes. Although there is no clear guidance on what an ideal number of outcomes should be in a COS, based on the OMERACT guidance (Maxwell et al., 2019), the aim

was to generate a list of approximately 10 outcomes for the ease of implementation and feasibility.

2.8 | Ethics statement

A consent statement featured in the registration page of the Delphi survey, and only those who consented to participate could progress through the survey pages. Ethical approval for the consensus meeting was granted by North of Scotland Research Ethics Committee (19/NS/0153).

3 | RESULTS

3.1 | Delphi

Figure 2 summarizes the flow of participants through the Delphi survey. Demographic and clinical data were collected at the start of the survey as well as participant rates, which are in Table S2, pages 4–7 in the appendix.

Of the 31 outcomes suggested by participants after round one, two were selected by the research team to be included in the two subsequent rounds (Table S1, appendix pp2-3). After three rounds, no outcomes met the criteria for exclusion, 17 outcomes met the criteria for inclusion and 23 did not meet consensus. Table 1 summarizes the provisionally included and non-consensus outcomes.

Information on how outcomes were scored by each stakeholder group can be seen in Table 2. Attrition rates between the mean scores in different rounds are outlined in the appendix (Tables S3 and S4, pp8-15).

3.2 | Online consensus meeting

Thirteen participants attended the online consensus meeting (five clinicians, two researchers and six patients)—see

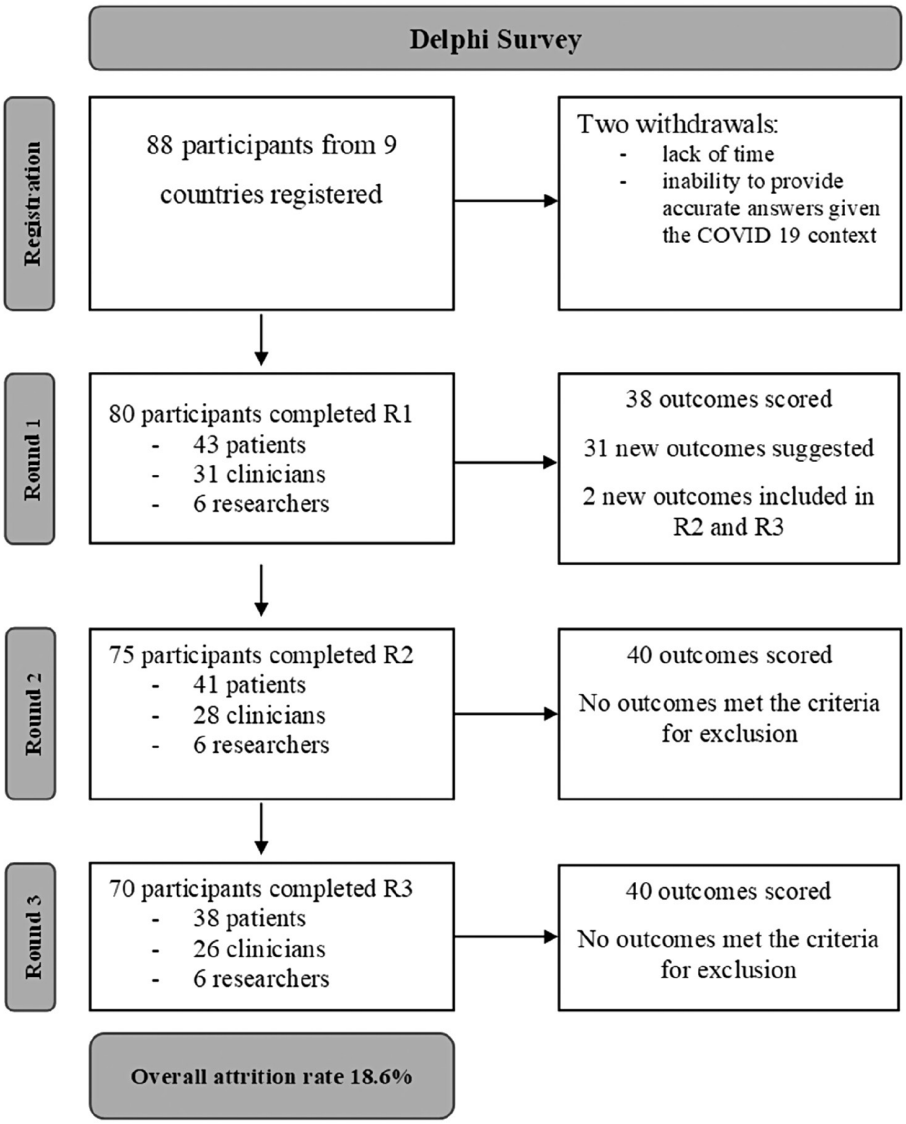

FIGURE 2 Flow chart of the Delphi survey.

TABLE 1 Provisionally included and non-consensus outcomes after round 3 of the Delphi survey

Outcomes *in* **Criteria: 70% or more scored it as a 7–9 and <15% scored it as 1–3**	***No consensus* outcomes** **Criteria for either *consensus in* or *consensus out* not met**
Access to a specialist TN clinic	Ability to participate in social roles and activities
Coping	Anxiety
Duration of pain relief	Avoidance behaviour
Eating	Catastrophising
Fear of pain or fear of an attack	Depression
Health related quality of life	Effect of TN on Family and friends
Literacy of GPs and Dentists about TN	Illness beliefs
Overall response to treatment	Intimacy
Pain intensity	Pain free off medication
Pain interference	Pain free on medication
Pain relief	Patient's literacy about TN
Quality of the pain – electric shock	Peer support
Satisfaction with treatment	Quality of the pain - constant burning
Self-care	Reduction in the need for rescue medication
Side effects of medication	Self-efficacy
Side effects of surgery	Self-efficacy on managing chronic conditions
Talking	Self-efficacy on managing emotions Social validation Social withdrawal and isolation Temporal aspects of pain Time to return to work/family responsibilities after surgery Trigger sensitivity Work ability

Abbreviations: GP, general practitioner; TN, trigeminal neuralgia.

Table S2 pp4-7 in the appendix, for demographic data of participants. Twenty-three outcomes that did not meet consensus were informally discussed in breakout rooms. Following discussions, the outcomes were presented for anonymous scoring using the same scoring system as that of the Delphi. Only two outcomes met the criteria for inclusion ('pain free on medication' and 'ability to participate in social roles and activities') and were brought forward to the final poll. Of the 19 outcomes provisionally included in the COS, 11 were deemed 'mandatory' to be included in the COS, 6 were deemed 'important but not critical' and two reached a tie (quality of the pain—electric shock/access to a specialized TN clinic). See Figure 3 for the final list of outcomes.

4 | DISCUSSION

This is the first study to develop a COS for TN. Patients, clinicians and researchers identified 11 outcomes to be used, as a minimum, in future TN clinical trials—pain relief, duration of pain relief, pain intensity, pain interference, pain free on medication, health-related quality of life, ability to participate in social roles and activities, overall response to treatment, satisfaction with treatment, side effects of medication and of surgery.

This is an important first step in improving outcome measurement and if used widely, will contribute to improved combination and contrasting of results, improved use of research data, and importantly, to improved patient care.

The results of the study confirmed, unsurprisingly, that pain dimensions are important in TN as five outcomes relating to pain were included in the COS. The burden of TN has been previously reported and a relationship between pain and ability to participate has been identified (Zakrzewska et al., 2017), which is in line with the fact that 'ability to participate in social roles and activi' was included in the COS.

There were, however, some unexpected exclusions from the COS, for example, the impact of treatment

TABLE 2 Scoring of outcomes by stakeholder group—Round 3 of the Delphi survey.

	Patients *n* = 38								Clinicians n = 26	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
	1–3		4–6		7–9		10		1–3	
Outcomes	**Not important**		**Important but not critical**		**Critical**				**Not important**	
Ability to participate in social roles and activities	0	0.0	4	10.5	34	89.5	0	0.0	0	0.0
Access to a specialist TN clinic	0	0.0	3	7.9	35	92.1	0	0.0	0	0.0
Anxiety	0	0.0	4	10.5	34	89.5	0	0.0	0	0.0
Avoidance behaviour	2	5.3	15	39.5	20	52.6	1	2.6	0	0.0
Catastrophising	3	7.9	11	28.9	24	63.2	0	0.0	0	0.0
Coping	1	2.6	5	13.2	32	84.2	0	0.0	0	0.0
Depression	0	0.0	2	5.3	36	94.7	0	0.0	0	0.0
Duration of pain relief	0	0.0	0	0.0	38	100.0	0	0.0	1	3.8
Eating	0	0.0	1	2.6	37	97.4	0	0.0	0	0.0
Effect of TN on Family and friends	2	5.3	8	21.1	27	71.1	1	2.6	0	0.0
Fear of pain or fear of an attack	2	5.3	9	23.7	27	71.0	0	0.0	0	0.0
HRQOL	0	0.0	0	0.0	38	100.0	0	0.0	0	0.0
Illness beliefs	4	10.5	18	47.4	15	39.5	1	2.6	1	3.8
Intimacy	1	2.6	14	36.8	22	57.9	1	2.6	0	0.0
Literacy of GPs and Dentists about TN	0	0.0	1	2.6	37	97.4	0	0.0	0	0.0
Overall response to treatment	0	0.0	3	7.9	35	92.1	0	0.0	0	0.0
Pain free off medication	0	0.0	5	13.2	32	84.2	1	2.6	2	7.7
Pain free on medication	0	0.0	9	23.7	29	76.3	0	0.0	1	3.8
Pain intensity	0	0.0	0	0.0	38	100.0	0	0.0	1	3.8
Pain interference	0	0.0	1	2.6	36	94.7	1	2.6	0	0.0
Pain relief	0	0.0	0	0.0	38	100.0	0	0.0	1	3.8
Patient's literacy about TN	0	0.0	1	2.6	37	97.4	0	0.0	0	0.0
Peer support	1	2.6	10	26.3	27	71.1	0	0.0	0	0.0
Quality of the pain - electric shock	1	2.3	0	0.0	37	97.4	0	0.0	1	3.8
Quality of the pain - constant burning	1	2.3	7	18.4	25	65.8	5	13.2	1	3.8
Reduction in the need for rescue medication	2	5.3	9	23.7	26	68.4	1	2.6	0	0.0
Satisfaction with treatment	0	0.0	4	10.5	33	86.8	1	2.6	0	0.0
Self-care	0	0.0	3	7.9	34	89.5	1	2.6	0	0.0
Self-efficacy	0	0.0	4	10.5	34	89.5	0	0.0	0	0.0
Self-efficacy on managing chronic conditions	0	0.0	5	13.2	33	86.8	0	0.0	0	0.0
Self-efficacy on managing emotions	0	0.0	8	21.1	30	78.9	0	0.0	0	0.0
Side effects of medication	0	0.0	3	7.9	35	92.1	0	0.0	1	3.8
Side effects of surgery	0	0.0	1	2.6	32	84.2	5	13.2	0	0.0
Social validation	1	2.6	15	39.5	22	57.9	0	0.0	0	0.0
Social withdrawal and isolation	5	13.2	10	26.3	22	57.9	1	2.6	0	0.0
Talking	0	0.0	5	13.2	33	86.8	0	0.0	0	0.0
Temporal aspects of pain	0	0.0	6	15.8	32	84.2	0	0.0	1	3.8

Researchers n = 6													
n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
4–6		7–9		10		1–3		4–6		7–9		10	
Important but not critical		Critical				Not important		Important but not critical		Critical			
2	7.7	24	92.3	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0
7	26.9	19	73.1	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
4	15.4	22	84.6	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0
5	19.2	21	80.8	0	0.0	0	0.0	4	16.7	5	83.3	0	0.0
9	34.6	17	65.4	0	0.0	1	16.7	0	0.0	5	83.3	0	0.0
3	11.5	23	88.5	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
5	19.2	21	80.8	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0
2	7.7	23	83.5	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
2	7.7	23	88.5	1	3.8	0	0.0	0	0.0	6	100.0	0	0.0
16	61.5	10	38.5	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
5	19.2	21	80.8	0	0.0	0	0.0	0	0.0	6	100.0	0	0.0
1	3.8	25	96.2	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
8	30.8	17	65.4	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0
2	7.7	24	92.3	0	0.0	1	16.7	0	0.0	4	66.7	1	16.7
4	15.4	22	84.6	0	0.0	0	0.0	0	0.0	6	100.0	0	0.0
1	3.8	25	96.2	0	0.0	0	0.0	0	0.0	6	100.0	0	0.0
9	34.6	15	57.7	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0
9	34.6	16	61.5	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
2	7.7	23	88.5	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
1	3.8	25	96.2	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
1	3.8	24	92.3	0	0.0	0	0.0	0	0.0	6	100.0	0	0.0
5	19.2	21	80.8	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0
12	46.2	14	53.8	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
5	19.2	20	76.9	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
12	46.2	13	50.0	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0
14	53.8	12	46.2	0	0.0	1	16.7	2	33.3	3	50.0	0	0.0
3	11.5	23	88.5	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
2	7.7	24	92.3	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
9	34.6	17	65.4	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0
8	30.8	18	69.2	0	0.0	0	0.0	1	16.7	4	66.7	1	16.7
8	30.8	18	69.2	0	0.0	1	16.7	1	16.7	4	66.7	0	0.0
3	11.5	22	84.6	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
2	7.7	24	92.3	0	0.0	0	0.0	0	0.0	6	100.0	0	0.0
15	57.7	11	42.3	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
5	19.2	21	80.8	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0
0	0.0	25	96.2	1	3.8	0	0.0	0	0.0	6	100.0	0	0.0
5	19.2	20	76.9	0	0.0	1	16.7	1	16.7	4	66.7	0	0.0

(Continues)

TABLE 2 (Continues)

Outcomes	Patients *n* = 38								Clinicians n = 26	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
	1–3		4–6		7–9		10		1–3	
	Not important		Important but not critical		Critical				Not important	
Time to return to work/family responsibilities after surgery	1	2.6	12	31.6	20	52.6	5	13.2	1	3.8
Trigger sensitivity	1	2.6	1	2.6	35	92.1	1	2.6	1	3.8
Work ability	0	0.0	7	18.4	30	78.9	1	2.6	0	0.0

Note: Outcomes that reached consensus to be included in the core outcome set, i.e., >70% voted 7–9 and < 15% voted 1–3 in all stakeholder groups. Outcomes for which there was no consensus during the e-Delphi, taken forward to discussion at the online consensus meeting.

Abbreviations: GP , general practitioner; HRQOL, health related quality of life; *n*, number; TN, trigeminal neuralgia.

The grey shaded values are those outcomes which were voted 7-9 (critical) by 70% or more of the participants.

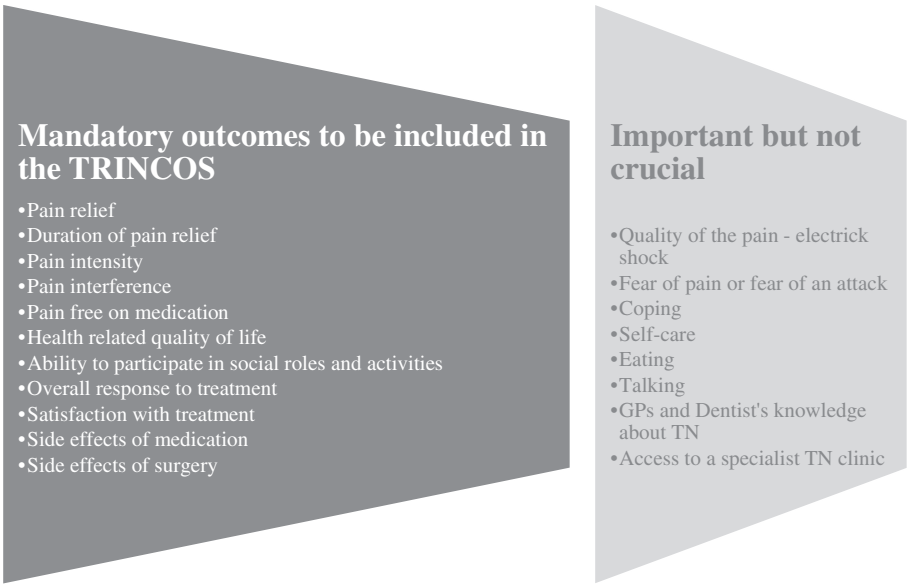

FIGURE 3 Panel on the left - Trigeminal Neuralgia Core Outcome Set (COS). Panel on the right—Important but not crucial outcomes for the COS. GP, general practitioner; TN, trigeminal neuralgia.

on mood, specifically anxiety and depression, as the literature supports the understanding that TN pain causes an impact on mental well-being(Zakrzewska et al., 2017).

During the Delphi survey these outcomes were voted 'critical' by more than 70% of participants in two stakeholder groups but not in all three. The same weight was given to all stakeholder groups to account for the disparity in the numbers in each group. Our consensus definition was decided 'a priori'; had the cut off been more relaxed, other outcomes could have been considered, but it could also mean that a larger list of outcomes was produced. Anxiety and depression did not reach the cut-off point during the consensus meeting, which had the advantage of allowing participants to discuss their views on each outcome for which consensus had not been met.

These results differ somewhat from the recommendations made by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for inclusion of emotional impact on chronic pain COSs (Turk et al., 2003). A possible explanation for this might be the inclusion of health-related quality of life (defined in the Delphi as 'An individual's perceived well-being in physical, mental and social aspects of health') via our Delphi process.

						Researchers n = 6							
n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
4–6		7–9		10		1–3		4–6		7–9		10	
Important but not critical		Critical				Not important		Important but not critical		Critical			
11	42.3	13	50.0	1	3.8	0	0.0	3	50.0	3	50.0	0	0.0
8	30.8	17	65.4	0	0.0	1	16.7	0	0.0	5	83.3	0	0.0
5	19.2	21	80.8	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0

Health related quality of life is as a multidimensional concept representing the impact of pain on mental well-being (Fayers & Machin, 2016). Similarly, a COS developed for preventative trials of episodic migraines, did not include outcomes relating to the impact of migraines on mood, and the final list included pain intensity, pain frequency and migraine-related quality of life (MRQoL). Interestingly, participants on this study chose the Migraine Functional Impact Questionnaire to assess MRQoL which addresses emotional functioning among other domains (Haywood et al., 2021). This requires further exploration in TN as HRQOL questionnaires have not yet been validated in this ~~patient~~ population. It is also worthwhile acknowledging the prominent role ~~the~~ patients with TN had in this study, in contrast to that of the IMMPACT group. The outcome set recommendations are therefore bound to differ due to the differing stakeholders involved in the respective study methodologies employed.

By including clinicians, researchers and patients in a shared decision-making process, the results of the present study reflect the views of many, and their different opinions and perspectives complement each other, contributing to the quality and relevance of the study (Elberse et al., 2011). Importantly, 44 patients participated in the Delphi and consensus meeting. As TN is a rare disease, and although consensus processes do not rely on statistical power, having a high number of patients in the study contributes to the generalizability of results. In addition, the international panel of clinicians and researchers able to complete the Delphi and participate in the consensus meeting, reinforced the generalizability of results, although, a case study from a consensus process in gastric cancer, involving 952 participants from 55 countries, concluded that there was little variation in outcome scoring, when considering the region of origin, which is reassuring (Alkhaffaf et al., 2021).

Besides the number of participants, another strength of this study was the low attrition rate of 18.6%. Although there is no defined threshold for what is an adequate attrition rate, based in the guidance for randomized controlled trials, attrition rates >20% can be a source of bias (Dumville et al., 2006). The differences in the mean scores for each outcome between rounds were, for the majority of outcomes, not statistically significant (appendices pp8-15, Tables S3 and S4), which suggests that, although some participants did not complete the three rounds, attrition bias is not likely to have affected the results(Williamson et al., 2017).

During the focus group work that preceded the consensus stages, patients were clear and adamant on how crucial a timely and adequate referral to a specialist was to their experience (Venda Nova et al., in press). This was validated during the Delphi by the high level of importance attributed to 'Access to a specialist clinic' and 'Literacy of GPs and Dentists about TN' by all stakeholder groups as seen by these outcome's mean scores (appendix pp8–15, Tables S3 and S4). These non-clinical outcomes would not traditionally be included in a clinical trial; however, it can be argued that in the case of TN, their importance deserves at least some consideration. Firstly, it was important to acknowledge these outcomes as they reflect patient's unmet needs, which is good practice in any patient centred research (de Wit et al., 2019) and a specific recommendation of the COMET initiative in COS development. Secondly, recruitment and retainment of patients in clinical trials is a difficult task, especially in the context of a rare disease (Taft et al., 2020; Zakrzewska et al., 2018). Improving the knowledge of primary care clinicians about a disease, not only gives patients better chances of an adequate care

pathway but also GPs may play a fundamental role in motivating and supporting patients to participate in clinical trials (Taft et al., 2020). Although treatment might be started in more specialized settings, patient's GPs will continue to be involved and provide support to this cohort of patients, and some patients might even be discharged to their care, once stable (RCS, 2021).

4.1 | Limitations

Side effects of treatment have been identified as crucial outcomes to be included in the COS, however details on which specific side effects of medication and of surgical procedures were more important to the different stakeholders were not addressed, as this would create an interminable list and could compromise the survey's response rate.

Our patient recruitment was restricted to patients in the United Kingdom. It was also conducted in English and clinicians and researchers invited from non–English-speaking countries could have declined due to the language barrier.

Our study was done exclusively online. Studies conducted online have the advantage of including participants from geographically disperse areas, but can exclude those not familiar with technology, which according to the Organization for Economic Co-Operation and Development (OECD), are those of older generations (in 2019, over 95% of 16–24-year-olds in the OECD versus 71% of 65–74-years-olds, used the internet) (OECD, 2020).

5 | CONCLUSIONS

The TRINCOS study aimed to develop the COS for TN and the aim was achieved by involving patients, clinicians and researchers in an iterative and dynamic consensus process, whereby important outcomes to all were identified. The future implementation of this COS will contribute to a more transparent, systematic and rigorous reporting of research results which will ultimately facilitate the choice of treatment and improve the patient's journey.

5.1 | Future work

The development of a COS is an important step towards improving research results and their clinical implications. It is of utmost importance that the COS is implemented and for that its endorsement is crucial. One of the factors that contributes to the uptake of a COS is providing researchers not only with the 'what to measure' information but also with 'how to measure' details (Stage 5). Work will be conducted to identify what questionnaires are valid, reliable and responsive to be used in research studies of TN, in accordance with guidance provided by the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) group (COSMIN, 2005; Prinsen et al., 2016).

Future validation studies of this COS by other research groups, especially those from outside the United Kingdom would be welcomed. The United Kingdom has a unique healthcare system, and patients from other countries might have different type of expectations about research and clinical care. Additionally, cultural variations might play a role in the prioritizing of outcomes.

Another area of future research would be to explore in details the specific side effects of the different treatments and their place in the TN COS.

Finally, COSs are not static and are supposed to be reviewed periodically; outcomes which have been included might be removed and future research might indicate that other outcomes should be included.

AUTHOR CONTRIBUTIONS

CVN conceptualized the study and drafted the manuscript with supervision from JMZ, SRB and RNR. CVN performed the data analysis. JMZ, SRB and RNR screened the study's findings and critically revised the article providing intellectual contributions to the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

Declaration of interests: All authors declare no competing interests.

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REFERENCES

Alkhaffaf, B. A.-O., Metryka, A. A.-O., Blazeby, J. M., Glenny, A. M., Williamson, P. R., & Bruce, I. A. (2021). How are trial outcomes prioritised by stakeholders from different regions? Analysis of an international Delphi survey to develop a core outcome set in gastric cancer surgery. *PLoS One*, *16*, e0261937. https://doi.org/10.1371/journal.pone.0261937

Bendtsen, L., Zakrzewska, J. M., Abbott, J., Braschinsky, M., Di Stefano, G., Donnet, A., Eide, P. K., Leal, P. R. L., Maarbjerg, S., May, A., Nurmikko, T., Obermann, M., Jensen, T. S., & Cruccu, G. (2019). European academy of neurology guideline on trigeminal neuralgia. *European Journal of Neurology*, *26*, 831–849. https://doi.org/10.1111/ene.13950

Brookes, S. T., Macefield, R. C., Williamson, P. R., McNair, A. G., Potter, S., Blencowe, N. S., Strong, S., & Blazeby, J. M. (2016). Three nested randomized controlled trials of peer-only or multiple stakeholder group feedback within Delphi surveys during core outcome and information set development. *Trials*, *17*, 409. https://doi.org/10.1186/s13063-016-1479-x

COMET. (2022). *Delphi Manager*. Available from: https://www.comet-initiative.org/delphimanager/index.html.

COSMIN. (2005). *COnsensus-based Standards for the selection of health Measurement Instruments*. Available from: https://www.cosmin.nl/.

Cruccu, G., Gronseth, G., Alksne, J., Argoff, C., Brainin, M., Burchiel, K., Nurmikko, T., Zakrzewska, J. M., & American Academy of Neurology Society; European Federation of Neurological Society. (2008). AAN-EFNS guidelines on trigeminal neuralgia management. *European Journal of Neurology*, *15*, 1013–1028. https://doi.org/10.1111/j.1468-1331.2008.02185.x

De Toledo, I. P., Conti Reus, J., Fernandes, M., Porporatti, A. L., Peres, M. A., Takaschima, A., Linhares, M. N., Guerra, E., & De Luca, C. G. (2016). Prevalence of trigeminal neuralgia: A systematic review. *Journal of the American Dental Association (1939)*, *147*, 570–576. https://doi.org/10.1016/j.adaj.2016.02.014

de Wit, M., Cooper, C., & Reginster, J. Y. (2019). Practical guidance for patient-centred health research. *Lancet*, *393*, 1095–1096. https://doi.org/10.1016/S0140-6736(19)30034-0

Dumville, J. C., Torgerson, D. J., & Hewitt, C. E. (2006). Reporting attrition in randomised controlled trials. *BMJ (Clinical research ed)*, *332*, 969–971. https://doi.org/10.1136/bmj.332.7547.969

Elberse, J. E., Caron-Flinterman, J. F., & Broerse, J. E. W. (2011). Patient-expert partnerships in research: How to stimulate inclusion of patient perspectives. *Health Expectations*, *14*, 225–239. https://doi.org/10.1111/j.1369-7625.2010.00647.x

Fayers, P. M., & Machin, D. (2016). *Quality of life: The assessment, analysis and interpretation of patient-reported outcomes* (3rd ed.). Wiley Blackwell.

Gorst S. L., Barrington H., Brookes S. T., Chalmers J. R., Devane D., Fledderus A. C., Grosskleg S., Hall, D. A., Harman N. L., Hoffmann C., Katiri R., Maeso R., Saldanha I. J., Tong A., & Williamson PR. (2021). Online consensus meetings for COS development: Issues to consider. https://comet-initiative.org/Downloads/Issues%20to%20consider%20for%20online%20consensus%20meetings.pdf

Haywood, K., Potter, R., Froud, R., Pearce, G., Box, B., Muldoon, L., Lipton, R., Petrou, S., Rendas-Baum, R., Logan, A.-M., Stewart, K., Underwood, M., & Matharu, M. (2021). Core outcome set for preventive intervention trials in chronic and episodic migraine (COSMIG): An international, consensus-derived and multistakeholder initiative. *BMJ Open*, *11*, e043242. https://doi.org/10.1136/bmjopen-2020-043242

ICOP. (2020). International classification of orofacial pain, 1st edition. *Cephalalgia*, *40*, 129–221. https://doi.org/10.1177/0333102419893823

Keeney, S., Hasson, F., & McKenna, H. (2010). Analysing data from a Delphi and reporting results. In *The Delphi technique in nursing and Health Research*. Wiley-Blackwell.

Kirkham, J. J., Gorst, S., Altman, D. G., Blazeby, J. M., Clarke, M., Devane, D., Gargon, E. A.-O., Moher, D., Schmitt, J., Tugwell, P., Tunis, S., & Williamson, P. R. (2016). Core outcome set-STAndards for reporting: The COS-STAR statement. *PLoS Medicine*, *13*, e1002148. https://doi.org/10.1371/journal.pmed.1002148

Maxwell, L. J., Beaton, D. E., Shea, B. J., Wells, G. A., Boers, M., Grosskleg, S., Bingham, C. O., 3rd, Conaghan, P. G., MA, D.'. A., de Wit, M., Gossec, L., March, L., Simon, L. S., Singh, J. A., Strand, V., & Tugwell, P. (2019). Core domain set selection according to OMERACT filter 2.1: The OMERACT methodology. *The Journal of Rheumatology*, *46*, 1014–1020. https://doi.org/10.3899/jrheum.181097

OECD. (2020). *Digital uptake, usage and skills, in OECD digital economy outlook*. Paris.

Okoli, C., & Pawlowski, S. D. (2004). The Delphi method as a research tool: An example, design considerations and applications. *Information & Management*, *42*, 15–29. https://doi.org/10.1016/j.im.2003.11.002

Petrosky, E., Harpaz, R., Fowler, K. A., Bohm, M. K., Helmick, C. G., Yuan, K., & Betz, C. J. (2018). Chronic pain among suicide decedents, 2003 to 2014: Findings from the national violent death

reporting system. *Annals of Internal Medicine*, *169*(7), 169–455. https://doi.org/10.7326/M18-0830

Prinsen, C. A. C., Vohra, S., Rose, M. R., Boers, M., Tugwell, P., Clarke, M., Williamson, P. R., & Terwee, C. B. (2016). How to select outcome measurement instruments for outcomes included in a "Core Outcome Set" - a practical guideline. *Trials*, *17*, 449. https://doi.org/10.1186/s13063-016-1555-2

RCS. (2021). Guidelines for the management of trigeminal neuralgia. Faculty of Dental Surgery Royal College Surgeons of England. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwibte22y636AhVNXcAKHQVhDbMQFnoECBIQAQ&url=https%3A%2F%2Fwww.rcseng.ac.uk%2F-%2Fmedia%2Ffiles%2Frcs%2Ffds%2Fguidelines-%2Ftrigemina-neuralgia-guidelines_2021_v4.pdf&usg=AOvVaw1Ei2iMTTekZyHNCoBpyoVy

Skulmoski, G. J., Hartman, F. T., & Krahn, J. (2007). The Delphi method for graduate research. *Journal of Information Technology Education: Research*, *6*, 1–21.

Taft, T., Weir, C., Kramer, H., & Facelli, J. C. (2020). Primary care perspectives on implementation of clinical trial recruitment. *Journal of Clinical and Translational Science*, *4*, 61–68. https://doi.org/10.1017/cts.2019.435

Turk, D. C., Dworkin, R. H., Allen, R. R., Bellamy, N., Brandenburg, N., Carr, D. B., Cleeland, C., Dionne, R., Farrar, J. T., Galer, B. S., Hewitt, D. J., Jadad, A. R., Katz, N. P., Kramer, L. D., Manning, D. C., McCormick, C. G., McDermott, M. P., McGrath, P., Quessy, S., … Witter, J. (2003). Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*, *106*, 337–345. https://doi.org/10.1016/j.pain.2003.08.001

Venda Nova, C., Zakrzewska, J. M., Baker, S. R., & Ni Riordain, R. (2020). Treatment outcomes in trigeminal neuralgia-a systematic review of domains, dimensions and measures. *World Neurosurg X*, *6*, 100070. https://doi.org/10.1016/j.wnsx.2020.100070

Venda Nova, C., Zakrzewska, J. M., Ni Riordain, R., & Baker, S. R. "They could have cut my head off and I wouldn't have cared" - a qualitative study of patients' experiences and the impact of trigeminal neuralgia. *Journal of Oral & Facial Pain and Headache* In press.

Venda Nova, C., Zakrzewska, J. M., Baker, S. R., & Ni Riordain, R. (2021). Patient reported outcome measures in trigeminal neuralgia - a systematic review of psychometric performance. *European Journal of Pain*, *25*, 1449–1461. https://doi.org/10.1002/ejp.1779

Williamson, P. R., Altman, D. G., Bagley, H., Barnes, K. L., Blazeby, J. M., Brookes, S. T., Clarke, M., Gargon, E., Gorst, S., Harman, N., Kirkham, J. J., McNair, A., Prinsen, C. A. C., Schmitt, J., Terwee, C. B., & Young, B. (2017). The COMET handbook: Version 1.0. *Trials*, *18*, 280–10.1186/s13063-017-1978-4.

Williamson, P. R., Altman, D. G., Blazeby, J. M., Clarke, M., Devane, D., Gargon, E., & Tugwell, P. (2012). Developing core outcome sets for clinical trials: Issues to consider. *Trials*, *13*, 1–8. https://doi.org/10.1186/1745-6215-13-132

Zakrzewska, J. M., Palmer, J., Bendtsen, L., Di Stefano, G., Ettlin, D. A., Maarbjerg, S., Obermann, M., Morisset, V., Steiner, D., Tate, S., & Cruccu, G. (2018). Challenges recruiting to a proof-of-concept pharmaceutical trial for a rare disease: The trigeminal neuralgia experience. *Trials*, *19*, 704. https://doi.org/10.1186/s13063-018-3045-1

Zakrzewska, J. M., Wu, J., Mon-Williams, M., Phillips, N., & Pavitt, S. H. (2017). Evaluating the impact of trigeminal neuralgia. *Pain*, *158*, 1166–1174. https://doi.org/10.1097/j.pain.0000000000000853

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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