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Title: Development and feasibility of the use of an assessment tool measuring treatment efficacy in patients with Trimethylaminuria: a mixed methods study.

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Abstract

Background: Trimethylaminuria is a rare metabolic condition characterised by an unpleasant smell resembling rotting fish. Currently, the only measure of treatment efficacy is urine Trimethylamine levels which do not always reflect the patient's experience of symptoms. A literature review did not find a specific tool to assess treatment efficacy from the patient's perspective.

The aim of this study was to develop an assessment tool to provide a quantitative measure of treatment efficacy in patients diagnosed with TMAU before and after treatment and assess its acceptability (feasibility of use and face and content validity) to people living with TMAU.

Design: Mixed methods - a modified, four-round Delphi by email and Semi-structured interviews conducted after clinical appointments.

Participants: Delphi: Eight individuals living with TMAU from the TMAU forum, six medical consultants and four dieticians in Metabolic Medicine in four National Health Service hospitals in England. Semi-structured interviews: three patients with TMAU in two National Health Service hospitals, UK.

Results: The assessment tool contains 27 items distributed across four domains: Odour characteristics with six items, Mental well-being with 13 items, Social well-being with five items and Health care professionals support with three items. Semi-structured interviews: views on the content and design of the tool.

Conclusion: A co-produced tool was successfully developed and considered acceptable to people living with TMAU. While further testing is needed to further evaluate the validity and reliability of the assessment tool, meanwhile the tool may serve as a prompt for questioning for clinicians diagnosing and treating TMAU.

A concise 1 sentence take-home message (synopsis) of the article, outlining what the reader learns from the article

The reader will learn that it is feasible to co-produce an acceptable assessment tool measuring TMAU treatment efficacy from the patient's perspective using sequential methods and steps of tool development.

Details of the contributions of individual authors

KR conceived the study and designed it in collaboration with YR and MH. KR recruited to the study and collected data. KR and MH analysed the data, with input from YR. KR, YR and MH drafted this paper. All authors contributed intellectually to all stages of the study and its write up.

Name of the corresponding author: Krzysztof Rutkowski

Conflict of Interest:

Krzysztof Rutkowski declares that he has no conflict of interest.

Yusof Rahman declares that he has no conflict of interest.

Mary Halter declares that she has no conflict of interest.

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Ethics approval: The study was approved by the London - Surrey Borders Research Ethics Committee.

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Informed consent:

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised

in 2000. Informed consent was obtained from all patients for being included in the study. Proof that informed consent was obtained is available upon request.

Animal Rights

This article does not contain any studies with human or animal subjects performed by the any of the authors.

Keywords:

Trimethylaminuria, TMAU, Fish Odour Syndrome, Metabolism Inborn, patient-reported experience measures, patient-reported outcome measures, Symptom Assessment, Coproduction.

1 **Introduction**

2 Trimethylaminuria (TMAU), also known as Fish Odour Syndrome, is a rare metabolic and
3 psychologically disabling condition where affected individuals emit a foul odor resembling the smell of
4 rotting fish faeces or garbage (Messenger et al 2013).

5 The true prevalence of this disorder is unknown (Shephard et al 2015). While primary TMAU is more
6 prevalent, secondary cases of TMAU have been described in parts of the world affecting both genders
7 (Wise et al 2011).

8 In primary TMAU trimethylamine (TMA), which derives from the intestinal bacterial degradation of
9 food rich in choline, lecithin and carnitine, is emitted in urine, sweat, breath and other bodily secretions
10 (Mackay et al 2011) due to a fault in Flavin monooxygenase 3 enzyme (FMO3) which otherwise
11 converts TMA into odourless trimethylamine N-oxide (TMANO) (Shephard et al 2015). Conversely, in
12 secondary TMAU TMA is emitted due to hormonal modulation, liver damage, renal disease or viral
13 infection (Mitchell 1999).

14 In the absence of physical symptoms, diagnosis of TMAU is established by measuring oxidising ratios
15 of TMA and TMANO in urine (Mackay et al 2011) or genetic testing (Shephard et al 2015).

16 Nevertheless, diagnosis of the condition is challenging and an assumption can be made that it is a
17 psychological problem (Shephard et al 2015). TMAU has been shown to negatively affect the
18 psychological and social well-being of the affected individuals (Lateef and Marshall-Lucette 2017) and
19 may result in depression, anxiety, social isolation, difficulties with employment (Shephard et al 2015)
20 and potentially attempted suicide (Dolphin et al 1997).

1 Currently there is no cure for TMAU, however, life style changes such as reducing the dietary
2 precursors of TMA are recommended as first line management of this condition (Messenger et al
3 2013). The malodorous smell has been variously reported to be alleviated by antibiotics, laxatives,
4 supplements of riboflavin, charcoal, copper chlorophyllin, shampoos, soaps with a pH between 5.5 &
5 6.5 (Wise et al 2011). Psychological counselling from a specialist in a safe environment has been
6 reported by people living with TMAU to play a vital part in the management of this condition (Lateef
7 and Marshall-Lucette 2017, Fraser-Andrews et al 2003). Consequently, these treatments are
8 recommended in consultation with a metabolic medicine team and its associated dietetics and
9 counselling services.

10 A number of articles highlight challenges in TMAU management due to the available treatment not
11 being universally efficacious (Shephard et al 2015, Messenger et al 2013, Danks et al 1976). In clinical
12 practice the only markers of treatment effectiveness e.g response to antibiotics, riboflavin are TMA and
13 TMA/TMANO ratios and the suggested threshold for the detection of symptoms is TMA concentration
14 of 18–20 $\mu\text{mol}/\text{mmol}$ creatinine in urine (Mackay et al 2011), however, this do not always reflect the
15 patient's experience of symptoms.

16
17 In these circumstances, an approach which focuses on patient-reported outcome measures (PROMs)
18 and patient-reported experience measures (PREMs) may be more appropriate to inform future TMAU
19 treatment outcomes pre and post intervention (Monmouth Partners 2014). PROMs and PREMs are
20 reported to narrow the gap between the clinician's and patient's view of clinical reality as they
21 participate in the design of care delivery themselves, a process which is also known as co-production

1 and sees patients and clinical staff as equal partners to optimise the best outcome for each individual
2 patient's journey (O'Connell et al 2018).

3 In this context, the aim of this study was to develop an assessment tool to provide a quantitative
4 measure of treatment efficacy in patients diagnosed with TMAU before and after treatment and assess
5 its acceptability (feasibility of use and face and content validity) to people living with TMAU.

6 **Methods**

7 A mixed methods sequential study, in which equal weighting to qualitative and quantitative findings
8 was given (Creswell and Clark 2017), was selected in the absence of primary research findings
9 (Keeney et al 2011). This involved using a modified Delphi technique (Keeney et al 2011) and semi-
10 structured interviews (Silverman 2017) to determine face validity of the tool, its acceptability and
11 comprehension of the questions.

12 **Study Setting**

13 The modified Delphi was conducted by email with eight people living with a diagnosis of TMAU who
14 participate in an online forum (<http://www.tmau.org.uk>), five medical consultants and four dieticians
15 who work in four centres for metabolic diseases in NHS hospitals in England. The interviews were
16 conducted with three patients in two hospitals in a metropolitan region in the UK.

17 Delphi study: Experts were recruited via two routes - by approaching metabolic clinicians known to the
18 research team with a request to assist with the study and by approaching a representative from the
19 TMAU forum located via internet searching, who gained an agreement with people with TMAU to
20 email their contact details. They were then emailed the study information and gave consent to
21 participate.

1 Interviews: Patients attending their TMAU-related outpatient appointment were approached by their
2 metabolic consultants at the end of the appointment who explained the study, and gave a patient
3 information sheet and expression of interest form which clinicians passed onto KR if completed by the
4 patient. KR then contacted the patients to arrange an interview. Written consent to participate was
5 gained prior to the interview being conducted.

6 **Data Collection**

7 The modified Delphi technique was conducted by email in four rounds between November 2016 and
8 February 2017. In round one, the concepts of potential areas of impact of illness on a person formed
9 initial domains of interest (Ritenbaugh et al 2011, Cleeland and Ryan 1994) (supplementary file 1) and
10 participants were asked to list items which they thought would measure TMAU treatment efficacy
11 within these domains. In round two, participants were asked to rate each individual item summarised
12 by the researchers individually (from those collected in the first round) in terms of their perceived
13 importance to measure treatment efficacy in TMAU on a low (0) to high (10) point scale of importance.
14 In round three, participants were asked to rank each of the items within each domain in the order of
15 their perceived importance from within the list of items provided to measure the effectiveness of
16 TMAU treatment. In round four, participants were asked to comment on the draft content of the TMAU
17 treatment efficacy patient self-report survey, that had been developed from analysis of round three,
18 including listing any statements that they continued to have any concerns with, ranking the domains
19 headings in order of relative importance and commenting on the clarity of the instructions and the
20 layout of the tool.

21 The interviews were conducted in-person (KR) between May and July 2017 straight after patients'

1 clinical appointments. Interviews followed a topic guide that focused on three areas – the content of the
2 proposed tool, ease of use of the tool, and feelings and comfort/discomfort with completing the tool.
3 Open ended questions were asked to allow discussion with patients. The interviews were digitally
4 recorded and transcribed verbatim.

5 Prior to the interviews, the draft survey was piloted with two healthcare professionals (one working in a
6 hospital trust pain department and one with a nursing educational background) to gain feedback on the
7 appropriateness of the content, its layout and instructions and to reflect on the interviewing process.
8 This process was facilitated through maintaining a personal reflective diary and critical discussions
9 with peers and resulted in altering some of the questions on the topic guide and their order.

10 **Data analysis**

11 The Delphi analysis was qualitative at each round and quantitative at round two, three and four. In
12 round one, the items put forward by participants were grouped by aligning similar items and moving
13 them into a relevant domain in a qualitative process. The language used by participants was maintained
14 in the items to reflect the original content. The pool of items collected in round one was reduced by
15 excluding items which were rated, in round two, below the 3rd quartile of the median by $\geq 70\%$ of
16 participants (Hsu and Sandford 2007). All remaining items were re-grouped thematically by two
17 researchers (KR and MH). In round three, the pool of items in each domain was reduced further by
18 excluding items ranked above the 3rd quartile of the median (Hsu and Sandford 2007). In addition, the
19 retained items were: translated into statements to make sense for the patient completing the tool and to
20 be measurable; moved between domains for best fit; and arranged in the order of their importance
21 according to the rankings. In round four, the order of the overarching domains was established

1 according to the rankings of the experts and a further qualitative process involved aligning similar
2 items into grouped items and moving them into a relevant domain by researchers (KR and MH).

3 A thematic analysis (Braun and Clarke 2006) of the qualitative data obtained from the interviews was
4 undertaken by KR and MH and involved transcribing, familiarising with data (reading and listening),
5 generating independent coding, indexing of transcripts and naming themes through an iterative process
6 with any differences resolved through discussion.

7 **Results**

8 Delphi and semi-structured interview participants' characteristics and respond rates are presented in
9 Table 1.

10 11 **Generating items for the survey via the Delphi study**

12 Round one generated 265 items distributed across 12 domains (table 2) with the largest number of
13 items in the 'Odour affecting psychological well-being – affective' and 'Odour affecting social well-
14 being' domains. The 265 items were reduced to 76 items across 10 domains by matching them
15 qualitatively to other items (see supplementary file 2 for the detail of item reduction). Through this
16 process the Odour affecting Physical Well-Being, Spirituality and Whole Person domains were
17 removed as separate entities and the 35 items from those domains assimilated into other domains where
18 similar concepts were already covered. Two new domains: Health Care Professionals and Work &
19 Finances were created.

20 As the median scores for importance of all items in round two were above the 3rd quartile, the 76 items
21 were reduced to 39 items by the qualitative method (supplementary file 3). However, one item 'I feel

1 suicidal' was added by the experts in this round thus resulting in 40 items carried forward to round
2 three. Following round three, the forty items were reduced to 27, ten items quantitatively as the median
3 scores for importance were above the 3rd quartile of the median and three items by matching
4 qualitatively to other items. The number of domains was also reduced qualitatively from 10 to five.
5 Four out of five items from the 'Comments from others' domain were moved to the 'Mental Well-being
6 – affective' domain. The remaining item from that domain and the items from the 'Coping
7 mechanism', 'Work/finance', 'Healthcare professionals' were moved to a newly created 'Functional
8 well-being' (supplementary file 4).

9 In round four there was no further item reduction. However, the 'affective and cognitive Mental Well-
10 being' domains were merged as they were perceived as a single entity by the experts and the
11 'Functional Well-being domain' name was changed to 'Other aspects affecting your life' as it better
12 represented the items in that domain and the final order of domains and statements were formed.

13 **Feasibility, acceptability, face and content validity of the survey**

14 One theme 'Need to measure TMAU impact and its challenges' emerged in relation to the content of
15 the tool and its impact on participants and one theme 'Views on tool design with suggestions for minor
16 refinement' in relation to the tool's design.

17 **Need to measure TMAU impact and its challenges**

18 Feedback on the content of the tool was encouraging. Participants suggested that the domains in the
19 assessment tool reflected their experiences with TMAU.

20 *participant (2): 'it does pin down the experience of having TMAU ... it does cover the actual*

1 *smell itself and it covers the emotional affect that it has on people and yeah and it talks about*
2 *the social effect which are the three main areas of TMAU'*

3

4 However, it was highlighted that the assessment tool focused on the impact TMAU had on quality of
5 life rather than on the treatment received. The participants noted that there is no cure and a limited
6 choice of TMAU treatment thus suggesting that scores after treatment may not be different from scores
7 before treatment. The participants emphasised the importance of support from healthcare professionals
8 in the management of TMAU

9 *participant (1): 'they can't do anything anymore for me but it's nice, like Dr X said today, 'I'm*
10 *really sorry I can't do any more' and just making that statement, helps me feel good'.*

11

12 All three participants agreed that the mental well-being domain was an important concept to measure,
13 however, they presented a different level of concern about asking people with TMAU questions on this
14 issue. One participant was unconcerned personally, seeing it as potentially helpful to be able to express
15 psychological issues:

16 *participant (3): 'I did not have any concerns about any of these questions and I understood why*
17 *they are being asked. ... I would have thought for some people it might be a relief to kind of get*
18 *down and actually say that they do feel anxious or something like that'.*

19

20 On the other hand, another participant considered that such questions might produce a more 'defensive'
21 response:

22 *participant (2): 'You are not necessarily going to get honest answers from everyone or it may*
23 *well upset some people a lot... some people would not be prepared to say yes I feel suicidal and*
24 *some people may feel very guilty that they feel suicidal they are not even going to admit that*
25 *(thinking)'*

26

1 All participants thought that the content in the social well-being domain was relevant and appropriate
2 to be included:

3 *participant (3) 'I think it's good questions to ask because I think this disorder does have an*
4 *impact on ... on social relationships... and I think they are fair questions because you cover*
5 *career and relationships'.*

6
7 The feedback relating to the content in the odour characteristics domain was also positive. All patients
8 thought it was relevant and appropriate to be included:

9 *participant (1) 'the first subsection, that was absolutely clear, I didn't have any problem with*
10 *any that'.*

11
12 During the interviews participants provided TMAU narratives relating to their difficulties with
13 achieving a diagnosis, TMAU as an illness, their perceptions on the intensity and variability of smell,
14 restrictions on life style, impact on mental well-being, negative reactions from others, support from
15 others and perceived effectiveness of TMAU treatment. It appeared that these narratives were triggered
16 by completing the assessment tool or the interview.

17 **Views on tool design with suggestions for minor refinement**

18 All participants provided positive feedback on the design of the assessment tool indicating no issue
19 with its layout or length.

20 Participants provided suggestions to improve the introduction section, scoring instructions and the use
21 of asterisks. Consequently, the asterisks were removed and the instructions in each sub scale were
22 improved to remind patients that the statements related to their experience with TMAU; one statement
23 'I am not tolerant of other attitudes' was removed from the Mental well-being domain; and one

1 statement ‘the odour comes from a particular part of the body’ was added to the Odour characteristics
2 domain. The refined instructions of the TMAU treatment efficacy tool are presented in figure 1, its
3 questions in figure 2 and its scoring and completion guide in supplementary file 5.

4 **Discussion**

5 The TMAU treatment efficacy tool was co-produced by 18 experts: eight individuals living with
6 TMAU, six medical consultants and four dieticians in four rounds of the Delphi process and tested with
7 three patients. It consists of 27 items distributed across four domains: Odour characteristics with six
8 items, Social well-being with five items, Health care professionals support with three items and Mental
9 well-being with 13 items which comprises 48 % of the tool’s content.

10 The evidence from the interviews reflect the findings from the Delphi study and literature confirming
11 that items in the assessment tool relate to TMAU disorder (Chalmers et al 2005, Kim et al 2017,
12 Mackay et al 2011) and importantly suggest that the items relating to feelings of depression and suicide
13 could be emotionally provoking and sensitive to measure (Blair 2015). The evidence from the
14 interviews also suggests that TMAU symptoms can vary from patient to patient. It seems likely that
15 the value of the assessment tool may lie in its use by clinicians and patients to aid discussion, on highly
16 sensitive topics that might otherwise be difficult to assess in the clinic, when patients are noted to
17 sometimes only send indirect signals regarding emotional expression and clinicians may have low
18 awareness or a lack of training in this area (Goto and Takemura 2016). That said, screening of general
19 hospital patients for suicide risk has previously been received positively (Horowitz et al 2013). In-
20 clinic or at-home completion could take place prior to a consultation to help inform this patient-
21 clinician decision making process, allowing tailoring of treatment plans to match an individual’s

1 response and preference and providing a framework to identify treatment outcomes which otherwise
2 could go unrecognised (O’Connell et al 2018). The tool as currently designed calls for assessment at a
3 moment in time (Brown and Ryan 2003), which may be coterminous with a medical outpatient review;
4 it is recognised that measurement over a period of time, in line with the measurement of similar
5 constructs such as psychological well-being (Deiner and Biswas-Deiner 2008).

6 Involving a heterogeneous sample of 18 experts (Hasson et al 2000) in the tool’s development met
7 recommendations by Okoli and Pawlowski (2004) suggesting that 10 to 18 experts are sufficient to obtain
8 a wide range of views and Sumison’s (1998) suggestion that 70% participant response rate is sufficient
9 to maintain validity of study results. The response rate in first round of the Delphi study was 100% and
10 over 75% in the remaining three rounds, however, more importantly the representation of TMAU
11 individuals across all rounds was greater than the representation of other experts. The mixed methods
12 approach also enabled gaining wider perspectives which would be beyond the scope of a single research
13 method (Creswell and Clark 2017). Additionally, every effort was made to increase transferibility of the
14 findings and limiting the researcher’s influence during the process: the items were aligned so that they
15 reflected the experts’ original language (DeVilles 2011). Furthermore, the experts were able to review
16 the items interpreted by the researcher and comment on them in each round of the Delphi process (Hasson
17 et al 2000). The transparency of data retrieval during the interviews was increased by a second researcher
18 who read the transcripts and commented on the outcome of the analysis (Silverman 2017).

19 **Limitations**

20 Consensus levels in Delphi studies vary between 51% and 100% (Stewart et al 1999), therefore it was
21 recognised that the existence of consensus or no consensus did not mean the correct answer would have

1 been found, however, statistical calculations were used to reduce items quantitatively (Hasson et al 2000).
2 A larger sample size of participants in the interviews may have generated more refinement of the
3 assessment tool. However, due to low prevalence of TMAU, the sample size needed to be realistic in
4 terms of the recruitment and data analysis requirements in a specified time period. Diagnostic detail from
5 our participants living with a diagnosis of TMAU was not collected as the Delphi participants were
6 mainly health care professional from a small number of UK metabolic specialist centres thus describing
7 any of their characteristics may enable them to be identified by others in the field.

8 **Conclusion**

9 The aspects of feasibility, acceptability, face and content validity of the tool presented in this paper
10 represents the first step in the process of the tool's development. While further development is needed to
11 address issues such as the time period being considered by the patient whilst completing the tool, and to
12 test for the validity and reliability of the assessment tool, it may serve as a useful discussion prompt
13 between clinicians and patients when diagnosing and treating TMAU. A patient centred approach in the
14 outpatient's clinic could yield more detailed information to target and tailor treatment strategies and
15 acknowledge the psychosocial aspects of the condition from a patient perspective. Following refinement
16 the tool could be useful in the measurement of effect in interventions focusing on treatment efficacy in
17 TMAU, in multi-centre trials.

18

19

20

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Table 1 Delphi participants’ characteristics, Delphi response rates and semi-structured interviews patients’ characteristics.

Delphi participants’ characteristics				
Experts	Number of Experts	% of Delphi participants	Gender	TMAU type
People living with TMAU	8	44	Female	Not collected
Metabolic Medicine Clinicians	6	33	Not displayed as potentially identifying	N/A
Metabolic Medicine Dieticians	4	22		N/A
Delphi Response rates				
Round	Number of Experts who responded	Number of Experts who did not respond	% of Respondents	% of Non-respondents
One	18	0	100%	0%
Two	15	3 (2 clinicians, 1 dietician)	83%	17%
Three	14	4 (2 clinicians, 1 dietician, 1 person with TMAU)	77%	13%
Four	14	4 (2 clinicians, 1 dietician, 1 person with TMAU)	77%	13%
Semi-structured interviews patients’ characteristics				
Patients approached	Patients participating	Gender	TMAU type	
6	3	F	Primary	

Table 2 Initial pool items

Source	Domain No	Domain Name	Number of Items generated by participants
Cleeland and Ryan (1994)	1	TMAU symptoms Domain	35
	2	Odour intensity and severity	17
Ritenbaugh et al (2011)	3	Odour affecting Physical Well-Being	9
	4	Odour affecting Social Well-Being	48
	5	Odour affecting Psychological Well-Being-cognitive	23
	6	Odour affecting Psychological Well-Being-affective	58
	7	Spirituality	8
	8	Whole person	18
Delphy Experts	9	Comments from others	30
	10	Coping mechanisms Domain	12
	11	Health Care Professionals	3
	12	Work/finance	4
Total			265

Figure 1 Trimethylaminuria (TMAU) treatment efficacy assessment tool instructions

Patient Identification number:

Date:

This is an assessment tool which aims to measure how a range of symptoms associated with TMAU affect you. This assessment is carried out before and after you receive treatment from your consultant at the hospital.

Due to the potentially sensitive nature of questions, it is possible that you may experience some temporary distress arising from the completion of the questionnaire. In the event of any distress, you will be asked if you need a comfort break or if you prefer to stop completing the questionnaire. Should any distress arise, you will have support of your team at the hospital, who will also sign post you to services which can be contacted, if any distress continues after completing this questionnaire.

Below there is a list of statements about those symptoms and their impacts which you may or may not experience.

Please read each statement and circle a value between 0-10 where 0 indicates that you disagree completely with the statement at the moment of completing the assessment tool and 10 indicates that you agree completely with it.

Example: - Where would you circle your score against this statement example?

Disagree
completely

Agree
completely

I eat healthily	0	1	2	3	4	5	6	7	8	9	10
-----------------	---	---	---	---	---	---	---	---	---	---	----

Figure 2 Trimethylaminuria (TMAU) treatment efficacy assessment tool questions

The first 6 statements relate to the aspects of the odour characteristics with regards to TMAU											
Disagree _____ Agree											
The odour is unpleasant	0	1	2	3	4	5	6	7	8	9	10
The odour is intense	0	1	2	3	4	5	6	7	8	9	10
The odour is constant	0	1	2	3	4	5	6	7	8	9	10
The odour comes from the whole body	0	1	2	3	4	5	6	7	8	9	10
I can sometimes smell the odour myself	0	1	2	3	4	5	6	7	8	9	10
Others state they experience the odour	0	1	2	3	4	5	6	7	8	9	10
The following 13 statements relate to the aspects of your mental well-being with regards to TMAU											
Disagree _____ Agree											
TMAU restricts the way I live my life	0	1	2	3	4	5	6	7	8	9	10
I worry about negative reactions or comments from others	0	1	2	3	4	5	6	7	8	9	10
I am not tolerant of other's attitudes	0	1	2	3	4	5	6	7	8	9	10
I feel resentment towards TMAU	0	1	2	3	4	5	6	7	8	9	10
I can not accept TMAU	0	1	2	3	4	5	6	7	8	9	10
I feel anxious	0	1	2	3	4	5	6	7	8	9	10
I feel ashamed or embarrassed	0	1	2	3	4	5	6	7	8	9	10
I feel depressed	0	1	2	3	4	5	6	7	8	9	10
I feel helpless or trapped	0	1	2	3	4	5	6	7	8	9	10
I feel paranoid	0	1	2	3	4	5	6	7	8	9	10
I feel suicidal	0	1	2	3	4	5	6	7	8	9	10
I feel guilt or self-blame	0	1	2	3	4	5	6	7	8	9	10
I do not feel positive	0	1	2	3	4	5	6	7	8	9	10
The following 5 statements relate to the aspects of your social well-being with regards to TMAU											
Disagree _____ Agree											
My social contact is limited	0	1	2	3	4	5	6	7	8	9	10
I do not feel confident	0	1	2	3	4	5	6	7	8	9	10
My relationships are adversely affected	0	1	2	3	4	5	6	7	8	9	10
I feel my condition has adversely affected my job/career	0	1	2	3	4	5	6	7	8	9	10
Other people avoid me	0	1	2	3	4	5	6	7	8	9	10
Additional (optional) 3 statements relate to healthcare delivery. Please circle whether you disagree or agree											
I feel misunderstood by healthcare professionals	Disagree		I do not know						Agree		
I feel supported by healthcare professionals	Disagree		I do not know						Agree		
I do not understand the role of medication/ /supplements/diet in the management of TMAU	Disagree		I do not know						Agree		

Supplementary file 1 Concepts of potential areas of impact of TMAU on a person

Column 1	Column 2	Column 3	Column 4
Domain	Your comments on these domains e.g. you agree, you suggest alternative wording, you disagree with its inclusion	Examples of items for the questionnaire	Your suggestions for items for the questionnaire
TMAU Symptoms		I smell I feel	
Smell intensity and severity			
Smell affecting Physical Well-Being		I felt drained. I was tired/I had no energy/I was exhausted. I felt depleted. I didn't sleep well.	
Smell affecting Social Well-Being		I felt alone. I feel connected.	
Smell affecting Psychological Well-Being -cognitive		I was unable to focus. I couldn't think clearly. I am forgiving. I have learned new things about myself. I feel empowered.	
Smell affecting Psychological Well-Being -affective		I was anxious about the future. I was depressed. I laugh. I am content. I am joyful.	
Spiritual Well-Being		I had no hope. I am on a spiritual path. I feel spiritual.	
Whole person		My life was a mess. I just kept doing the same thing over and over.	

		<p>I was really stuck in some parts of my life. I feel more complete. I am awake. I am aware. I'm living my life to the fullest.</p>	
Comments from others		Other people have told me ...	
Your suggestions for other domains			

Supplementary file 2 Items reduction in round 2

	Items rated on a 10 point scale where 1 was extremely important and 10 was least important in 10 Domains	Median	Quartile 3	Items rated below the 3rd quartile	Percentage of participants who rated the item below the 3rd quartile of the median importance score	Items reduction through Qualitative analysis
	1 TMAU symptoms n=6					
1	Smell experienced by others	1	4.3	10.0	71.4	Merged with 58
2	Smell oneself	2.5	4.8	10.0	71.4	I can smell myself
3	The smell comes from specific areas of the body	3	4.8	10.0	71.4	Extend of the odour e.g. specific area or whole body
4	The smell comes from the whole body	3	5.0	11.0	78.6	Merged with 3
5	The smell follows	4	5.8	10.0	71.4	The smell lingers or persists
6	The smell is unpleasant e.g. rotten fish	1.5	4.8	10.0	71.4	The odour is unpleasant
	2 Odour intensity and severity n=4					
7	Distance the smell can travel	3	4.8	10.0	71.4	The smell can travel
8	Smell frequency	1	2.8	10.0	71.4	Merged with 10
9	Smell intensity	1.5	3.0	11.0	78.6	Smell intensity
10	Smell varies with triggering factors	1.5	3.8	10.0	71.4	Smell is constant or triggered by particular factors
	3 Odour affecting Physical Well-Being n=2					
11	Energy level	4	6.5	10.0	71.4	Merged with 44
12	Physical symptoms other than smell	5	8.0	11.0	78.6	Excluded based on experts feedback
	4 Odour affecting Social Well-Being n=10					
13	Avoidance by others	1	3.8	10.0	71.4	Avoidance by others
14	Avoidance of other people	1	2.0	11.0	78.6	Merged with 21
15	Feeling supported by others	2.5	6.3	10.0	71.4	Feeling supported by others
16	Impact on confidence	1	2.5	10.0	71.4	Confidence
17	Impairment of friendships	1.5	3.8	10.0	71.4	Impairment of friendships & intimate relationships
18	Impairment of intimate relationships	1	2.0	11.0	78.6	Merged with 17
19	Feeling helpless or not	2.5	4.8	10.0	71.4	Merged with 51

20	Feeling isolated or not	1	2.8	10.0	71.4	Feeling isolated or not
21	Limitations on social contact	1	1.8	10.0	71.4	Limitations on social contact
22	Worrying about other reacting to TMAU	1	3.3	10.0	71.4	Merged with 33
23	Avoidance of other people	1	3.8	10.0	71.4	Excluded - already in social WB 14
24	Feeling of Resilience	4.5	7.0	12.0	85.7	Feeling of Resilience
25	Feeling Strong	5	6.5	10.0	71.4	Merged with 24
26	Having a purpose in life	4	5.0	11.0	78.6	Having a purpose in life
27	Life limiting	3	6.5	10.0	71.4	Restricting the way my life is lived
28	Resentment	3	5.0	11.0	78.6	Resentment
29	Resignation to the condition	2.5	6.5	10.0	71.4	Resignation to TMAU
30	TMAU acceptance	1.5	4.8	10.0	71.4	Excluded - already in psychological well-being
31	Tolerance of others' attitudes	3.5	6.8	10.0	71.4	Tolerance of others' attitudes
32	Worrying about others making comments	2.5	6.8	10.0	71.4	Merged with 33
33	Worrying about the reactions of others	2	6.8	10.0	71.4	Worrying about the reactions or comments of others
34	Appreciating diagnosis	1	5.0	12.0	85.7	Merged with 73
35	Blaming oneself	2.5	5.8	10.0	71.4	Merged with 42
36	Burden of TMAU	3.5	6.8	10.0	71.4	Merged with 27
37	Concern about the future	1.5	5.8	10.0	71.4	Merged with 27
38	Feeling anxious	1	5.5	10.0	71.4	Feeling anxious
39	Feeling ashamed	1	5.0	10.0	71.4	Feeling ashamed or embarrassed
40	Feeling depressed	1	5.5	10.0	71.4	Feeling depressed
41	Feeling embarrassed	1	3.5	10.0	71.4	Merged with 39
42	Feeling guilty	3	5.0	11.0	78.6	Feeling guilty or self-blame
43	Feeling humiliated	1.5	7.5	10.0	71.4	Feeling humiliated
44	Feeling lethargic	4	6.0	11.0	78.6	Feeling lethargic
45	Feeling need to please others	3.5	5.8	10.0	71.4	Feeling need to please others
46	Feeling normal or abnormal	1.5	4.5	10.0	71.4	Feeling normal
47	Feeling ostracised	4	6.8	10.0	71.4	Merged with 9
48	Feeling paranoid	1	5.0	10.0	71.4	Feeling paranoid
49	Feeling scared	1	4.3	10.0	71.4	Merged with 10
50	Feeling tearful	2.5	5.5	10.0	71.4	Merged with 10
51	Feeling trapped	1	5.5	10.0	71.4	Feeling helpless or trapped
52	Feeling understood or not	2	5.0	11.0	78.6	Merged with 33
53	Life limiting	1	4.3	10.0	71.4	Excluded - already in psychological WB cognitive 27
54	Living in the moment	5	6.0	12.0	85.7	Merged with 22

55	Positive experience	3.5	5.0	11.0	78.6	Feeling positive
56	TMAU acceptance	1.5	5.0	11.0	78.6	Merged with 22
57	Victimisation and bullying	1.5	3.8	10.0	71.4	Merged with 58
7 Comments from others Domain n=5						
58	Others feeling uncomfortable experiencing the smell	1.5	4.5	10.0	71.4	Negative reactions of others
59	Others making loud comments	3	5.8	10.0	71.4	Merged with 58
60	Others' reactions	1.5	4.5	10.0	71.4	Merged with 58
61	Relying on others' reactions	1.5	6.5	10.0	71.4	Merged with 58
62	Shock in others experiencing the smell	2.5	4.8	10.0	71.4	Merged with 58
8 Coping mechanisms Domain n=10						
63	Coping	1.5	5.8	10.0	71.4	Excluded as this is the name of the domain
64	Controlling anxiety with medication	2.5	6.0	11.0	78.6	Controlling negative impact with medication
65	Controlling depression with medications	2.5	6.0	11.0	78.6	Merged with 64
66	Mental well-being	1	3.8	10.0	71.4	Used it to name Mental WB domain
67	Seeking advice from healthcare professionals	5	7.8	10.0	71.4	Merged with support from health care professionals
68	Symptoms recognition	2.5	4.5	10.0	71.4	Symptoms recognition
69	Use of medication to control psychological symptoms	6	9.5	10.0	71.4	Merged with 72
70	Use of medication to control physical symptoms	5.5	10.0	14.0	100.0	Excluded based on experts feedback
71	Use of supplements to control TMAU	4.5	6.0	11.0	78.6	Use of supplements to control TMAU
72	Use of medication to control TMAU	2.5	6.5	10.0	71.4	Use of medication to control TMAU
9 Health Care Professionals Domain n=2						
73	Support from healthcare professionals	3.5	4.8	10.0	71.4	Support from healthcare professionals
74	Being understood by healthcare professionals	3	4.0	11.0	78.6	Being understood by healthcare professionals
10 Work/finances Domain n=2						
75	Financial impact	1.5	5.5	10.0	71.4	Financial impact
76	Impact on job/career	1	3.8	10.0	71.4	Impact on job/career

Supplementary file 3 Items reduction in round 3

Items number	Domain Name/Number of items	Overall Rank	Quartile 3	Items reduction through Quantitative and Qualitative analysis
	1 TMAU odour characteristic Domain n= 7			
1	Extent of the odour (eg specific areas or whole body)	4	5.5	The odour comes from the whole body
2	I can smell myself	5		I can smell the odour myself
3	The odour is unpleasant	1		The odour is unpleasant
4	The smell lingers or persists	6		Statistically excluded as >5.5
5	Smell is constant or triggered by particular factors	3		The odour is constant
6	Smell intensity	2		The odour is intense
7	The smell can travel	7		Statistically excluded as >5.5
	2 Odour affecting Social Well-Being Domain n=5			
8	Avoidance by others	4	4	Other people avoid me
9	Confidence	2		I feel confident
10	Feeling supported by others	5		Statistically excluded as >4
11	Impairment of friendships and intimate relationships	3		My friendships or intimate relationships are affected
12	Limitations on social contact	1		My social contact is limited
	3 Odour affecting Mental Well-Being –cognitive Domain n= 7			
13	Feeling of Resilience	6	5.5	Statistically excluded as >5.5
14	Having a purpose in life	7		Statistically excluded as >5.5
15	Resentment	4		I feel resentment towards TMAU
16	Resignation to TMAU	4		I am resigned to TMAU
17	Restricting the way my life is lived	1		TMAU restricts the way I live my life
18	Tolerance of others' attitudes	3		I am tolerant of other's attitudes
19	Worrying about the reactions or comments of others	2		I worry about negative reactions or comments from others
	4 Odour affecting Mental Well- Being –affective Domain n=11			
20	Feeling anxious	2	8.5	I regularly feel anxious
21	Feeling ashamed or embarrassed	1		I regularly feel ashamed or embarrassed
22	Feeling depressed	3		I regularly feel depressed
23	Feeling helpless or trapped	4		I regularly feel helpless or trapped
24	Feeling guilt or self-blame	7		I regularly feel guilt or self-blame
25	Feeling lethargic	10		Statistically excluded as >8.5
26	Feeling normal	9		Statistically excluded as >8.5
27	Feeling paranoid	5		I regularly feel paranoid
28	Feeling need to please others	11		Statistically excluded as >8.5
29	Feeling positive	8		I regularly feel positive
30	Feeling suicidal	6		I regularly feel suicidal
	5 Functional Well-Being Domain n=10			
31	Negative reactions of others	1	7.75	Merged with 19
32	Others state they experience the smell	2		Others state they experience the smell

33	Controlling negative psychological impact with medication	8		Statistically excluded as >7.75
34	Symptoms recognition	4		Merged with 2
35	Use of supplements to control TMAU			This item was not ranked due to a mistake in the layout of the form therefore merged as Understanding the role of medications or supplements in the management of TMAU
36	Use of medication to control TMAU			As in 35
37	Being understood by healthcare professionals	5		I feel misunderstood by health care professionals
38	Support from healthcare professionals	6		I feel supported from healthcare professionals
39	Financial impact on earning potential	7		Statistically excluded as >7.75
40	Impact on job/career promotion	3		I feel my condition has adversely affected my job/career

Supplementary file 4 Final order of domains and statements

	Groupings from Round Three	Statements in Round Four presented in new, shorter Domains Headings showing excluded items and grouped items
Rank of the item in each domain	TMAU odour characteristic Domain	TMAU odour characteristic
1	The odour is unpleasant	The odour is unpleasant
2	Smell intensity	The odour is intense
3	Smell is constant or triggered by particular factors	The odour is constant
4	Extent of the odour (eg specific areas or whole body)	The odour comes from the whole body
5	I can smell myself	I can smell the odour myself
4	Symptoms recognition - moved from functional WB	
6	The smell lingers or persists	Statistically excluded
7	The smell can travel	Statistically excluded
	Odour affecting Social Well-Being Domain	Social Well-being
1	Limitations on social contact	My social contact is limited
2	Confidence	I feel confident
3	Impairment of friendships and intimate relationships	My friendships or intimate relationships are affected
4	Avoidance by others	Other people avoid me
5	Feeling supported by others	Statistically excluded
	Odour affecting Mental Well-Being–cognitive Domain	Mental Well-being
1	Restricting the way my life is lived	TMAU restricts the way I live my life

1	Negative reactions of others	I worry about negative reactions or comments from others
2	Worrying about the reactions or comments of others'	
3	Tolerance of others' attitudes	I am tolerant of other's attitudes
4	Resentment	I feel resentment towards TMAU
4	Resignation to TMAU	I am resigned to TMAU
6	Feeling of Resilience	Statistically excluded
7	Having a purpose in life	Statistically excluded
	Odour affecting Mental Well-Being –affective Domain	
1	Feeling ashamed or embarrassed	I regularly feel anxious
2	Feeling anxious	I regularly feel ashamed or embarrassed
3	Feeling depressed	I regularly feel depressed
4	Feeling helpless or trapped	I regularly feel helpless or trapped
5	Feeling paranoid	I regularly feel paranoid
6	Feeling suicidal	I regularly feel suicidal
7	Feeling guilt or self-blame	I regularly feel guilt or self-blame
8	Feeling positive	I regularly feel positive
9	Feeling normal	Statistically excluded
10	Feeling lethargic	Statistically excluded
11	Feeling need to please others	Statistically excluded
	Functional Well-Being Domain	Other aspects affecting your life
1	Negative reactions of others	moved to MWB cognitive
2	Others state they experience the smell	Others state they experience the odour
3	Impact on job/career promotion	I feel my condition has adversely effected my job/career
4	Symptoms recognition	moved to TMAU Characteristics

5	Being understood by healthcare professionals	I feel misunderstood by healthcare professionals
6	Support from healthcare professionals	I feel supported by healthcare professionals
7	Financial impact on earning potential	Statistically excluded
8	Controlling negative psychological impact with medication	Statistically excluded
These items were not ranked by all due to a mistake in the layout of the form	Use of supplements to control TMAU	Understanding of the role of medication or supplements in the management of TMAU
	Use of medication to control TMAU	

Supplementary file 5 Refined Assessment Tool Completing and Scoring Guide

Trimethylaminuria (TMAU) treatment efficacy assessment tool

Patient Identification number:

Date:

This is an assessment tool which aims to measure how a range of symptoms associated with TMAU affect you. This assessment is carried out before and after you receive treatment from your consultant at the hospital.

Due to the potentially sensitive nature of questions, it is possible that you may experience some temporary distress arising from the completion of the questionnaire. In the event of any distress, you will be asked if you need a comfort break or if you prefer to stop completing the questionnaire. Should any distress arise, you will have support of your team at the hospital, who will also sign post you to services which can be contacted, if any distress continues after completing this questionnaire.

Below there is a list of statements about those symptoms and their impacts which you may or may not experience.

Please read each statement and circle a value between 0-10 where 0 indicates that you disagree completely with the statement at the moment of completing the assessment tool and 10 indicates that you agree completely with it.

Example: - Where would you circle your score against this statement example?

Disagree
completely

Agree
completely

I eat healthily	0	1	2	3	4	5	6	7	8	9	10
-----------------	---	---	---	---	---	---	---	---	---	---	----

Beginning of the questionnaire

The first 6 statements relate to the aspects of the odour characteristics with regards to TMAU												
											Disagree _____ Agree	
The odour is unpleasant	0	1	2	3	4	5	6	7	8	9	10	
The odour is intense	0	1	2	3	4	5	6	7	8	9	10	
The odour is constant	0	1	2	3	4	5	6	7	8	9	10	
The odour comes from the whole body	0	1	2	3	4	5	6	7	8	9	10	
I can sometimes smell the odour myself	0	1	2	3	4	5	6	7	8	9	10	
Others state they experience the odour	0	1	2	3	4	5	6	7	8	9	10	
The following 13 statements relate to the aspects of your mental well-being with regards to TMAU												
											Disagree _____ Agree	
TMAU restricts the way I live my life	0	1	2	3	4	5	6	7	8	9	10	
I worry about negative reactions or comments from others	0	1	2	3	4	5	6	7	8	9	10	
I am not tolerant of other's attitudes	0	1	2	3	4	5	6	7	8	9	10	
I feel resentment towards TMAU	0	1	2	3	4	5	6	7	8	9	10	
I can not accept TMAU	0	1	2	3	4	5	6	7	8	9	10	
I feel anxious	0	1	2	3	4	5	6	7	8	9	10	
I feel ashamed or embarrassed	0	1	2	3	4	5	6	7	8	9	10	
I feel depressed	0	1	2	3	4	5	6	7	8	9	10	
I feel helpless or trapped	0	1	2	3	4	5	6	7	8	9	10	
I feel paranoid	0	1	2	3	4	5	6	7	8	9	10	
I feel suicidal	0	1	2	3	4	5	6	7	8	9	10	
I feel guilt or self-blame	0	1	2	3	4	5	6	7	8	9	10	
I do not feel positive	0	1	2	3	4	5	6	7	8	9	10	
The following 5 statements relate to the aspects of your social well-being with regards to TMAU												
											Disagree _____ Agree	
My social contact is limited	0	1	2	3	4	5	6	7	8	9	10	
I do not feel confident	0	1	2	3	4	5	6	7	8	9	10	
My relationships are adversely affected	0	1	2	3	4	5	6	7	8	9	10	
I feel my condition has adversely affected my job/career	0	1	2	3	4	5	6	7	8	9	10	
Other people avoid me	0	1	2	3	4	5	6	7	8	9	10	
Additional (optional) 3 statements relate to healthcare delivery. Please circle whether you disagree or agree												
I feel misunderstood by healthcare professionals				Disagree				I do not know				Agree
Agree												
I feel supported by healthcare professionals				Disagree				I do not know				Agree
Agree												
I do not understand the role of medication/ /supplements/diet in the management of TMAU				Disagree				I do not know				Agree

End of the questionnaire. Thank you.

Completing and Scoring Guide of the Trimethylaminuria (TMAU) treatment efficacy assessment tool

This tool has been developed to assess whether the treatment offered to patients diagnosed with TMAU has worked when we consider a range of symptoms associated with TMAU and some of the impacts these may have on patients. The tool has been co-produced as part of a master's dissertation by 2 researchers and 18 'experts' in TMAU: people living with TMAU and clinicians (medical consultants and dieticians actively involved in the care of people with TMAU in England), using a Modified Delphi technique. This study was a collaboration between St George's, University of London, Kingston University, Guy's and St Thomas' NHS Foundation Trust and University College London Hospitals NHS Foundation Trust. All intellectual property (IP) created relating to the Tool shall be jointly owned by the collaborators, but the Joint Research and Enterprise Office at St George's University of London will lead on the management and exploitation of IP created during this project.

Who is the tool for?

Newly diagnosed patients with TMAU and those already diagnosed with TMAU who are commencing a new treatment regime. The assessment tool should be administered before the treatment commences and three months after the treatment commenced. Lower scores after completing the treatment indicate an improvement in symptoms, that is, can imply treatment efficacy.

How do patients complete the tool?

For each statement patients should circle a value between 0-10 where 0 indicates they disagree completely with the statement at the moment of completing the assessment tool and 10 indicates that they agree completely

How should the tool be scored?

The 24 items on the scale are aggregated into the following 3 sub scales:

- TMAU Odour Characteristics (6 items)
- Mental Well-being (13 items)
- Social Well-being (5 items)

Each subscale is scored by summing the items completed within that scale. Any non completed item within each scale is to be recorded along with a reason for no completion. The subscales are not weighted – the sub scale score should only be viewed in relation to the potential best case and worst case scenario scores for each subscale as follows:

Odour characteristics (6 items): Range 0 - 60

Mental Well-being (13 items): range 0 - 130

Social Well-being (5 items): range 0 - 50

The overall TMAU scale is scored by summing scores across all 24 items, with a range of 0 – 240.

Clinical importance of any decrease or increase in score

The tool has not been fully validated and clinically important changes in scores have not been considered in the tool's testing. It is for the patient and their clinician to interpret any changes in score and consider treatment options on the basis of this.

Please note: If the patient answers yes to suicidal and depression feelings, please inform a clinician for appropriate referral.

Healthcare delivery evaluation

In addition, to the 24 items there are 3 items relating to health care evaluation. The scoring is only an indicator of healthcare delivery and is not included in the overall score of the TMAU treatment efficacy assessment tool.