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Suicidality Treatment Occurring in Paediatrics (STOP) Medication Suicidality Side Effects Scale in young people in two cohorts across Europe

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In Memoriam of Professor Alessandro Zuddas (1957-2022), Dept. Biomedical Sciences, Sect. Neuroscience & Clinical Pharmacology, University of Cagliari, Italy & Child & Adolescent Neuropsychiatry Unit, "A.Cao" Paediatric Hospital, Cagliari, Italy.

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ABSTRACT

Objectives As part of the 'Suicidality: Treatment Occurring in Paediatrics (STOP)' study, we developed and performed psychometric validation of an electronic-clinical-outcome-assessment (eCOA), which included a patient-reported-outcome (ePRO), an observer-rated-outcome (eObsRO) for parents/carers and a clinician-reported-outcome (eClinRO) that allows identification and monitoring of medication-related suicidality (MRS) in adolescents.

Design STOP: Prospective study: A two phase validation study to assess the impact of medication on suicidal ideations.

Setting Six participating countries: Netherlands, UK, Germany, France, Spain and Italy that were part of the Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 261411.

Participants Cohort 1 consisted of 41 adolescent-completions, 50 parent-completions and 56 clinician-completions. Cohort 2 consisted of 244 adolescent-completions, 198 parent-completions and 240 clinician-completions from across the six countries. The scale was administered only to participants who have screened positive for the STOP-Suicidality Assessment Scale (STOP-SAS).

Results A total of 24 items for the development of the STOP-Medication Suicidality Side Effects Scale (STOP-MS[3]) were identified and three versions (for patients, parents and clinicians) of the STOP-MS[3] were developed and validated in two separate study cohorts comprising of adolescents, their parents and clinicians. Cronbach's α coefficients were above 0.85 for all domains. The inter-rater reliability of the STOP-MS[3] was good and significant for the adolescent (ePRO), clinician (eClinRO) (r=0.613), parent (eObsRO) versions of the scale (r=0.394) and parent and clinician (r=0.347). Exploratory factor analysis identified a 3-factor model across 24 items for the adolescent and parent version of the scale: (1) Emotional Dysregulation, (2) Somatic Dysregulation and (3) Behavioural Dysregulation. For the clinician version, a 4-factor model defined the scale structure: (1) Somatic Dysregulation, (2) Emotional Dysregulation, (3) Behavioural Dysregulation and (4) Mood Dysregulation.

Conclusion These findings suggest that the STOP-MS[3] scale, a web-based eCOA, allows identification and monitoring of MRS in the adolescent population and shows good reliability and validity.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The web-based Suicidality: Treatment Occurring in Paediatrics (STOP)-Medication-Related Suicidality Side Effects Scale is a useful web-based electronic clinical outcome assessment for identifying and monitoring medication-related suicidality in adolescents.
⇒ The electronic patient-reported outcome version, the observer-rated outcome version for parents/carers and the clinician-reported outcome version allows different modes for the identification and monitoring of MRS in adolescents.
⇒ It is available in multiple languages (English, Spanish, Italian, German, French and Dutch).
⇒ Being web-based may appeal more to young people due to the increased accessibility and the anonymity web-based platforms can provide.
⇒ Only participants who screened positive on the screening questionnaire of the STOP-Suicidality Assessment Scale were included.

INTRODUCTION

Suicide is one of the leading causes of mortality among children and adolescents and is a major public health concern.[1 2] The construct of suicidality is multifaceted, ranging from ideations and behaviours to completions and suicide mortality is dependent on several factors[3] including age, gender, ethnicity and the presence of psychiatric disorders such as mood disturbances, substance-related and addictive disorders, anxiety, psychotic and personality disorders.[4 5] Importantly, there is mounting evidence to suggest that the risk

of suicide is high among young people and adolescents (aged 12–26 years), and women were reported to have a high risk of suicide attempt, while men were more likely to complete suicide than their peers.[3] While the risk of suicide-related mortality is comparatively low among those younger than 12 years, suicide is the fourth leading cause of mortality in this older age group of people (aged 15–29 years old).[6] It is noteworthy indeed that suicidal behaviours become increasingly apparent during the mid-adolescent years, and women have elevated rates of suicidal ideation and behaviours than their counterparts.[7] However, there is only limited data available on potential risk factors of suicidality in this group of people, hence suicide risk assessment in adolescents is particularly challenging for clinicians. Therefore, better insights into the risks and mediators of suicidality within this vulnerable age group is pivotal for its prevention and early intervention.

Of note, the advent of medication-triggered new-onset suicidal ideation and behaviours, especially with selective serotonin reuptake inhibitors, some antipsychotics, atomoxetine, antiepileptics and montelukast in children and adults is of particular concern, and intensely debated especially with its potential association with death by suicide.[8 9] Medication-related suicidality (MRS), defined as all suicide-related symptoms that are reported during the period of treatment with the medication, and is a major public health concern. Indeed, a black box label has been mandated by the Food and Drug Administration (FDA) for over 130 medications regarding the risk of increased suicidal ideation or behaviour.[10] We have, however, few data regarding the impact of this warning on prescribing to patients and their families. Importantly, the onset of MRS occurs over differing time frames for different medications due to varied pharmacokinetic and pharmacodynamic profiles, mechanisms of action and inter-individual differences in drug metabolism. Our current inability to predict these differences highlights the need for improved approaches to screening and monitoring of the risks of medications regarding suicidal ideation and behaviours in adolescents.

While the assessment of suicidality in post-marketing surveillance of new medications has been highlighted as a critical component in the drug development process,[11] the majority of the study instruments currently used to evaluate suicidality were primarily designed for the adult population,[12–15] and bear several limitations including false positives, poor predictive validity and inability to capture symptom change across time.[16] Therefore, risk assessment of suicidality among children and adolescents, both in research and clinical practice, remains a major clinical challenge and there is an urgent need to develop and evaluate instruments designed for children and adolescents that can comprehensively capture the bio-psycho-social mediators and risk factors for suicidality in this age group. The STOP programme (Suicidality: Treatment Occurring in Paediatrics; grant agreement number: 261411) was developed in response to a specific research call made under the Seventh Framework Programme (FP7), 'HEALTH.2010.4.2-3: Adverse drug reaction research' with an overarching aim to develop and validate a web-based protocol for the assessment and monitoring of suicidality and its mediators in children and adolescents.

Patient-reported outcome measures (PROMs) are instruments that collect health outcomes based on self/proxy assessments and have been promoted across primary care for monitoring of common mental health disorders, including suicidal ideation and behaviour.[17] As part of the STOP study, we have previously developed PROMs for a Suicidality Assessment Scale (SAS) that specifically assesses suicidality in children and/or adolescents,[17] and the STOP-Risk and Resilience Scales.[18] We have also developed the Profile Of Neuropsychiatric Symptoms scale that captures symptoms of developmental disorders, disruptive disorders, emerging personality disorders and anxiety/depressive disorders.[19]

Here we describe the development and psychometric validation of an electronic clinical outcome assessment (eCOA), the STOP-Medication-Related Suicidality Side Effects Scale (MS^3), which has a patient-reported outcome (ePRO) version, an observer-rated outcome (eObsRO) version for parents/carers and a clinician-reported outcome (eClinRO) version that allows identification and monitoring of MRS in adolescents. The three versions have been designed to capture different reports of MRS which together facilitate a comprehensive identification and monitoring of MRS in adolescents (12–18 years old).

METHODS

As part of the STOP study (www.stop-study.com), we developed a web-based 'Suite of Suicidality Measures' that together provide a comprehensive assessment of suicidality in children and adolescents.[17] These measures were developed using the HealthTracker platform, a web-based health-monitoring system to host the study instruments (in multiple languages) that has been used in other European Union FP7 funded studies.[20 21] The HealthTracker (https://www.healthtracker.co.uk) is a multimodal real-time, web-based monitoring and risk-stratification tool that can gather longitudinal clinical data including psychosocial data, behavioural data, medication side effects, cognitive functions, medication adherence, quality-of-life and post-marketing surveillance of experimental medications.[22] The study participants, parents and clinicians completed a comprehensive set of study instruments that assessed suicidality, medication adherence and compliance and quality-of-life. The UK (London) was the lead site for the STOP project.[17] Informed consent was provided by all parents and/or legal tutors of the study participants.

In the present study, we included participants who were screened positive for suicidality on the STOP-SAS.[17]

We conducted a two-phase programme: Phase 1 focused on the development of the STOP-MS[3] scale and phase 2 involved the validation of the psychometric properties of the scale. This STOP-MS[3] instrument consists of an adolescent version, parent or carer version and a clinician version that is designed to capture different components of MRS.

Phase 1: development of the STOP-MS[3]

The general methodology of developing the STOP suite of questionnaires has previously been described.[17 18] In brief, the development of the STOP-MS[3] scale followed the recommendations of the FDA for PROMs.[23] Initial items identified were generated based on an extensive literature search, experts' opinion, and an examination of items from several medication side effect questionnaires such as the UK Side Effects Rating Scale for the Registration Of Unwanted Effects Of Psychotropics[24] and the Paediatric Adverse Event Rating Scale.[25] A panel of child psychiatrists with extensive experience in paediatric psychopharmacology used this information to develop a first draft of the STOP-MS[3] scale. This draft measure was then further discussed and refined by experts within the STOP consortium and the STOP scientific advisory board.

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[26] to identify the core domains. The experts within the STOP consortium and the STOP scientific advisory board then reviewed the identified domains. To gauge participant (parent/carer and young person) understanding of the draft scale, eight focus groups were conducted at the Child and Adolescent Psychiatry Department of the Hospital Clinic of Barcelona. The procedure of these focus groups has already been described in a previous paper.[17] In brief, these focus groups consisted of three or four individuals, and participants were representative of the population seen in clinical routinely.[17 19] With informed consent from participants, the content of focus group discussions was videotaped, transcribed and analysed using thematic analyses. A detailed summary report was written regarding each transcription. Following this stage, some items were re-worded, and others removed (figure 1). Linguistic experts reviewed the final version of the study tools to ensure comparability and enhance communication with participants.[27]

Discussions between experts from the UK and Spain were held to develop final versions of the scale in English and Spanish. A clinician version was developed based on the questionnaires designed for adolescents and parents. These instruments were reviewed by a professional translator to check whether the meaning of the questions was the same in both languages. The English versions of the scale were then translated into German, French and Italian and then back translated into English. The three versions of the STOP-MS[3] were uploaded into the HealthTracker system with all language options.

Phase 2: psychometric evaluation of the STOP-MS[3] scale

Subjects and procedures

Psychometric evaluation was conducted in two study cohorts. The STOP-MS[3] questionnaire was only completed by adolescents (and the associated parent and clinician) who had suicidal ideation or behaviour as assessed by the STOP Screening Questionnaire (STOP-SQ). This questionnaire cannot be used without the STOP-SQ as the STOP-MS[3] specifically evaluates the impact of side effects on suicidality.

Cohort 1: Included 41 adolescent-completions (12–18 years old, mean age 16.27, SD 1.42), 50 parent-completions and 56 clinician-completions of the scale with repeat completion once with a maximum time of 3

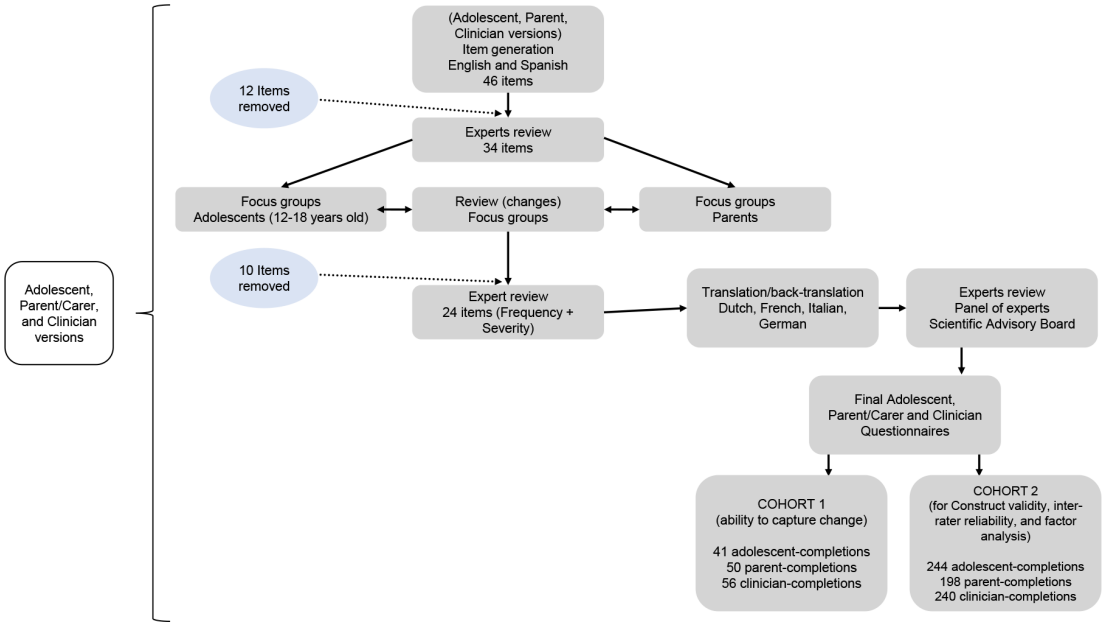

Figure 1 Development of the Suicidality: Treatment Occurring in Paediatrics-Medication-Related Suicidality Side Effects Scale.

Table 1 Baseline characteristics of Cohort 1

	STOP-MS[3] version		
	Adolescent	Parent/carer*	Clinician*
	Test–retest	Test–retest	Test–retest
	(N=41)	(N=50)	(N=56)
Age			
Mean	16.27	12.80*	13.64*
SD	±1.42	±3.07	±3.20
Gender of patients			
Male	19	33	31
Female	22	17	25
Questionnaire versions based on developmental age			
Adolescent (12 to 18 years)	41	21	30
Child (8 to <12 years)	NA	29	26
Ethnicity			
White	33	38	39
Asian	0	2	2
Black	0	0	1
Chinese	1	0	1
Hispanic	3	3	2
Not specified	4	7	11
Language			
French (France)	5	11	11
German (Germany)	5	4	4
Italian (Italy)	5	4	3
Spanish (Spain)	26	31	38

*Mean age of children whose parents/clinicians completed the questionnaires.
STOP-MS[3], Suicidality: Treatment Occurring in Paediatrics-Medication-Related Suicidality Side Effects Scale.

weeks between completions (see table 1). Descriptives of individuals with one completion or no completions are presented in online supplemental table 1. Participants were recruited from the various participating centres to explore the ability to capture change of ratings of all versions of the STOP-MS[3] across time.

For Cohort 1, we assessed completions by triads, dyads and single individuals. There are 13 complete triads (adolescent, parent/carer and clinician completed the scale at both times); 40 dyads (23 dyads of parents/carers and clinicians, 13 dyads of adolescents and clinicians and 4 dyads of adolescents and parents/carers); and 28 individual completions (11 adolescents, 10 parents/carers and 7 clinicians). The remaining subjects from Cohort 1 did not complete scales at two time points and hence were not used for test–retest reliability.

Cohort 2: Included 244 adolescent, 198 parent and 240 clinician-completions from across the six countries that were part of the STOP project. Data were collected from the various cohorts (healthy subjects, subjects with respiratory illness, subjects with psychiatric diagnoses without depression and subjects with depression) investigated in the STOP project. Completion rates varied, because an adolescent might have completed the scale but not his/her parent or the related clinician (see table 2 for the descriptive details).

All study scales were completed using the web-based HealthTracker platform which automatically scored the questionnaires and stored it in the database.

An inclusion criterion for the STOP project was that those participants on treatment should have had it initiated in the month of baseline data collection.

For Cohort 2, there were 59 complete triads (adolescent, parent/carer and clinician completed the scale at both times); 135 dyads (37 dyads of parents/carers and clinicians, 71 dyads of adolescents and clinicians and 27 dyads of adolescents and parents/carers); and 235 individual completions (87 adolescents, 75 parents/carers and 73 clinicians).

Statistical analysis

Descriptive statistics were used to characterise the study cohorts. Reliability was assessed using Cronbach's alpha, inter-rater reliability through correlations between the

Table 2 Baseline characteristics of Cohort 2

	STOP-MS^3 version					
	Adolescent version		Parent/carer version		Clinician version	
	Completed (N=244)	Not completed (N=185)	Completed (N=198)	Not completed (N=231)	Completed (N=240)	Not completed (N=189)
Treatment group						
Aripiprazole	30	32	34	28	43	19
Cognitive behavioural therapy	39	26	25	40	49	16
Fluoxetine	59	38	42	55	72	25
Risperidone	43	57	56	44	60	40
Montelukast	9	3	3	9	4	8
Other asthma or allergy medication	10	8	7	11	1	17
General population	54	21	31	44	11	64
Ethnicity						
White	195	140	156	178	189	145
Asian	10	4	5	6	2	6
Black	7	5	7	8	10	6
Mixed	9	7	10	3	10	4
Chinese	2	3	2	3	0	2
Hispanic	6	4	6	3	9	3
Gypsy/traveller	2	0	1	1	2	0
Arabic	1	0	1	0	0	1
Not set	12	22	10	29	18	22
Patient gender						
Male	87	110	112	85	92	105
Female	157	74	85	146	147	84
Not set*	0	1	1	0	1	0
Patient age						
Mean	15.13	13.37	13.89†	14.78	14.80†	13.83
SD	±1.55	2.696	±2.54	1.96	±2.13	2.373

*One patient did not identify as male or female.
†Mean age of the child whose parents/clinicians completed the questionnaires.
STOP-MS^3, Suicidality: Treatment Occurring in Paediatrics-Medication-Related Suicidality Side Effects Scale.

three versions of the scales and exploratory factor analyses (EFA) were performed. In the EFA the extraction method used principal axis factoring with Promax rotation. All p values are for two-tailed tests with α=0.05. Data were analysed using SPSS V.23.0, Chicago, Illinois, USA.

Patient and public involvement

- In this study, subjects were involved in the development of the STOP-MS^3.
- Eight focus groups at the Child and Adolescent Psychiatry Department of the Hospital Clinic of Barcelona were done to gather participant (parent/carer and young person) understanding of the draft version of the (STOP-MS^3).

RESULTS

Phase 1: Development of the STOP-MS^3

The first draft included 46 items, each of which describes a side effect potentially related to suicidality (figure 1). The final STOP-MS^3 adolescent version consisted of 24 items for each version of the scale (ie, adolescent, parent/carer and clinician) with a recall period of 3 weeks. Each item included a domain name and a brief description of the side effect. Each domain had two subquestions which were rated on a 5-points Likert scale. One subquestion was about severity of the side effect (scored from 0 (not present) to 4 (extreme)) and the second subquestion specifically explored the impact of the side effect on thoughts or behaviours of hurting oneself (scored from 0 (not at all) to 4 (a great deal)). The score of each item

Table 3 Correlations (inter-rater reliability) from the STOP-MS[3]

STOP-MS[3] version		Adolescent	Parent/carer	Clinician
Adolescent	Pearson correlation	–	0.394*	0.613*
	Sig. (two-tailed)	–	<0.001	<0.001
	N	244	86	130
Parent/carer	Pearson correlation	0.394*	–	0.347*
	Sig. (two-tailed)	<0.001	–	<0.001
	N	86	198	96
Clinician	Pearson correlation	0.613*	0.347*	–
	Sig. (two-tailed)	<0.001	<0.001	–
	N	130	96	240

*Correlation is significant at the 0.01 level (two-tailed).
STOP-MS[3], Suicidality: Treatment Occurring in Paediatrics-Medication-Related Suicidality Side Effects Scale.

was obtained by the sum of the scores of the two subquestions divided by two. Subjects were not excluded from the analyses if they had missing values. The online HealthTracker platform used to complete the questionnaires, ensures that the data set is always complete, as it does not allow raters to proceed if there are unanswered questions. Therefore, there are no missing responses. However, based on focus group feedback when the questionnaire was developed, we allowed a response of 'I don't know', when study participants were unsure about the relationship between side effects and suicidality. The percentage of the 'I don't know' responses in each version of the scale for Cohort 1 was: adolescents 1.26%, parents/carers 2.47% and clinicians 18.31%. In Cohort 2 the percentages were: adolescents 1.76%, parents/carers 5.65% and clinicians 2.91%. To prepare the data of Cohort 1 and 2 for analyses a composite score for each item was estimated. When the answer to one subquestion was 'I don't know', the answer was coded as an empty data cell, which works like a zero. When the answers to both subquestions regarding a specific side effect were rated as 'I don't know' the data was coded as an empty cell, and that questionnaire completion was excluded from the analysis. A sample screenshot of the questionnaire is shown in online supplemental figure 1.

Phase 2: Psychometric properties of the STOP-MS[3]

Reliability: Internal consistency (Cohort 2): Cronbach's alpha was excellent for the adolescent (α=0.941), parent/carer (α=0.925) and clinician versions (α=0.877) of the STOP-MS[3].

Inter-rater reliability (Cohort 2): As shown in table 3, the correlations were all significant: adolescent and parent/carer (r=0.394; p<0.001), adolescent and clinician (r=0.613; p<0.001) and parent/carer and clinician (r=0.347; p<0.001).

Validity

Ability to capture change (Cohort 1)

Analysis was conducted to demonstrate the ability of the scale to capture change of ratings across time. Our findings suggest that the scale has the potential to capture change within a space of 3 weeks. The items in the STOP-MS[3] cover medication side effects and associated suicidality. We found a significant difference for the clinician version (p=0.004). This demonstrates the ability of the STOP-MS[3] to capture change (see table 4).

Exploratory factor analyses (Cohort 2)

The EFA for the adolescent version (online supplemental table 2) of the STOP-MS[3] resulted in a 3-factors model that best fitted the data. Similar results were found for the parent/carer version of the scale (online supplemental table 3). Differently, we found that the clinician version of the scale best fitted with a 4-factors model (online supplemental table 4). The EFAs were performed using Eigen values >1.25 with the minimum loading for EFA threshold of 0.200.[18] Based on the pattern of symptom domain

Table 4 Paired differences of the STOP-MS[3]

	Paired differences							
				95% CI of the difference				
STOP-MS[3] version	Mean	SD	SEM	Lower	Upper	t	df	Two-sided p
Adolescent	2.402	8.745	1.366	-0.358	5.163	1.759	40	0.086
Parent/carer	2.060	10.015	1.416	-0.786	4.906	1.454	49	0.152
Clinician	2.143	5.382	0.719	-0.702	3.584	2.980	55	0.004

STOP-MS[3], Suicidality: Treatment Occurring in Paediatrics-Medication-Related Suicidality Side Effects Scale.

loadings in the factors across the adolescent and parent/carer versions of the scales, the factors were named: (1) Emotional Dysregulation, (2) Somatic Dysregulation and (3) Behavioural Dysregulation. For the Clinician version of the scale the factors were named: (1) Somatic Dysregulation, (2) Emotional Dysregulation, (3) Behavioural Dysregulation and (4) Mood Dysregulation.

DISCUSSION

The key finding of this study is that the STOP-MS[3] is a reliable instrument for the assessment and monitoring of medication side effects related to suicidality in adolescents. The STOP-MS[3] adolescent, parent and clinician versions are web-based measures that consist of 24 items, each of which has a 'severity' subquestion and an 'impact on suicidality' subquestion that are rated on a 5-point Likert scale. The STOP-MS[3] has items that cover symptoms associated with emotional, somatic, behavioural and mood dysregulation, and is concise and easy to use. Of note, the questionnaire cannot be used without the STOP-SQ as the STOP-MS[3] specifically evaluates the impact of medication on suicidality.

From a psychometric perspective we observed good internal consistency for all the versions of STOP-MS[3], suggesting good reliability and providing preliminary evidence that the symptom domains measure a common underlying construct. We also found significant correlations between the three versions of the STOP-MS[3], with a good correlation between the adolescent and clinician versions. This could be interpreted as a robust agreement between their views on the severity and impact of MRS on suicidal thoughts and behaviours. It supports the notion that adolescents can communicate their views on side effects and suicidality with clinicians and highlights the importance of conducting face-to-face interviews with them. A possible factor contributing to this observation may be the use of web-based tools, which may appeal more to adolescents and young people due to their increased accessibility and the anonymity they can provide. We also showed that there is a correlation between parent and adolescent ratings on the questionnaire. This is understandable, as adolescents may be more able to discuss difficult information such as suicidality, with both parents and clinicians.

Our findings suggest that the scale has the potential to capture change within a space of 3 weeks. We observed changes within this period for the adolescent rating of suicidality and side effects suggesting that side effects and associated suicidality fluctuate rapidly and can be reported by the individual experiencing it. This is not surprising because both side effects and suicidality are often subjective experiences, that have previously been shown to be rated better by the adolescent themselves.[28 29]

The factor structure generated by the EFA for each version of STOP-MS[3] was similar across the adolescent and parent/carer versions of the scale. However, the clinician version of the scale is best fitted with a model composed of four factors. These findings suggest that although the adolescent and parent/carer versions of the STOP-MS[3] can capture the impact of medication on suicidal ideations and behaviours, the clinician version was better at capturing change. The STOP-MS[3] factor structure for all three versions also broadly aligns with the domain framework of the Patient-Reported Outcomes Measurement Information System (PROMIS) (www.nihpromis.org), which proposes factors for Anger, Anxiety and Depression and Pain and Fatigue domains.

To the best of our knowledge, this is the first study that used web-based assessments for the identification and monitoring of MRS. Our findings suggest that the STOP-MS[3] can comprehensively capture the frequency and severity of MRS in adolescents, and can also be used by their parents/carers and clinicians. The HealthTracker-web-based PROM uses intelligent branching, audio-assistance for those with reading difficulties, adaptions for visual impairment (with large font-size adaptations) and availability in multiple languages (English, Spanish, Italian, German, French and Dutch).[21] This allows adolescents, parents and clinicians to complete it effortlessly in a few minutes. In addition, it allows clinicians to monitor MRS in adolescents and assists medication-decision-making, optimise use of clinical time and has the potential to be used in prospective clinical trials to identify medication-related suicidality and its time-course.

Of note, we acknowledge the limitations of this study. We only included subjects who were screened positive on the screening questionnaire of the STOP-SAS.[17] We deemed it inappropriate to ask all participants about the impact of the medication side effect on suicidality if there was no suicidality and therefore the STOP-MS[3] is only to be used when the STOP-screening is positive. In this study, approximately 80% of the sample was white and 99% cis gender. The study findings would therefore probably not apply for those individuals who do not fall into these socio-demographic categories. Further work would be needed to address representation of the wider clinical population especially from ethnically diverse backgrounds. This element will be crucial to address given that a recent combined systematic review and meta-analysis has highlighted the importance of addressing the differences of suicide risk in groups from ethnic minority backgrounds.[30]

CONCLUSION

In summary, our findings suggest that the HealthTracker eCOA of STOP-MS[3] adolescent, parent/carer and clinician versions are PROMs and clinician instruments with good psychometric properties that have the potential to identify and monitor MRS in adolescents, using self and proxy measures from parents/carer and clinicians. The STOP-MS[3] should be tested in clinical populations in routine clinical care as well as those recruited in clinical trials, to ensure that it can capture the information in non-research settings. Baseline evaluation is essential

to ensure that the findings can be attributed to medication initiation. When high scores are detected, it should lead to an in-depth clinical assessment as to the safety of continuing with the medication and to ensure that appropriate risk management strategies are implemented. These patients may require more frequent clinical reviews till they are stabilised.

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REFERENCES

1 Wasserman D, Cheng Q, Jiang GX. Global suicide rates among young people aged 15-19. *World Psychiatry* 2005;4:114–20.
2 Soole R, Kõlves K, De Leo D. Suicide in children: a systematic review. *Arch Suicide Res* 2015;19:285–304.
3 Miranda-Mendizabal A, Castellví P, Parés-Badell O, *et al*. Gender differences in suicidal behavior in adolescents and young adults: systematic review and meta-analysis of longitudinal studies. *Int J Public Health* 2019;64:265–83.
4 Hawton K, van Heeringen K. Suicide. *Lancet* 2009;373:1372–81.
5 Pelkonen M, Marttunen M. Child and adolescent suicide: epidemiology, risk factors, and approaches to prevention. *Paediatr Drugs* 2003;5:243–65.
6 World Health Organisation. Statistics. n.d. Available: https://www.who.int/news-room/fact-sheets/detail/suicide
7 Canetto SS, Sakinofsky I. The gender paradox in suicide. *Suicide Life Threat Behav* 1998;28:1–23.
8 Stübner S, Grohmann R, Greil W, *et al*. Suicidal Ideation and suicidal behavior as rare adverse events of antidepressant medication: current report from the AMSP multicenter drug safety surveillance project. *Int J Neuropsychopharmacol* 2018;21:814–21.
9 Reith DM, Edmonds L. Assessing the role of drugs in suicidal ideation and suicidality. *CNS Drugs* 2007;21:463–72.
10 Gibbons R, Hur K, Lavigne J, *et al*. Medications and suicide: high dimensional empirical Bayes screening (iDEAS). *Harvard Data Science Review* 2019;1:2.
11 Klein DF. The flawed basis for FDA post-marketing safety decisions: the example of anti-depressants and children. *Neuropsychopharmacology* 2006;31:689–99.
12 Gutierrez PM, Osman A, Barrios FX, *et al*. Development and initial validation of the self-harm behavior questionnaire. *J Pers Assess* 2001;77:475–90.
13 Miranda R, Ortin A, Scott M, *et al*. Characteristics of suicidal Ideation that predict the transition to future suicide attempts in adolescents. *J Child Psychol Psychiatry* 2014;55:1288–96.
14 Thompson EA, Eggert LL. Using the suicide risk screen to identify suicidal adolescents among potential high school dropouts. *J Am Acad Child Adolesc Psychiatry* 1999;38:1506–14.
15 Larzelere RE, Smith GL, Batenhorst LM, *et al*. Predictive validity of the suicide probability scale among adolescents in group home treatment. *J Am Acad Child Adolesc Psychiatry* 1996;35:166–72;
16 Boege I, Corpus N, Schepker R, *et al*. Pilot study: feasibility of using the suicidal Ideation questionnaire (SIQ) during acute suicidal crisis. *Child Adolesc Psychiatry Ment Health* 2014;8:28.
17 Flamarique I, Santosh P, Zuddas A, *et al*. Development and psychometric properties of the suicidality: treatment occurring in paediatrics (STOP) suicidality assessment scale (STOP-SAS) in children and adolescents. *BMC Pediatr* 2016;16:213.
18 Rodríguez-Quiroga A, Flamarique I, Castro-Fornieles J, *et al*. Development and psychometric properties of the "suicidality: treatment occurring in paediatrics (STOP) risk and resilience factors scales" in adolescents. *Eur Child Adolesc Psychiatry* 2020;29:153–65.
19 Santosh P, Gringras P, Baird G, *et al*. Development and psychometric properties of the parent version of the profile of neuropsychiatric symptoms (PONS) in children and adolescents. *BMC Pediatr* 2015;15:62.
20 Santosh P, Adams L, Fiori F, *et al*. Protocol for the development and validation procedure of the managing the link and strengthening

transition from child to adult mental health care (MILESTONE) suite of measures. *BMC Pediatr* 2020;20:167.
21 Santosh P, Tarver J, Gibbons F, *et al*. Protocol for the development and validation of a questionnaire to assess concerning behaviours and mental health in individuals with autism spectrum disorders: the assessment of concerning behaviour (ACB) scale. *BMJ Open* 2016;6:e010693.
22 Gringras P, Santosh P, Baird G. Development of an internet-based real-time system for monitoring pharmacological interventions in children with neurodevelopmental and neuropsychiatric disorders. *Child Care Health Dev* 2006;32:591–600.
23 United States Food and Drug Administration. *Guidance for industry: suicidality: prospective assessment of occurrence in clinical trials. Draft Guidance*. 2014.
24 Lingjaerde O, Ahlfors UG, Bech P, *et al*. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl* 1987;334:1–100.
25 Wehmeier PM, Schacht A, Lehmann M, *et al*. Emotional well-being in children and adolescents treated with atomoxetine for attention-deficit/hyperactivity disorder: findings from a patient, parent and physician perspective using items from the pediatric adverse event rating scale (PAERS). *Child Adolesc Psychiatry Ment Health* 2008;2:11.
26 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
27 Alzyood M, Jackson D, Aveyard H, *et al*. Use of focus group data from countries with linguistic differences: translation, analysis and presentation. *Nurse Res* 2020;28:17–24.
28 Czyz EK, Horwitz AG, King CA. Self-rated expectations of suicidal behavior predict future suicide attempts among adolescent and young adult psychiatric emergency patients. *Depress Anxiety* 2016;33:512–9.
29 Harris IM, Beese S, Moore D. Predicting future self-harm or suicide in adolescents: a systematic review of risk assessment scales/tools. *BMJ Open* 2019;9:e029311.
30 Troya MI, Spittal MJ, Pendrous R, *et al*. Suicide rates amongst individuals from ethnic minority backgrounds: a systematic review and meta-analysis. *EClinicalMedicine* 2022;47:101399.