PROJECT FINAL REPORT

Grant Agreement number:	**261411**
Project acronym:	**STOP**
Project title:	**Suicidality: Treatment Occurring in Paediatrics**
Funding Scheme:	**FP7-CP-FP**
Period covered:	**from 01.11.2010 to 30.04.2015**

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1 An executive summary

The overarching long term goal of the 'Suicidality: Treatment Occurring in Paediatrics' STOP project was to develop a comprehensive HealthTracker™ based methodology for the assessment and monitoring of suicidality and its mediators in children and adolescents. This was achieved through the development of the STOP Suite of Suicidality Measures. The STOP Suite of Suicidality Measures was developed on the HealthTracker™ platform and consists of the STOP-Suicidality Assessment Scale (SAS), the STOP-Medication Suicidality Side-effects Scale (MS^3), STOP Terminating Medication Scale (TMS), STOP Suicidality Resilience Scale (SRS) and the STOP Suicidality Risk Factors Scale (SRFS). Collectively, these scales allowed for the prediction of the adolescent model of suicidal behaviour to be performed which lead to the identification of specific domains for suicidality that were developed into a single HealthTracker™ based scale to predict the risk of suicidality in children and adolescents. This scale was called the Suicidality Prediction and Optimising Treatment Scale (SPOTS)
The scales were validated in three paediatric observational trials involving 1002 children and adolescents aged from 8-18 years of age consisting of seven cohorts: Cohort 1, Risperidone (n=235); Cohort 2, Aripiprazole (n=156); Cohort 3, Fluoxetine (n=128); Cohort 4, Cognitive Behavioural Therapy (CBT, n=96); Cohort 5, Montelukast (n=62); Cohort 6, non-Montelukast (n=103) and Cohort 7, healthy controls (n=222).

In pursuing this goal the following key objectives were explored:

- To develop a comprehensive assessment of suicidality and its bio-psycho-social mediators (including medication characteristics, psychopathology, psychological and social risk and protective factors) in children and adolescents.
- To standardize the newly developed HealthTracker™ based assessment and monitoring measures using data obtained in seven cohorts (as part of three observational trials of children and adolescents aged between 8-18 years).
- To address scientific questions about suicidality and its bio-psycho-social mediators (with a focus on medication-related suicidality), through using the HealthTracker™ based methodology in seven cohorts (as part of three observational trials).
- To disseminate the extension of knowledge acquired by the proposed studies and make available the HealthTracker™ based STOP Suite of Suicidality Measures developed through this project to regulatory authorities, researchers, pharmaceutical companies, and medical and mental health professionals under appropriate IP arrangements.

When standardising the newly developed HealthTracker™ based assessment and monitoring measures using data obtained in the three observational trials of children and adolescents, the HealthTracker™ based presentation of the scales allowed an efficient method of skipping unnecessary questions, by having screening questions for specific topics. This ensured much better scale completion as it was very time efficient and was user friendly. Both parent and patients found the STOP study interesting (with adolescents less enthusiastic than parents), reporting that the HealthTracker™ system made filling out the questionnaires easier and that participation to the study helped parents (but not patients) to better understand suicidality, without increasing their suicidal thoughts, worry, and anxiety. The majority of both adolescents and patients did not find it difficult to complete the questionnaires and stated they would like to participate in similar study again (about 50% of adolescents, 74% of parents). The majority of clinicians reported that the participation to the STOP study increased their understanding of suicidality, decreased their fears and worries in approaching parents and adolescents on this topic, leading to a better consideration of risk and resilience factors, and helped parents and adolescents in dealing with the barriers in discussing suicidality (with parents more fearful than adolescents in dealing with the topic). Almost all clinicians reported the use of an electronic tool significantly helped to capture information about suicidality from parents and adolescents.To address scientific questions about suicidality and its bio-psycho-social mediators a Standard Operating Procedure (SOP) was developed on how suicidality as a side-effect could be reported and a biological sampling methodology for the investigation of mediators of suicidality in saliva was established.

The key objective of the STOP project was to develop a comprehensive cross-sectional assessment scale for the longitudinal monitoring of suicidality and its bio-psycho-social mediators (including psychopathology, other risk and protective factors, and medication characteristics) in children and adolescents. Based on longitudinal data modelling, the predictive modelling allowed identification of specific domains for suicidality leading to the predictors of suicidality in children to be developed into a single scale. This study succeeded in developing this model and the list of domains have been developed into a single HealthTracker™ based scale called "**S**uicidality **P**rediction and **O**ptimising **T**reatment **S**cale" (**SPOTS**) scale for adolescents, clinicians, parents and children. The adolescent predictive model for suicidal behaviour was shown to be fair (r^2=0.459) for cohorts 1, 2, 3 and 4 (i.e. children with conduct disorder, psychoses or developmental disorders on atypical antipsychotics Risperidone or Aripiprazole [WP7] and children on Fluoxetine or non-medication strategies [CBT] for depression [WP8]). This was also true (r^2=0.433) for cohorts 1 and 2 i.e. those prescribed antipsychotics (Risperidone and/or Aripiprazole [WP7]).

However, where the primary diagnosis was depression (i.e. those prescribed Fluoxetine or and/or CBT [WP8]) the predictive value of the model was good (r^2=0.764). The psychometric properties of the HealthTracker™ based SPOTS showed very good internal consistency for the adolescent version of the scale and a strong correlation between the SPOTS and the C-SSRS for clinicians and adolescents; however, the correlation was rather weak (fair) for parents. The Exploratory Factor Analysis for the adolescents' version showed a 5-factor model. Based on the pattern of symptom domain loading the 5 factors were named: (1) Suicidal Thoughts, (2) Medication Related Depressive Mood and Thinking, (3) Medication Related Somatic Symptoms, (4) Medication Related Mood Dysregulation and (5) Suicidality Related Stressors. The ROC area was the highest for the clinician version and good for the adolescent and parent versions of the scale.

Summing up, the STOP project was highly valuable in the sense that:

- It helped to standardize the newly developed HealthTracker™ based STOP assessment and monitoring measures using data obtained in seven cohorts (as part of three observational trials of children and adolescents aged between 8-18 years) in different languages and across multiple countries.
- It allowed for the development of the HealthTracker™ based STOP Suite of Suicidality Measures that consists of STOP-Suicidality Assessment Scale (SAS), the STOP-Medication Suicidality Side-effects Scale (MS^3), STOP Terminating Medication Scale (TMS), STOP Suicidality Resilience Scale (SRS) and the STOP Suicidality Risk Factors Scale (SRFS).
- The HealthTracker™ based STOP Suite of Suicidality Measures allowed for predictive modelling to be performed and collectively led to the development of the single HealthTracker™ based Suicidality Prediction and Optimising Treatment Scale (SPOTS) to predict the risk of suicidality in children and adolescents.
- The developed HealthTracker™ based SPOTS can be used as a stand-alone single scale to be used for pharmacovigilance whenever a new drug is introduced in children and adolescents (or for that matter in adults) so that medication related suicidality can be prospectively monitored.

2 A summary description of project context and objectives

Background

Suicide is one of the major causes of death worldwide with self-inflicted death being the tenth leading cause for deaths worldwide contributing 1.5% of all deaths (Levi *et al*., 2003). Onset of suicidal behaviours are consistent worldwide and evidence form the World Health Organisation (WHO) has shown that the risk of onset of suicidal ideation increases rapidly during adolescence and young adulthood, which then stabilises in early midlife (Nock *et al*., 2008). The greatest risk for suicidal behaviour is in adolescence and early adulthood (Kessler *et al*., 1999). Rates of suicide in childhood and early adolescence suicide are rare. However, in adolescents and young adulthood suicide rates become increasingly more prevalent. Current data showing the latest mean worldwide annual rates of suicide per 100 000 were 0.5 for females and 0.9 for males among 5-14-year-olds, and 12.0 for females and 14.2 for males among 15-24-year-olds, respectively (Pelkonen & Marttunen, 2003). Due to the growing risk for suicide with increasing age, adolescents are the main target of suicide prevention as less than half of young people who have committed suicide had received psychiatric care.

The emergence of suicidal ideation and suicide-related behaviour in patients receiving drug treatment is of concern because of the overall burden of these conditions and the possible link with completed suicide. Some observational studies have been useful in generating hypotheses of causality but there interpretation is complicated by the association between various disease states and increased suicide-related behaviour and completed suicide. The demonstration of causality requires experimental studies, especially randomised controlled trials and meta-analyses. However, there is paucity in the literature with regards to defining, detecting and recording suicidal ideation, suicide-related behaviour and completed suicide which precludes meaning comparisons between studies from being made (Reith and Edmonds, 2007). Despite this, evidence indicates an association between selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants with treatment-related suicidal ideation and suicide-related behaviour in both children and adults, however, an increase in completed suicide, as a treatment with SSRIs and other newer antidepressants has not been demonstrated. Based on the results of meta-analyses, other agents such as atomoxetine and some antiepileptic's have also been associated with treatment-related suicidality. The European Child and Adolescent Psychopharmacology Network (ECAPN) is a well-established network of child and adolescent psychiatrists, representing several EU countries, all of whom are experts in paediatric psychopharmacology and the majority of the partners involved in this project are members of this network. The ECAPN is supported by the European College of Neuropsychopharmacology (ECNP) and its aims include the identification of unmet needs in child and adolescent psychopharmacology, conducting collaborative scientific studies and clinical trials, and the development of strategies to improve state-of-the-art prescribing of medication to children and adolescents with psychiatric disorders in clinical practice.

This core of this project was built around a specific call of the FP7 Cooperation Work Programme "HEALTH.2010.4.2-3: Adverse drug reaction research''. In responding to this call and in taking account of the European Medicines Agency (EMA) 2010 Priorities for Drug Safety research, the ECAPN focused on the 'Suicidal Behaviour in Relation to Certain Drug Use" component. This project has clearly delineated itself as restricting itself to children and adolescents because this age-group has specific needs in comparison to adults and the partners of this consortium have the best expertise in Europe to develop the methodology necessary in this age group.

Rationale

The term 'Medication-Related Suicidality' (MRS) is a reported adverse event and is defined as any suicide-related symptoms that are reported during the period of treatment with the drug. Symptoms include suicidal ideation, suicidal plans and suicidal behaviours. There are at present no prior clinical cohorts of children and adolescents in which all relevant bio-psycho-social mediators have been simultaneously collected in order to study their relevance. MRS has been associated with drugs that affect the CNS, and also with some drugs that are not primarily neuropharmaceuticals. As a consequence, the assessment of suicidality in both pre- and post-marketing clinical trials of neuropharmaceuticals has become a major issue. Prevention of suicide, particularly suicide in young people, is a health priority in a number of countries and as a consequence regulatory agencies would be particularly concerned at the prospect of treatment-emergent suicidal ideation. The prospect of black box warnings or having to withdraw drugs from the market would be of great concern to pharmaceutical developers, given the considerable investment involved in bringing new drugs to market. However, experience with the assessment of suicidality in relation to drugs has highlighted a number of serious methodological difficulties in investigating treatment-emergent suicidal ideation and suicide-related behaviour (Reith and Edmonds, 2007). The STOP project was designed to explore the premise whether there is a need for the assessment of MRS in Children and Adolescents. In view of this the following questions were asked:

I. Can instruments that are developed for adults be used in children and adolescents?
II. Why are instruments for assessing suicidality in psychiatric disorders in children and adolescents not sufficient to measure medication-related suicidality?
III. What are the specific issues that new methodology will need to address?

There are probably several reasons why instruments developed in adults may not be appropriate to be used in children and adolescents. Cognitive and developmental mechanisms such as self-awareness, self-reflection, ability to communicate about inner feelings and emotion, abstract thinking, and concept of death significantly differ between children, adolescents and adults and hence a child-specific and adolescent specific instrument needs development. In terms of suicidality associated with medications, this may be different in terms of phenomenology, clinical expression and time course, with different clinical signals from that associated with the psychiatric disorders themselves, requiring the development of an instrument with new or modified items. These may even vary between children and adolescents. Therefore, using the "standard instruments" could lead to both under-diagnosing and over-diagnosing suicidality. Unlike psychopathology related suicidality, medication-related suicidality may be associated with emergence of suicide-related ideation and behaviour over different time-frames based on possible differences in drug pharmacokinetics (PK), suicidality or precursors to suicidality being severe or abrupt in onset, and/or the absence of suicidality as part of the patient's presenting symptoms, as well as the emergence of co-morbidities that may be associated with an increase in the risk of suicidal ideation and/or behaviour. It is possible that assessment and monitoring of suicidality may have to be different for different drugs (possibly based on PK) and indication (may be in the first weeks of treatment with antidepressants, while it might be delayed in antipsychotics and Montelukast). In the Food and Drug Administration (FDA) analyses of suicide-related behaviour and antidepressants, methodology was developed to enable comparability between studies (Hammand, 2004). The FDA used a standardised assessment process, where individual patient data were used and categorized by a panel of expert reviewers using a coding scheme. The reviewers also underwent training in order to calibrate their responses. Despite attempting to standardise the assessment process, this method failed to overcome the problems associated with data capture, whereby there is variability between trials in the notification and recording of suicide-related behaviour and ideation. Such meta-analyses, using standardised classification schemas, can only be performed where there is access to individual patient data (Reith and Edmonds, 2007). Based on this information there is a pressing need to define suicidality and assess the relationship between this construct and risk of suicide attempts and completed suicide in general populations and in populations known to be at elevated risk of suicide.

Objective

The key objectives of the STOP Study were:

- To develop a comprehensive HealthTracker™ based assessment of suicidality and its bio-psycho-social mediators (including medication characteristics, psychopathology, psychological and social risk and protective factors) in children and adolescents
- To standardize the HealthTracker™ based assessment and monitoring measures using data obtained in three observational trials of children and adolescents
- Address scientific questions about suicidality and its bio-psycho-social mediators (with a focus on medication-related suicidality), through using the new HealthTracker™ based methodology in three clinical samples
- Disseminate the extension of knowledge acquired by the proposed studies and make available the technology developed through this project to regulatory authorities, researchers, pharmaceutical companies, and medical and mental health professionals

This HealthTracker™ based STOP Suite of Suicidality Measures was developed on the HealthTracker™ platform and consists of the STOP-Suicidality Assessment Scale (SAS), the STOP-Medication Suicidality Side-effects Scale (MS^3), STOP Terminating Medication Scale (TMS), STOP Suicidality Resilience Scale (SRS), the STOP Suicidality Risk Factors Scale (SRFS) and the Suicidality Prediction and Optimising Treatment Scale (SPOTS).

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3 A description of the main S&T results/foregrounds

3.1 Summary of the main results/foreground of STOP

Subject demographics for all seven cohorts in the STOP study are presented in Table 3.1A and numbers for each of these cohorts split by recruitment site is shown in Table 3.1B. One of the overarching long term goals of the STOP project was to develop a comprehensive HealthTracker™ based assessment for the monitoring of suicidality and its mediators in children and adolescents. This was achieved through the development of the HealthTracker™ based STOP-Suite of Suicidality Measures that consists of the STOP-Suicidality Assessment Scale (SAS), the STOP-Medication Suicidality Side-effects Scale (MS^3), STOP Terminating Medication Scale (TMS), STOP Suicidality Resilience Scale (SRS), the STOP Suicidality Risk Factors Scale (SRFS) and the Suicidality Prediction and Optimising Treatment Scale (SPOTS). The scales were developed and validated using the HealthTracker™ platform in three paediatric observational trials involving 1002 children and adolescents aged from 8-18 years of age and consisted of seven cohorts: Cohort 1, Risperidone (n=235); Cohort 2, Aripiprazole (n=156); Cohort 3, Fluoxetine (n=128); Cohort 4, Cognitive Behavioural Therapy (CBT, n=96); Cohort 5, Montelukast (n=62); Cohort 6, non-Montelukast (n=103) and Cohort 7, healthy controls (n=222). The HealthTracker™ platform allowed the scales to be used by children, adolescents, parents, teachers as well as clinicians. HealthTracker™ (https://www.healthtracker.co.uk) is ideal for post-marketing surveillance of medication as it can capture longitudinal data about behaviour, emotions, side-effects, cognitive functions, quality of life of both child and family along with details of all medication used as well as compliance. The HealthTracker^T -based presentation of the scales allowed an efficient method of skipping unnecessary questions, by having screening questions for specific topics. This study showed that both parents and patients found the STOP study interesting (with adolescents less enthusiastic than parents), reporting that the HealthTracker™ system made completion of the questionnaires easier. The use of the HealthTracker™ platform also indicated that participation to the study helped parents (but not patients) to better understand suicidality, without increasing their suicidal thoughts, worry, and anxiety. The majority of both adolescents and patients did not find it difficult to complete the questionnaires and stated they would like to participate in similar study again (about 50% of adolescents, 74% of parents). The majority of clinicians reported that the participation to the STOP study increased their understanding of suicidality, decreased their fears and worries in approaching parents and adolescents on this topic, leading to a better consideration of risk and resilience factors, and helped parents and adolescents in dealing with the barriers in discussing suicidality (with parents more fearful than adolescents in dealing with the topic). Almost all clinicians reported the use of an electronic tool significantly helped to capture information about suicidality from parents and adolescents.

Regarding the HealthTracker™ based STOP-Suite of Suicidality Measures, the psychometric properties of the scales indicated that internal consistency was good for all versions of the Suicidality Assessment Scale (SAS). In addition, there was a strong correlation between the clinicians, adolescents, parents and children's SAS total scores and the clinician-rated gold standard Columbia Suicide Severity Rating Scale (C-SSRS) total score. The results from the Receiver Operating Characteristic (ROC) analysis showed that the SAS is a valid instrument for assessing suicidal ideations, plans and preparations and suicidal behaviours for adolescents. For parents, whilst the instrument was good in detecting suicidal ideations, it was modest for detecting suicidal behaviours but weak in detecting suicidal plans and preparations. Conversely, the clinician version was excellent in detecting suicidal ideation, good for detecting suicidal behaviours and modest in detecting suicidal plans and preparations.

The originally planned HealthTracker™ based STOP-Medication Suicidality Side-effects Scale (MS^3) had to be split into two scales – the Medication Suicidality Side-effects Scale (MS^3) and the Terminating Medication Scale (TMS). For the MS^3, internal consistency was good for all versions of the scale. There was however, a poor correlation between the total scores of the clinicians, adolescents, parents and children's scale and the clinician-rated C-SSRS total score. The overall ROC analysis indicated that the MS^3 scale was a valid instrument in detecting medication induced emotional and behavioural dyscontrol. Amongst the versions, the adolescent was the best in detecting these changes followed by the parent and clinician version. For the TMS, good internal consistency was found for the clinician version but low internal consistency was shown for adolescents and parents versions. Exploratory factor analysis showed a 1-factor model. The ROC area was modest for all versions of the scale in that although the scales were high in specificity, they were rather weak in detecting the measure

Based on data analyses, the intended HealthTracker™ based STOP-Risk and Resilience Scale (RSS) had to be split into the Suicidality Resilience Scale (SRS) and the Suicidality Risk Factors Scale (SRFS). Good internal consistency was found for clinicians, adolescents and parent versions of the SRS. Exploratory factor analysis revealed a 2-factor model. These factors were named as (1) External Resilience Factors and (2) Internal Resilience Factors. Overall the accuracy of the adolescent, parent and clinician version to predict resilience was modest In general, factor 1 'External Resilience Factors' showed a better accuracy in predicting resilience in the parent and clinician version when compared to the adolescent version. For the SRFS, fair internal consistency was found for clinicians whilst good internal consistency was seen for adolescents and parents versions. The overall ROC area was good for clinicians but modest for adolescents and parents. The Exploratory Factor

Analysis for the clinicians' version of the SRFS showed a 4-factor model and based on the pattern of symptom domain loading the 4 factors were named as: (1) 'Depression', (2) 'Chronic stress', (3) Historical risk and (4) 'Bullying'. Further ROC analyses showed that the predictive value of factor 1 'Depression' was the highest for all versions of the scale.

As described above, one of the major outcomes of the STOP project was to develop a comprehensive cross-sectional assessment scale for the longitudinal monitoring of suicidality and its bio-psycho-social mediators (including psychopathology, other risk and protective factors, and medication characteristics) in children and adolescents. Based on longitudinal data modelling, the predictive modelling allowed identification of specific items for suicidality leading to the predictors of suicidality in children to be developed into a single scale. This study succeeded in evaluating the predictive model and the list of domains were developed into a single HealthTracker™ based scale called "**S**uicidality **P**rediction and **O**ptimising **T**reatment **S**cale" (**SPOTS**) as part of the STOP Suite of Suicidality Measures. The adolescent suicidal behaviour predictive model was shown to be fair (r^2=0.459) for cohorts 1, 2, 3 and 4 (i.e. children with conduct disorder, psychoses or developmental disorders on atypical antipsychotics Risperidone or Aripiprazole [WP7] and children on Fluoxetine or non-medication strategies [CBT] for depression [WP8]). This was also true (r^2=0.433) for cohorts 1 and 2 i.e. those prescribed antipsychotics (Risperidone and/or Aripiprazole [WP7]). However, where the primary diagnosis was depression (i.e. those prescribed Fluoxetine or and/or CBT [WP8]) the predictive value of the model was good (r^2=0.764). The psychometric properties of the HealthTracker™ based SPOTS showed very good internal consistency for the adolescent version of the scale and a strong correlation between the SPOTS and the C-SSRS for clinicians and adolescents; however, the correlation was fair for parents. The Exploratory Factor Analysis for the adolescents' version showed a 5-factor model. Based on the pattern of symptom domain loading the 5 factors were named: (1) Suicidal Thoughts, (2) Medication Related Depressive Mood and Thinking, (3) Medication Related Somatic Symptoms, (4) Medication Related Mood Dysregulation and (5) Suicidality Related Stressors. The sensitivity and specificity was very good for all versions of the scale. Amongst the scales, the ROC area was the highest for the clinician version followed by the adolescent and parent versions.

The list of domains for the adolescent model is shown below:

1. Thoughts of being dead
2. Thoughts of hurting self
3. Thoughts of ending life
4. Thoughts of harming self to feel better
5. Thoughts to end my life but would not
6. Thoughts of being certain to end my life
7. In ability to control my thoughts of killing myself
8. I have started to plan how to end my life
9. I have made preparations to kill myself
10. Am worried about being judged socially
11. Medication related hypomanic symptoms
12. Medication related self-injury
13. Medication related nightmares
14. Medication related daytime drowsiness
15. Medication related somatic symptoms (aches and pains)
16. Medication related inattention
17. Medication related anger/temper
18. Stopped medication due to side-effects
19. Chronic physical illness as risk
20. Bullying as risk
21. Chronic Pain as risk
22. Depressive thinking as risk
23. Anxiety at risk
24. Low self-esteem as risk
25. History of suicide attempt
26. Family history of suicide as risk
27. Change of residence as risk

These 27 domains have been developed into a single HealthTracker™ based scale: SPOTS and will have versions for clinicians, parents and children on the HealthTracker™ platform.

This validated HealthTracker™ based STOP-Suite of Suicidality Measures (including the SPOTS as a pharmacovigilance tool) will provide a mechanism by which active pharmacovigilance can be done whenever a new drug is introduced in children and adolescents (or for that matter in adults) so that medication related suicidality can be monitored. This will have immense value because risk of medication related suicidal behaviour can be identified early and intervention provided. If certain medication side-effects are highly correlated to suicidality, those side-effects could be identified that would alert clinicians to explore further about suicidality in routine clinical practice and provide active interventions.

3.2 Main results/foreground of the different work package

WP 1: Project management

Background
Effective project management is a central element of successful research. This is because large research projects often entail a lot of administrative work which needs to be dealt in an efficient and timely manner. In view of this, the purpose of WP 1 was project management for the STOP project. This took care of all administrative and coordinating tasks.

Project Management
In order to support the Coordinator in monitoring the compliance by beneficiaries with their obligations under the grant agreement, the project management office at concentris routinely monitored the partners' performance based upon the following:

- To ensure that tasks assigned to them were correctly and timely performed.
- Reports were submitted according to the guidelines and on time.
- Funds were used and claimed according to the rules.
- The partners fulfilled their obligations regarding dissemination and funding acknowledgements.
- Any changes to the work plan were communicated to the European Commission (EC) efficiently.
- Compliant to ethical regulations.

The project office acted as a helpdesk for all participants; it was the central node of communication on a day-by-day basis and communicated with the EC on behalf of the Coordinator regarding administrative and managerial issues (i.e. contract, amendment, reporting etc.).

WP 2: Signal generation and meta-analysis on medication-induced suicidality

Background
Recently published systematic literature reviews and meta-analyses on medication-induced suicidality (self-harm, suicidal behaviour, suicide attempts and completed suicides) in children and young people have focused on a particular drug or group of drugs such as serotonin-specific reuptake inhibitors (SSRIs) and the serotonin noradrenaline reuptake inhibitors. The purpose of this WP was to develop a novel methodology using data from spontaneous reporting systems, including the WHO Individual Case Safety Reports (ICSR) database to identify all signals of drug-induced suicidal behaviour/suicidality; a selection of which were then investigated by meta-analytical methods to report their frequencies in published literature. The outputs generated by the two methods were then compared in order to make recommendations with regard to the future detection and reporting of medication-associated suicidality.

Overall Objectives
1. To devise a methodology for generating signals of Medication Related Suicidality (MRS) in children and young people from a pharmacovigilance database.
2. To conduct a systematic review on published literature to investigate medication-associated suicidality signals of selected drugs generated by Objective 1.
3. To identify medication-induced suicidality events reported, and to summarise the frequency of these events.
4. To compare the signal generated by the Objective 1 and Objective 2.
5. To develop recommendations on how to report MRS events in the published literature.

Results
A methodology was designed for detecting signals of suicide-related adverse events (SRAEs) related to medication, using data from the Vigibase database (maintained by the WHO Uppsala Monitoring Centre in Sweden) (Task 1). Following on from this a systematic review was conducted on medications identified as having signals of SRAEs in Objective 1 (Task 2). The methodology from Objective 1 was used to identify medications-SRAE pairs and the frequency of reports in the Vigibase. Two deliverable reports were prepared (Task 3). The first deliverable report (D02.1) reported on 'Drugs associated with suicidality.' An important aspect of this report was to identify other adverse events (AEs) commonly reported alongside reports for SRAEs to Fluoxetine, Montelukast and Risperidone, to inform the clinical work packages within the STOP project. The second deliverable report (D02.2) 'Signal detection of medication induced suicide related adverse events' provided results from the literature review. A comparison of signals detected for each medication identified (Task 5) and recommendations for reporting MRS events in published literature were provided.

Conclusion
Although spontaneous reporting is highly valuable for the detection of rare unknown adverse reactions, an improvement in the quality of reporting of SRAEs in both the literature and spontaneous reporting systems is required. A greater awareness of the concept of drug related suicidality should be made more apparent in different medical specialties, so that physicians are inquisitive about medication exposure prior to a SRAE upon encountering cases. Suggestion of methods to improve reporting quality include: the introduction of follow up questionnaires to receive standardised information, the performance of causality assessments at regulatory centres, and the development of suicide registries are recommended.

WP 3: Establishing Biological Sampling Methodology for Investigation of Mediators of Suicidality

Background
Suicide is multifactorial in nature and literature evidence suggests that it is a complication of all existing psychiatric disorders. Numerous factors are thought to contribute to suicide such as hopelessness, impulsivity, aggression or a psychosocial crisis. Suicide is never the consequence of one single cause or stressor. Certain neurotransmitters, for example those belonging to the serotonin class are thought to play a role in suicidal ideation and behaviour. In particular, serotonergic input into a part of the brain known as the ventromedial prefrontal cortex is thought to play a key role in suicide behaviour. Literature evidence has also indicated that genetic factors, a deprived upbringing or childhood abuse, low cholesterol, cigarette smoking and substance abuse are associated with or induce lower serotonergic activity and this can be associated with suicidal behaviour. A reduction in serotonergic function in humans increases aggressive behaviour and impulsivity, where improvement in serotonergic function is thought to decrease such behaviours. At present there is no clinical data in children and adolescents in which all relevant biological data has been collected to explore mediators of suicidality and capture the putative molecular signatures of suicide ideation and behaviour. This WP was necessary to collect relevant biological data to investigate mediators of suicidality, including not only the medication of interest (and its metabolites), but also confounders such as indication for which the medication is prescribed (which may be at least partly indexed by genetic and epigenetic factors) and other confounders such as the ingestion of other substances (e.g. through substance abuse, as well as concomitant medications and dietary factors that may interact). Moreover, the type of samples that are feasible and acceptable to patients, carers, and clinical teams to collect from such cohorts, and fit for their intended purpose, may be different in children and adolescents compared to adults.

Overall Objective
The overall objective of this WP was to establish what types of clinical samples may be collected, by what methods, and at what frequencies in the clinical studies. The potential types of clinical samples included samples for DNA, concentrations of medications under study and their metabolites (therapeutic drug monitoring or TDM), urine drug screen (UDS), and metabolomics. The pilot work was conducted on samples for genetic analyses including methylation, TDM, and UDS, with any other type of samples being taken in order to investigate feasibility, and if feasible, store for future analyses.

WP 3 had six tasks:
Task 1: This task was to establish a method of sample collection, transport and storage (generation of a SOP) for DNA that was acceptable to patients, carers, and clinicians, and also produced DNA of adequate quality for genotyping.
Task 2: To genotype a few candidate markers of potential relevance to suicidality.
Task 3: To pilot the DNA sampling SOP i.e. with an appropriate sample treated with an antipsychotic.
Task 4: To conduct pilot analyses for the medications and their metabolites under study from both venous blood and blood spot samples, and to generate a SOP for the best method of sampling for this purpose for use in the clinical studies.
Task 5: To generate a SOP for sampling of urine for metabolomics.

Task 6: To generate a SOP for serial urine testing for UDS in children and adolescents.

Results
Tasks 1 – 3 were completed successfully i.e. a method was established and a SOP written. Task 4 was to conduct analyses of the medications being studied in WPs 7-9. Standards for analysis of Montelukast and its metabolites were obtained, and assays set up for medications of interest and their metabolites. Pilot work on blood spots proved to be unsatisfactory, and therefore work was broadened to include saliva sampling. The findings from the saliva sampling study indicated that a strong association existed between age and the variability observed in the concentration of DNA isolated from saliva samples, and showed that DNA concentrations rose proportionally with age, obtaining values 3.5-fold higher in the oldest age than in the youngest (Gassó P and STOP Consortium, 2014). In addition, significantly lower DNA quality was detected in DNA samples from children below 12 years and this fact should be taken account for a better standardization of the DNA isolation to ensure DNA banking in large-scale genetic studies involving children (Gassó P and STOP Consortium, 2014). Finally, a SOP for sampling for metabolomics (task 5) and for ascertaining substance abuse (task 6) was established.

Conclusions
- We showed that although the yield from 2.5 ml of saliva processed using Oragene.Dx® kit in adults is approximately half that from a 5 ml blood sample, the quality was good and "fit for purpose," specifically, for a range of genomic applications, including single nucleotide polymorphism (SNP) analysis, variable number tandem repeat (VNTR) genotyping, long-range polymerase chain reaction (long-PCR), and genotyping using microarray technology.
- Methylation assays were possible on saliva processed using Oragene.Dx® kit with the caveat that there were tissue-specific differences in methylation.
- The findings showed that for children <12 years of age, a modified extraction protocol should be employed.
- A SOP for DNA sampling in children and adolescents was generated.

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WP 4: Methodology – Psychosocial Mediators of Suicidality

Background
Suicide is one of the major causes of death worldwide, approximately one million people commit suicide each year worldwide (WHO, 2002). Moreover, suicide rates consistently increase from childhood to adolescence. Complete suicide is rare prior age 10 but during adolescence suicidal behaviour increases sharply. Suicidal behaviour is a matter of great concern for clinicians who deal with mental health problems of children and adolescents. Suicide prevention, especially in underage population is a priority for many countries. Clinicians need to know how to identify individuals at greatest risk for suicide (Bridge *et al*., 2006). Therefore, a reliable methodology for collecting comprehensive data on psychosocial mediators of suicidality for use in prospective clinical drug trials in child and adolescent populations is needed. Several biological, social, and psychological risk factors for suicide attempts during adolescence and childhood have been proposed. Previous research has documented that psychological and clinical factors are related to an increased risk for suicide.

Several psychological and psychiatric factors have been associated to suicidal behaviour. Major depressive disorder is associated with the higher risk for suicide attempt (Goldston *et al*., 2009). A previous suicide attempt is one of the strongest risk factors for repetition of suicide attempt (Hulten *et al*., 2001), suicide plans (McKeown *et al*., 1998) and complete suicide (Kessler *et al*., 1999). It is also widely documented that suicidal behaviour in children and adolescents may also be related to other psychiatric diagnoses such as, eating disorders, bipolar disorders and schizophrenia. Drug and alcohol use is also a predictor of a suicidal event (Brent *et al*., 2009). Moreover, an adverse event usually precedes a suicidal behaviour in young people. In children and adolescents stressful life events include but are not limited to family conflicts, changes of residence, romantic break-up, conflict with peers (bullying included) and academic failing.

Based on this information, a standardized tool for collecting comprehensive data on psychosocial factors for use in prospective clinical drug trials in child and adolescent populations is needed.

Overall Objective

Several social and psychological risk factors for suicide attempts during adolescence and childhood have been proposed. The aims of this work package were to first consolidate the existing evidence pertaining to the psychological and sociological risk factors for suicidal behaviours in children and adolescents and then to establish and test a reliable methodology for collecting comprehensive data on these risks for use in prospective clinical drug trials in child and adolescent populations.

Primary objectives:

1. To design a methodology for assessing psychosocial mediators (risk factors) of suicidality in children and adolescents including developing the suicidality-related psychiatric and medical illness assessment module and adaptation of clinical, temperamental, and life events tools.
2. To translate the rating scales into all the languages of the countries collaborating in the study and to carry out a first evaluation of the psychometric properties of the resulting scales.
3. To validate the above developed methodology through administering it to a large sample of children and adolescents treated and followed in different psychiatric settings and to establish the sensitivity, specificity and predictive value of the instrument.

Results

After reviewing the literature regarding risk factors for suicidality in children and adolescent, we developed a scale capable to assess them. The development of the scale was collaboratively done by CIBERSAM, KCL and FCRB. Five versions of the scale were developed: a version for children under 8 years, a version for children 8-11 years old, a version for adolescents, a version for parents, and a version for clinicians. To ensure that questions are appropriate for each target population, focus groups were carried out. In addition, suggestions from all members of STOP project were taken into account. The scale was developed simultaneously in Spanish and English, and then, translated and back translated in the other languages of the Consortium (German, Italian, French and Dutch).

The samples obtained from the cohort studies (763 children and adolescents) from the different centres participating in the study (King's College London (KCL), Stichting Katholieke Universiteit – Radboud university medical center (RUMC), Academisch Ziekenhuis Groningen (UMCG), Zentralinstitut für Seelische Gesundheit (CIMH), Universität Ulm (UULM), University of Dundee (UNIVDUN), Assistance Publique – Hôpitaux de Paris (APHP), Centro de Investigación Biomédica en Red (CIBER), Fundació Privada Clínic per a la Recerca Biomèdica (FCRB), Universitá a degli Studi di Cagliari (UNICA), and Centre Hospitalier Universitaire Montpellier (CHU)) allowed us to do psychometric testing of the instruments.

Sensitivity, specificity, predictive value and convergent validity of the instrument showed that the STOP Suicidality Risk and Resilience Scale (STOP-RRS) had to be split into the Suicidality Resilience Scale (SRS) and the Suicidality Risk Factors Scale (SRFS) and that some items had to be dropped in order to achieve acceptable psychometric properties.

Conclusions

In conclusion, the results showed that the SRS and the SRFS are comprehensive, rapid-to-use, HealthTracker™ based measures of suicidality risk and resilience factors for children, adolescents, parents and clinicians.

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WP 5: Development of Suicidality Assessment Scale

Background

The emergence of suicidality in patients receiving drug treatment is of concern because of the overall burden it produces and the possible link with completed suicide. However, there are currently no uniform requirements for defining, detecting and recording suicidality, and the presence of disease-related confounders could also be problematic. Indeed, medication-related suicidality might differ from psychopathology-related suicidality in terms of phenomenology, clinical expression and time course, and there may also be differences between children and adults.

Overall Objective

The goal of this WP was to develop a low burden, reliable and efficient screening tool for suicidal ideation and suicide risk in children and adolescents specifically addressed to capture the possible influence of medication side effects. The proposed instrument comprised two modules: Medication Module and Suicidality Module. Each of them comprises two self-report instruments, one for adolescents and one for children, as well as a further two instruments for parents and clinicians.

Results

Item Generation and Preliminary Scale Development

The development of the instruments followed the Food and Drug Administration recommendations for Patient-Centered Outcome Measures (PCOMS). The initial item pool for the instruments was based on potential screening questions from several sources, including previous literature, existing scales and the clinical experience of various experts. The instrument consisted of two modules, one that assessed suicidal ideation and behaviour (Suicidality Module) and another that specifically assessed medication side effects and their possible relationship with suicidality (Medication Module).

The initial items of the Suicidality Module were developed by considering the aspects assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner *et al*., 2007), the Classification of Suicide-Related Thoughts and Behaviour developed by Silverman and colleagues (Silverman *et al*., 2007) and other scales such as the Suicidal Ideation Questionnaire (Junior High School Version). The initial Suicidality Module included 14 items that enquired about suicidal ideation, suicide communication, suicide plans and suicidal behaviour. The initial Medication Module consisted of 46 items, each of which included the name of the side effect (e.g. akathisia), a description of the side effect and two questions, the first about the frequency of the adverse event and the second about the possible relationship between the adverse event and suicidal ideation.

Review by experts

These first drafts were discussed with a panel of experts from different European countries (Spain, UK, France, Italy, The Netherlands and Germany). After discussion with a panel of experts some items from the Medication Module were removed because there was no literature relating them to suicidality or were not prevalent in the clinical practice. Items in the Suicidality Module were also reviewed. Some changes were suggested and implemented to generate second drafts of the instruments.

Focus Groups

Patients' understanding was assessed by means of cognitive interviewing, a qualitative research tool used to determine whether concepts and items are understood by patients in the same way as instrument developers intend. To this end, several focus groups were conducted with adolescents, parents and children, and in each case they were presented with the second drafts of the instruments. Groups were small, consisting of 3 or 4 individuals, and participants were representative of the population usually seen in our clinic. With the permission of participants, all the group sessions were recorded with a video camera. Among patients who attended our clinic, ten adolescents aged between 13 and 17 years old, 9 children between 8 and 11 years old and 5 parents participated in the focus groups. Participants were asked a combination of standard probes and on-the-spot probes (verbal probing method). After each focus group the content of the videotapes was transcribed. The transcripts were analysed using the thematic analyses and cut-and-paste method, and a detailed summary report was written regarding each focus group. Several changes to the instruments were performed based on what was suggested in the focus groups. A clinician's version was also created based on the parents' and adolescents' versions. The two versions for adolescents were then modified to produce the versions for children aged between 8 and 11 years. Specifically, a 4-point Likert scale was used for the Medication Module, and some items of the Medication Module, such as that referring to sexual adverse events, were removed as it was considered that they did not apply to this age group. Nine children participated in the focus groups and several changes were also suggested.

Final agreement between the experts' version

The last version of the Suicidality Module was reviewed by the UK and Spanish experts, who agreed to add a further two items about suicide plans, namely 'preparatory acts' and 'reasons' in order to include all the components of suicidality and to map the C-CASA algorithm. The resulting versions designed for adolescents, parents and clinicians had five items referring to suicidal ideation, six items to suicidal behaviour, four to suicide plans and one to suicide communication. On the advice of the STOP

Scientific Advisory Board, three items referring to suicidal ideation were added, as they felt that the scale required some questions assessing low-level suicidality. Thus, the final versions of the Suicidality Module for adolescents, parents and clinicians consisted of 19 questions. All three versions included the same items and the same content, with a slight change in the questions depending on the respondent to make it clear that the questions were about the child/adolescent. The panel of experts decided to add a stand-alone item to ask about potential lethality to the clinician's version. This question was only visible if there was a positive answer to behaviour and there were no injuries associated to that behaviour. This item was not considered a part of the questionnaire and it was not considered in the analysis. The Suicidality Module for children comprised five items on suicidal ideation, two on suicide plans and three on suicidal behaviour. Two new items about suicidal behaviour were added to the children's version: 'aborted attempt' and 'undetermined suicide behaviour', in order to cover the C-CASA algorithm. The children's version thus had 12 items. Based on the advice of the STOP Scientific Advisory Board, we added two items capturing low-level suicidality for children, making the final version 14 questions long.

These versions were then translated into Dutch, French, German and Italian, before being back-translated into English. The instrument that specifically assessed suicidal ideation and behaviour was led by FCRB and called the 'STOP Suicidality Assessment Scale' (SAS) and the one that assessed medication side effects and their possible relationship with suicidality was led by KCL and was called the 'STOP Medication Side-effects Suicidality Scale' (MS^3). The definitive questionnaires were developed on the HealthTracker™ platform, an online multimedia platform with a suite of questionnaires for monitoring health that allow accurate measurements of change across a wide range of symptoms, adverse events, psychological functions and quality of life.

Screening questions

Since the investigators, the Scientific Advisory Board, and several Ethics Committees recommended reducing the burden of answering a large number of questions regarding suicidality in non-suicidal subjects, the experts then identified a set of four questions from the SAS that could be used as screening questions (three of them for use with children, and all four for use with adolescents, parents and clinicians). These items were selected because they assess low level suicidality. Using data from a subsample of patients who responded to all the questions, we checked that if a patient or parent answered "never" to all the screening questions they also answered "never" to all the remaining questions of the SAS. This subsample comprised a total of 53 children, 93 adolescents and their parents and clinicians who answered all the questions. A negative answer to all the screening questions would then be considered as a total score of "zero" for the entire SAS and MS^3 questionnaires, while one positive answer to any of these questions would automatically require the participant to complete the entire questionnaires. Experts ensured that the set of four screening questions for adolescents, parents and clinicians, and the three for use by children fulfilled this criterion.

Psychometric Properties of the SAS scale

The Clinician, Adolescent and Parent versions of the HealthTracker™ based SAS were based on 19 standardised items whilst the Child version of the SAS was based on 14 items. Very good internal consistency was found for clinicians (Cronbach's alpha: 0.950), adolescents (Cronbach's alpha: 0.962), parents (Cronbach's alpha: 0.944) and children (Cronbach's alpha: 0.915) versions. For the assessment of convergent validity, the C-SSRS was used. A strong correlation was found between the SAS and the C-SSRS for clinicians (r: 0.899), adolescents (r: 0.753), parents (r: 0.593) and children (r: 0.698). Moreover, the ROC area was good for clinicians (0.973), adolescents (0.890), children (0.890) and parents (0.856).

Psychometric Properties of the MS^3

For the HealthTracker™ based MS^3 scale, the Clinician version of the scale based on 26 items showed very good internal consistency (Cronbach's alpha: 0.941), however for items 25 ("stopped due to side effects") and 26 ("medication made symptoms worse"), the corrected item correlations were <0.200. For this reason, these two items were removed and the scale re-analysed. This 24 item scale also showed very good internal consistency (Cronbach's alpha: 0.943) and the corrected total item correlations were >0.200 for all the items.

Conclusions

- Three new scales in Spanish and English were developed to assess suicidality related to medication including different versions for children, parents, and clinicians.
- The new HealthTracker™ based scales were translated and back translated into German, Dutch, Italian and French.
- The first initial evaluation of the psychometric properties had been carried out administering the questionnaires to a sample of adolescents and children from Spain, France, Italy, Germany and England. These results have been presented in the ESCAP congress in Dublin July 2013 as a Symposium and two Posters at the ECNP congress in Barcelona October 2013.

- The new HealthTracker™ based scales were administered to a larger sample of children and adolescents obtained from the cohort studies (763 children and adolescents) from the different centres participating in the study (King's College London (KCL), Stichting Katholieke Universiteit – Radboud university medical center (RUMC), Academisch Ziekenhuis Groningen (UMCG), Zentralinstitut für Seelische Gesundheit (CIMH), Universität Ulm (UULM), University of Dundee (UNIVDUN), Assistance Publique – Hôpitaux de Paris (APHP), Centro de Investigación Biomédica en Red (CIBER), Fundació Privada Clínic per a la Recerca Biomèdica (FCRB), Universitá a degli Studi di Cagliari (UNICA), and Centre Hospitalier Universitaire Montpellier (CHU)) allowing us to establish psychometric validation of the new instruments.
- A factor analysis of the SAS was carried out and showed three factors (Suicidal Ideation, Plans and Preparations, and Suicidal Behaviours). The SAS scale is a comprehensive, rapid-to-use; HealthTracker™ based measure of suicidality for children, adolescents, parents and clinicians. It has shown good internal consistency and good convergent validity with the C-SSRS.
- The factor analysis of the MS^3 showed that it had to be split into two scales – the STOP-Medication Side-effect Suicidality Scale (MS^3) the STOP-Terminating Medication Scale (TMS). The MS^3 and the TMS are HealthTracker™ based PCOMs which are rapid, easy to use, and comprehensive, designed for use by children, adolescents, parents and clinicians. It allows the evaluation of aspects of medication side effects related to suicidality.

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WP 6: E-Monitoring and Data Capture using the HealthTracker™ platform

Background

It is widely documented that technology can enhance the lives of most individuals, especially those with neurodevelopmental disorders. HealthTracker™ is an existing web-based health-monitoring platform that has been developed using input from patients, parents and expert clinicians. HealthTracker™ is an established platform for online collection and storage of medical data that allows multi-modal presentation of questionnaires (including animated scale presentations for young children) and assists in automatically allocating questionnaires based on developmental level rather than chronological age. In addition, being web-based, it allows for more frequent assessment without clinic visits and allows real-time symptom monitoring and patient experience feedback about care being provided. The overarching goal of this Work Package (WP) was to provide a means to convert all the assessment and monitoring scales being used in STOP project onto the HealthTracker™ system. The aim will be to attempt to obtain MHRA device license for the purpose of the SPOTS scale in due course to exploit IP appropriately.

Overall Objectives

The objectives of this WP were:

1. To develop the medication characteristic recording function in the HealthTracker™
2. To develop the HealthTracker™ based STOP Suite of Suicidality Measures
3. To assist and train all Centres to use the web-based customized HealthTracker™ system
4. To provide maintenance and support for the HealthTracker™ system
5. To get the HealthTracker™ based STOP Suite of Suicidality Measures for Post-marketing Surveillance and Pharmacovigilance (beyond the completion of the project)

WP 6 had eight tasks:

Task 1: To develop the medication recording function in the HealthTracker™ platform to allow adding data of the medicines being used, including dose and compliance.
Task 2: To develop the HealthTracker™ based STOP Suite of Suicidality Measures.
Task 3: To translate all the questions into French, Italian, German, Spanish and Dutch in the HealthTracker™ suite.
Task 4: To customize the HealthTracker™ to allow data entry of all the clinical and trial variables necessary for cohorts 1 and 2 (WP7), cohorts 3 and 4 (WP8), cohorts 5 and 6 (WP9) and cohort 7 (healthy controls).
Task 5: To ensure that the customized HealthTracker™ is health data monitoring compliant.
Task 6: To assist and train all Centres to use the customized HealthTracker™ monitoring system.
Task 7: To provide helpline and support with respect to maintenance of the HealthTracker™ during the period of the STOP.

Task 8: To get the HealthTracker™ based STOP Suite of Suicidality Measures for Post-marketing Surveillance and Pharmacovigilance (beyond the completion of the project)

Results

Task 1 was completed and the medication characteristic recording function added to the online system and used in the main cohort studies of WP7, 8 and 9. In addition, the HealthTracker™ based STOP Suite of Suicidality Measures were developed and these questionnaires were validated and used in the cohort studies of WP7 (children with conduct disorder, psychoses or developmental disorders on atypical antipsychotics Risperidone [n=235) or Aripiprazole [n=156]), WP8 (children on Fluoxetine [n=128] or non-medication strategies [CBT, n=96] for depression) and WP9 (children on Montelukast [n=62] or other medication for bronchial asthma and respiratory allergy [non-Montelukast, n=103) as well as healthy controls (n=222). Tasks 3, 4 and 6 were completed and HealthTracker Ltd. provided support for the maintenance of the HealthTracker™ platform during the period of the STOP reporting. Task 5 is ongoing and will take a few months to complete because we have only just obtained the predictive algorithm, which is underlying the STOP new decisions making tool.

HealthTracker™ (https://www.healthtracker.co.uk) is ideal for post-marketing surveillance of medication as it can capture longitudinal data about behaviour, emotions, side-effects, cognitive functions, quality of life of both child and family along with details of all medication used as well as compliance. Recently, the Profile Of Neuropsychiatric Symptoms (PONS) scale (parent version) has been developed as a web-based Patient Centred Outcome Measures (PCOMS) on the HealthTracker™ system. This system can report on the frequency and impairment produced by neuropsychiatric symptoms and neurodisability in children, and optimises clinician time by helping to profile children that allows for proficient diagnostic decision (Santosh et al., 2015). The HealthTracker™ platform can also be used in epidemiological studies, pharmacovigilance and clinical trials.

In view of Post-marketing Surveillance and Pharmacovigilance it is proposed that true long-term side-effects of medication such as suicidality has the possibility of affecting long-term outcomes and will need much longer pharmacovigilance than 12 months (possibly till the young adulthood - age of 25 years). The HealthTracker™ platform (background) has allowed for the HealthTracker™ based STOP Suite of Suicidality Measures to be developed for use as a Post-marketing Surveillance and Pharmacovigilance tool (foreground) (task 8) and allowed for an improved method of recording which has resulted in better surveillance and risk assessment, and therefore, more effective management, intervention, treatment, and prevention of individuals at risk for suicide. This platform can be procured by regulatory authorities, researchers, pharmaceutical companies for pharmacovigilance, which will improve the detection and management of medication-related suicidality and reduce morbidity and mortality.

A snap–shop of participants' experience of HealthTracker™ by answering the question "Filling questionnaires online (using the HealthTracker system) made things easier" indicated that the majority (8/12) of participants in WP7 agreed or strongly agreed that filling questionnaires online using the HealthTracker™ system made the task easier. This trend was also observed in WP9 whereby of the 14 participants who answered the question "Filling questionnaires online (using the HealthTracker system) made things easier" 13 agreed or strongly agreed that completing the questionnaires online using HealthTracker™ made things easier.

In order to investigate patient's and parent's experiences and dilemmas, as well as their understanding and concerning their experiences and the research process, specific questionnaires with five choice fixed answer (strongly agree, agree, neither agree nor disagree, disagree, strongly disagree) about research knowledge (including ethical issues) and patient/parent feeling about the study were developed and randomly distributed. 100 parent's and 54 adolescent's questionnaires were collected.

In general the answers by adolescents and parents were similar but not identical with a few differences for specific Centres. In general, both parent and patients described the STOP study as interesting (with adolescents less enthusiastic than parents), reporting that the HealthTracker™ system made easier filling the questionnaires (but CIMH and CAMS parents were neutral), that participation to the STOP study helped parents but not patients to better understand suicidality, without increasing suicidal thoughts, worry, and anxiety. The majority of both adolescents and patients did not find it difficult to complete the questionnaires and stated they would like to participate in similar study again (about 50% of adolescents, 74% of parents). They also reported the participation to the study did not change the relationship with the clinical staff. Clinicians participating in the study also completed a similar questionnaire. The majority of them found difficult to recruit and to maintain compliance of study participants and they found difficult to get all the questionnaires completed. Half of the clinicians reported they would participate in similar study again.

A second open-answer interview was administered to 15 clinicians from five clinical centres. Qualitative analysis showed different feeling among clinicians, sometime also from the same clinical centre, on several issues. The majority reported that the participation to the STOP study increased their understanding of suicidality, decreased their fears and worries in approaching parents and adolescents on this topic, leading to a better consideration of risk and resilience factors, and helped parents and adolescents in dealing with the barriers in discussing suicidality (with parents more scared than adolescents in dealing with the

topic). Some clinicians, however, reported their approach to adolescents and parents did not change significantly, some recognized that suicidality was usually deeply investigated only when suspected. Almost all clinicians reported the use of an electronic tool such as HealthTracker™ significantly helped them to capture information about suicidality from parents and adolescents. Finally, clinicians also from the same centre disagreed about the difficulties for parents and patients in staying involved in a long term study: many clinicians reported the need of many reminders, with difficulties related to the number and the length of the scales, rather than to the topic.

Prediction Model - Suicidality Prediction and Optimising Treatment Scale (SPOTS)

One of the key objectives of this study was to develop a comprehensive cross-sectional assessment scale for the longitudinal monitoring of suicidality and its bio-psycho-social mediators (including psychopathology, other risk and protective factors, and medication characteristics) in children and adolescents.

The adolescent suicidal behaviour prediction model was done on a split half sample that took into consideration the gender, the duration of the medication and age of the patient at the time of recruitment. These were imputed into the prediction model as covariate factors. This model was tested and validated in the other half of the sample (results to be described elsewhere).The adolescent split half model in cohorts 1, 2 3 and 4 (WP7+WP8) yielded an r^2 value of 0.459 based on 491 observations (n). For cohorts 1 and 2 (WP7), the r^2=0.433 (n=272) and for cohorts 3 and 4 (WP8) the r^2=0.764 (n=219). The remaining sample from the split-half procedure was used to estimate the psychometric properties of the new Suicidality Prediction and Optimizing Treatment Scale (SPOTS). These results showed very good internal consistency for the adolescent version of the SPOTS and a strong correlation between the SPOTS and the C-SSRS for clinicians and adolescents; however, the correlation was fair for parents. The Exploratory Factor Analysis for the adolescents' version showed a 5-factor model. Based on the pattern of symptom domain loading the 5 factors were named: (1) Suicidal Thoughts, (2) Medication Related Depressive Mood and Thinking, (3) Medication Related Somatic Symptoms, (4) Medication Related Mood Dysregulation and (5) Suicidality Related Stressors. The ROC area was the highest for the clinician version and good for the adolescent and parent versions of the scale.

The list of domains for the adolescent model is shown below:

1. Thoughts of being dead
2. Thoughts of hurting self
3. Thoughts of ending life
4. Thoughts of harming self to feel better
5. Thoughts to end my life but would not
6. Thoughts of being certain to end my life
7. In ability to control my thoughts of killing myself
8. I have started to plan how to end my life
9. I have made preparations to kill myself
10. Am worried about being judged socially
11. Medication related hypomanic symptoms
12. Medication related self-injury
13. Medication related nightmares
14. Medication related daytime drowsiness
15. Medication related somatic symptoms (aches and pains)
16. Medication related inattention
17. Medication related anger/temper
18. Stopped medication due to side-effects
19. Chronic physical illness as risk
20. Bullying as risk
21. Chronic Pain as risk
22. Depressive thinking as risk
23. Anxiety at risk
24. Low self-esteem as risk
25. History of suicide attempt
26. Family history of suicide as risk
27. Change of residence as risk

The HealthTracker™ based STOP Suite of Suicidality Measures (consisting of the STOP-Suicidality Assessment Scale [SAS], the STOP-Medication Suicidality Side-effects Scale [MS^3], STOP Terminating Medication Scale [TMS], STOP Suicidality Resilience Scale [SRS], the STOP Suicidality Risk Factors Scale (SRFS] and the Suicidality Prediction and Optimising

Treatment scale [SPOTS]) was developed to produce a valid, rapid to use, HealthTracker™ based measure of Suicidality detection in children, adolescents, parents and clinicians.

Internal consistency was good for all versions of the STOP-Suicidality Assessment Scale (SAS). In addition, there was a strong correlation between the total scores for the clinicians, adolescents, parents and children's SAS and the gold standard clinician-rated Columbia Suicide Severity Rating Scale (C-SSRS). The results from the Receiver Operating Characteristic (ROC) analysis indicated that in general the scales were specific in reporting the measures but were varied in their ability for assessing suicidality. The ROC analysis showed that the SAS is a valid instrument for assessing suicidal ideations, plans and preparations and suicidal behaviours for adolescents. For parents, whilst the instrument was good in detecting suicidal ideations, it was modest for detecting suicidal behaviours but weak in detecting suicidal plans and preparations. Conversely, the clinician version was excellent in detecting suicidal ideation, good for detecting suicidal behaviours and modest in detecting suicidal plans and preparations.

The results showed that the originally planned HealthTracker™ based STOP-Medication Suicidality Side-effects Scale (MS^3) had to be split into two scales – the Medication Suicidality Side-effects Scale (MS^3) and the Terminating Medication Scale (TMS). For the MS^3 scale, internal consistency was good for all versions of the scale. There was however, a poor correlation between the total scores of the clinicians, adolescents, parents and children's scale and the clinician-rated C-SSRS total score. The ROC analysis indicated that the MS^3 scale was a valid instrument in detecting medication induced emotional and behavioural dyscontrol. Amongst the versions the adolescent was the best in detecting these changes followed by the parent and clinician version. For the TMS, good internal consistency was found for the clinician version but low internal consistency was shown for adolescents and parents versions. Exploratory factor analysis showed a 1-factor model. The ROC area was modest for all versions of the scale in that although the scales were high in specificity, they were rather weak in detecting the measure

Based on the psychometric analyses, the originally intended HealthTracker™ based STOP-Risk and Resilience Scale (RSS) was split into the Suicidality Resilience Scale (SRS) and the Suicidality Risk Factors Scale (SRFS). Good internal consistency was found for clinicians, adolescents and parent versions of the scale. Exploratory factor analysis revealed a 2-factor model (1) External Resilience Factors and (2) Internal Resilience Factors. Overall the accuracy of the adolescent, parent and clinician version to predict resilience was modest In general, factor 1 'External Resilience Factors' showed a better accuracy in predicting resilience in the parent and clinician version when compared to the adolescent version. For the SRFS, fair internal consistency was found for clinicians whilst good internal consistency was seen for adolescents and parents versions. The overall ROC area was good for clinicians but modest for adolescents and parents. The Exploratory Factor Analysis for the clinicians' version of the SRFS showed a 4-factor model and based on the pattern of symptom domain loading the 4 factors were named as: (1) 'Depression', (2) 'Chronic stress', (3) Historical risk and (4) 'Bullying'. Further ROC analyses showed that the predictive value of factor 1 'Depression' was the highest for all versions of the scale.

The primary output of the STOP study was to develop a predictive model for the longitudinal monitoring of suicidality and its bio-psycho-social mediators (including psychopathology, other risk and protective factors, and medication characteristics) in children and adolescents aged 8-18 years. This study succeeded in developing this model and the list of domains were developed into a single scale called "**Suicidality Prediction and Optimising Treatment Scale" (SPOTS)** for adolescents, clinicians, parents and children. The adolescent predictive model of suicidal behaviour was shown to be fair (r^2=0.459) for cohorts 1, 2, 3 and 4 (i.e. children with conduct disorder, psychoses or developmental disorders on atypical antipsychotics Risperidone or Aripiprazole [WP7] and children on Fluoxetine or non-medication strategies [CBT] for depression [WP8]). This was also true (r^2=0.433) for cohorts 1 and 2 i.e. those prescribed antipsychotics (Risperidone and/or Aripiprazole [WP7]). However, where the primary diagnosis was depression (i.e. those prescribed Fluoxetine or and/or CBT [WP8]) the predictive value of the model was good (r^2=0.764). Very good internal consistency was found for the adolescent (Cronbach's alpha: 0.926) version of the SPOTS and a strong correlation was found between the SPOTS and the Columbia Suicide Severity Rating Scale, (or C-SSRS) for clinicians (r: 0.801) and adolescents (r: 0.683), however, the correlation was modest for parents (r: 0.485). The Exploratory Factor Analysis for the adolescents' version showed a 5-factor model. Based on the pattern of symptom domain loading the 5 factors were named: (1) Suicidal Thoughts, (2) Medication Related Depressive Mood and Thinking, (3) Medication Related Somatic Symptoms, (4) Medication Related Mood Dysregulation and (5) Suicidality Related Stressors. The sensitivity and specificity was very good for all versions of the scale. Amongst the scales, the ROC area was the highest for the clinician (0.912) version followed by the adolescent (0.825) and parent (0.763) versions.

HealthTracker Ltd has submitted an enquiry to the MHRA to confirm the device classification of the STOP Drug-Safety scale (SPOTS). The device might be either Class 1 or Class IIa. The requirements for Class IIa are stricter, and dictate other steps such as ISO 13485 implementation and Notified Body involvement. These steps all precede a CE marking proposal. Once this

scoping exercise is complete (HealthTracker Ltd are currently employing consultants from the Emergo Group to assist with this) we will be able to fully detail what the implications for the next steps are. It is impossible to predict the amount of work and subsequent costs to reach definitive CE marking, until this initial piece of work is complete.

Conclusions

Taken together the results indicate that both parent and patients found the STOP study interesting (with adolescents less enthusiastic than parents), reported that the HealthTracker™ system made it easier in completing the questionnaires and that participation to the study helped parents (but not patients) to better understand suicidality, without increasing their suicidal thoughts, worry, and anxiety. The majority of clinicians reported that participation to the STOP study increased their understanding of suicidality, decreased their fears and worries in approaching parents and adolescents on this topic, leading to a better consideration of risk and resilience factors; they also reported the participation to the study helped parents and adolescents in dealing with the barriers in discussing suicidality (with parents more scared than adolescents in dealing with the topic). In summary:

- The HealthTracker™ based STOP Suite of Suicidality Measures (SAS, MS^3, TMS, SRS and SRFS) were developed to assess suicidality and its mediators. These questionnaires were validated and used in the cohort studies of WP7, 8 and 9.
- The HealthTracker™ based presentation of the scales allowed an efficient method of skipping unnecessary questions, by having screening questions for specific topics. This ensured much better scale completion as it was very time efficient and was user friendly.
- For subjects in WP7 and WP9 who answered the question" Filling questionnaires online (using the HealthTracker system) made things easier", the vast majority agreed or strongly agreed that completing the questionnaires online using the HealthTracker™ system made the task easier.
- The development of a simple to use scale, the post-marketing surveillance and pharmacovigilance tool (Suicidality Prediction and Optimizing Treatment Scale [SPOTS]) allows for the HealthTracker™ platform based algorithm to predict degree of risk for suicidal behaviour during treatment in mental health settings in children and adolescents. This IP will be exploited in due course.
- The HealthTracker™ platform based set of suicidality measures can be procured by regulatory authorities, researchers, pharmaceutical companies for pharmacovigilance using existing agreements for Background and Foreground IP use, which will improve the detection and management of medication-related suicidality and reduce morbidity and mortality.

References

Santosh PJ, Gringras P, Baird G, Fiori F, Sala R. (2015). Development and psychometric properties of the parent version of the Profile of Neuropsychiatric Symptoms (PONS) in children and adolescents. BMC Pediatrics DOI: 10.1186/s12887-015-0376-x

WP7 Suicidality in Prospective Cohort Study of Children and Adolescents being treated with Risperidone or Aripiprazole

Background

Suicide and suicide attempts by children and adolescents are a major public health problem and have long been a matter of great concern to modern society, particularly for clinicians who deal with mental health problems of children and adolescents. During the mid-adolescent years, the incidence of suicide attempts reaches a peak and mortality from suicide is the third leading cause of death. Prevention of suicide, particularly suicide in young people, is a health priority in a number of countries.

Suicide is one of the major causes of death worldwide and suicide rates vary according to region, sex, age, time, ethnic origin, and, probably, practices of death registration. Most people who die by suicide have psychiatric disorders, notably mood, substance-related, anxiety, psychotic, and personality disorders, with high rates of comorbidity. Since reportedly less than half of young people who have committed suicide have received psychiatric care (Pelkonen & Marttunen, 2003), broad prevention strategies are essential in healthcare and social services. In particular, clinicians need to know how to identify individuals at greatest risk for suicide.

There is a lack of knowledge about the factors that make some children and adolescents more vulnerable than others to short-term and long-term suicidal ideation, and the effect of medication have not been assessed systematically. There are no clinical cohorts of children and adolescents in which all relevant mediators have been simultaneously collected in order to study the prevalence of suicidality.

The emergence of suicidal ideation and suicide related behaviour in patients receiving drug treatment is of concern because of the overall burden of these conditions and the possible link with completed suicide. Unfortunately, the lack of uniform requirements for defining, detecting and recording suicidal ideation, suicide related behaviour and completed suicide creates difficulties in comparing studies (Reith and Edmonds, 2007). There is some evidence of an association between some medication use (e.g., serotonin-specific reuptake inhibitor [SSRIs] and other newer antidepressants, atomoxetine, antiepileptics, Montelukast) and treatment-related suicidal ideation and suicide-related behaviour in children and adults. Antipsychotic treatment may lead to akathisia and drug-induced extrapyramidal symptoms which in turn have traditionally been associated with depression and suicidality (Holzer and Eap, 2006) and further lead to dysphoria (Voruganti and Awad, 2004). Dysphoria is a subtle and under-recognized side-effect of antipsychotic drugs that encompasses a variety of unpleasant subjective changes in arousal, mood, thinking and motivation induced by antipsychotic medications. Dysphoric responses typically occur early during treatment and may persist over time, leading to adverse clinical consequences such as treatment non-adherence and increased suicidality. Risperidone is the most widely prescribed antipsychotic agent in children and adolescents. Unlike psychopathology related suicidality, medication related suicidality may be associated with emergence of suicide related ideation and behaviour over different timeframes based on possible differences in drug pharmacokinetics.

Overall Objective
The overall objective of this work package is to explore the moderating and/or mediating risk and resilience factors of suicidality in children and adolescents with severe psychopathology who are being treated with antipsychotics such as Risperidone and Aripiprazole, and to identify the rates of suicidality reported in those taking different medication

Results
The t-test statistics for cohorts 1 and 2 i.e. children on atypical antipsychotics Risperidone or Aripiprazole (WP7) showed significant baseline differences between Risperidone and Aripiprazole in the clinician SRFS and PONS scale (see Table 3.1C).

Conclusions
For WP7, involving cohorts 1 and 2, the Clinician version of the SRFS and the PONS scale showed a significant difference in comparison to the Adolescent and Parent versions. This finding could suggest that the clinician version of the SRFS and PONS scale might be more sensitive in teasing out pertinent information in this population (i.e. those prescribed antipsychotics) in comparison to the adolescent and parent versions.

References
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Voruganti LP, Awad AG. (2004) Is neuroleptic dysphoria a variant of drug-induced extrapyramidal side effects? Can. J. Psychiatry. 49: 285-9.

WP 8: Suicidal Behaviour in a Prospective Observational/Naturalistic Cohort Study of Children and Adolescents Treated with Fluoxetine and Psychosocial Treatments (CBT) in Europe (EU): Piloting New Methods/Tools

Background
Suicidal behaviour/suicidality is considered an adverse event and major issue in the treatment of children and adolescents with psychotropic medication, with SSRIs and SNRIs in particular. Further, suicidal behaviour is an important public health concern since it is associated with increased mortality and morbidity in patients, may have major impact on family, friends and society in general and on socioeconomic costs as well. There are conflicting findings with respect to the increased risk of suicidal behaviour (or suicide-related events) associated with antidepressant medication depending both on design (randomized controlled studies, observational trials; length of observation) and methodology (outcome parameters: suicidal ideation, suicide attempt/suicide) aspects (Simon et al., 2006; Vitiello et al., 2009). Methodologies are needed to improve both estimation of the risk and early detection of the association

Overall Objective
To compare the effect of the antidepressant compound Fluoxetine on the risk of 'suicidal behaviour' (rates) to non-medication approaches (cognitive behaviour therapy (CBT), psychotherapy, psychoeducation, etc.) in treated in- and outpatient children and adolescents investigated in a prospective, naturalistic/observational 52 weeks study.

Results
The t-test statistics for cohorts 3 and 4 i.e. children on Fluoxetine or non-medication strategies (CBT) for depression (WP8) showed significant baseline differences between Fluoxetine and CBT in the SRS and PONS scale for the parent and clinician versions of the scale respectively (see Table 3.1D).

Conclusions
The results for the t-tests indicated that amongst the version of the scales, significant baseline differences were noted for the parent version of the SRS and clinician version of the PONS scale which could suggest that where the primary diagnosis was depression (i.e. those prescribed Fluoxetine and/or CBT), these scales were more sensitive.

References
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Vitiello B, Brent DA, Greenhill LL, et al. (2009). Depressive Symptoms and clinical status during the treatment of adolescent suicide attempters (TASA) study. Journal of the American Academy of Child and Adolescent Psychiatry 48: 997-1004.

WP 09: Mental health in Children and Adolescents taking Medication for Asthma or Respiratory Allergy

Background
In recent years, there has been an increase in the perception that certain prescription medications have a causative link to increase the risk of suicide. Montelukast is a potent leukotriene receptor antagonist that is administered orally for the treatment of mild to moderate persistent allergic rhinitis and allergic reaction disease. Side effects emerging from post marketing surveillance studies include Churg-Strauss syndrome (an autoimmune condition that causes inflammation of blood vessels), dream abnormalities, drowsiness, irritability, restlessness and insomnia. Recent evidence has suggested that there is an association between Montelukast and adverse physical and emotional outcomes in young people. In recent years, case reports linking Montelukast treatment to behavioural, emotional and mental health outcomes have been received by the European Medicines Agency (EMA). Notably, in 2005 a Swedish drug report showed that among the 30 most commonly used drugs in children; Montelukast had the greatest number of safety reports. In that report, the vast proportion of children were less than 5 years of age and experienced adverse drug including nightmares, sleep disorders, fatigue, anxiety and aggressiveness. In 2007, a completed suicide was linked to the use of Montelukast. The media reported that a teenager took his life in < 3 weeks after starting treatment with Montelukast. The concern about this potential side effect prompted the FDA to issue a warning and initiate a systematic review of the literature with regard to suicidality in those taking Montelukast (27 March 2008). Other medications with similar mechanism of action (e.g., zafirlukast and zileuton) were also included in the review by the FDA.
Despite these data, there is paucity in the literature investigating the association between Montelukast and adverse mental health outcomes in children. In view of this, the overarching aim of WP 9 was to address this gap in the research literature and to validate suicidality measures in children with a chronic physical illness, such as bronchial asthma or respiratory allergies, using the STOP-Suite of Suicidality Measures that that consists of the STOP-Suicidality Assessment Scale (SAS), the STOP-Medication Suicidality Side-effects Scale (MS^3), STOP Terminating Medication Scale (TMS), STOP Suicidality Resilience Scale (SRS) and the STOP Suicidality Risk Factors Scale (SRFS). These outcome measures were hosted on the HealthTracker™, a web-based multi-modal health monitoring system, and each of the above measures were developed taking into account the developmental level of children, the appropriateness of questions asked and the suitability of response options. There were different versions of the scales available for children aged 8 to 11 years and 12 to 18 years; parents or carers; and clinicians. The eventual goal of this suite would be to establish it as a pharmacovigilance tool that will be further developed to allow for alert systems to be set up to warn clinicians about increased suicidal risk in children and young persons, allowing for early intervention.

Objectives

Primary objective

- To use a mental health monitoring package in the general paediatric acute care setting to show feasibility in assessing the risk of adverse mental health outcomes associated with treatments (including Montelukast) for bronchial asthma and respiratory allergies in children and adolescents, including suicide, and other psychiatric morbidity in relation to this drug.

Secondary objectives

- To study an established THIN* data set of 5% of the UK 'population which records exposure to Montelukast and codes all associated mental health morbidity to understand what is already known of any ill effects in the under 18 age group. *The Health Improvement Network (THIN) contains anonymised computerised information entered by general practitioners in the UK. Data on around 2.9 million active patients are systematically recorded and sent anonymously to THIN. THIN collates and organizes this information in order for it to be used for research. The computerised information includes demographics, details from general practitioner's visits, diagnoses from specialist referrals and hospital admissions, and the results of laboratory tests. Prescriptions issued by the general practitioner are directly generated from the computer. The Read classification is used to code specific diagnoses, signs and symptoms; this is based on the WHO ICD-9 classification. A drug dictionary based on data from the MULTILEX® classification is used to code drugs. The latest dataset contains information on over 7.7 million patients from 429 general practices in the UK which use the Vision software system to record their consultations.
- To develop a consensus evidence-based clinical guideline to aid the prevention, early identification and management of adverse psychiatric morbidity associated with treatments for bronchial asthma and allergic reaction disease.

WP 9 had nine tasks:
Task 1: Preparatory activity with prior approvals
Task 2: Study of established dataset in order to interrogate THIN database with respect to quality and consistency of recording/ coding exposure and outcome variables.
Task 3: Study of children in a pragmatic general paediatric setting with bronchial asthma or allergic reaction disease given any medication (including Montelukast)
Task 4: Database variable manipulation and recoding as required to support the Statistical Analysis Plan (SAP).
Task 5: Performance of Statistical Analyses according to SAP; potentially secondary exploratory analyses based on data and findings.
Task 6: To continuously monitor the study regarding adherence to timelines and deliverables.
Task 7: To hold consensus guideline conferences and write the guideline report.
Task 8: To generate the final WP report, suitable for submission to the EMEA.
Task 9: To publish the results for the study in primary papers in international journals.

Results
The t-test statistics for cohort 5 and 6 (children on Montelukast [Montelukast] or other medication for bronchial asthma and respiratory allergy [non-Montelukast], WP9) revealed no significant baseline differences between Montelukast and non-Montelukast for the adolescent, parent or clinician versions of the different scales (see Table 3.1E).

Conclusion
The t-tests indicated that there were no significant baseline differences between Montelukast and non-Montelukast group in suicidality measures.

<u>WP 10: Training</u>

Background
This WP was responsible for monitoring the adherence to GCP guidelines concerning training procedures. Training was provided to ensure appropriate conduct of the trial in terms of assessment instruments and procedures including their precise application, evaluation and documentation of results. The adherence to GCP guidelines concerning training procedures and especially conduct of several studies was of utmost importance.

Overall Objective
The overarching goals of the training WP were to ensure appropriate conduct of the trial in accordance with GCP in regard to the assessment tools and to co-ordinate the training.

Results
In the run-up to the study start, the team around WP 10 participated in creating the project website, in preparing the kick-off meeting and also contributing to the development of the new scales and working on their translation into German – and together with our colleagues from concentris – back-translation. Considering formal aspects, the WP team annually checked the GCP certificate of the study staff and offered an alternative way to reach this based on an approved online course. The training offered consisted in written guidelines the most important instruments and two training workshops for the study personnel, each of them consisting of two days. During these training sessions each assessment was introduced and its purpose explained. With regard to an intended maximum certainty of use, the participants were provided with probe questions wherever reasonable and encouraged to discuss relevant details. With regard to the HealthTracker™ system and after an introduction in its application during the training workshops, a specific training in HealthTracker™ was offered under the lead of the Coordinator and his team. On the second training workshop, an inter-rater reliability related to the various aspects of suicidality required in the application of the C-SSRS was created. Both training workshops also provided an opportunity for colleagues to meet each other personally and therefore to create a lively basis for doing research together within a European network.

Conclusions
In summary, the implementation of the training for the various aspects of the project was successful. The WP lead and team were involved in various elements of the STOP project.

WP 11: Ethics

Background
This WP was finalized to ensure that medical-ethical considerations were integrated in all the studies of the project. Considering that suicide and suicidal ideation are among the more potentially severe medication induced adverse events, that most important risk factor for suicide remains depression and paradoxically the use of antidepressant medications that have been linked to an increase in suicidal ideation. The WP not only managed that all the studies were conducted according to the principles of ICH-GCP and legal regulations of the European Union and/or national legislation, but also investigated the personal feelings and the degree of satisfaction of the participant of the studies, administering specific questionnaires to patients, parent and clinicians, as well as an open answer interview to a group of participating clinicians.

Overall objectives
1. Allow appropriate Informed consent (Parent/ guardian) and assent (child/adolescents) (Tasks 1, 2,4,5)
2. Protection of research participants' confidentiality (Tasks 2 and 3)
3. Care and protection of research participants (Tasks 6, 7, 8)
4. Investigate the experience of taking part in paediatric psychopharmacology research (Tasks 9, 10)

Results
With the fundamental collaboration of the colleagues form the King College of London and from the University of Ulm, as well as the other partner of the projects, the following tasks were carried out:
Task 1, 2, 3 were completed:

Discussion of ethical aspects in the proposed trials, preparation of guidelines for protecting confidentiality and privacy of data of the patients and appointment of an Independent International Advisory Data Monitoring and Safety Board (IIADMSB). After discussing the crucial ethical aspects of investigation suicidality in a sensitive population of children and adolescents two specific guidelines were developed on the protection of children's personal data and on collection, storage and use of children's biological samples, respectively. A specific IIADMSB was appointed to discuss the content of the guidelines as well as all the ethical components of the studies; the IIADMSB includes Prof. Eric Taylor, Drs Benedetto Vitiello and Alessandro Serretti.

The guideline on protection of children's personal data included the requirement for data quality (purpose the data collection, their features, timing of retention), Legitimacy of processing data, Security and protection of the Rights of data subjects (safe retention, accession and the right of objecting).

The guideline on collection, storage and use of children's biological samples reported and discussed the legitimacy of collecting and using biological materials, the security of biological materials and the rights of data subject, as well as two appendices on

aspects to consider for writing a genetic research protocol and a genetic research informed consent, respectively. Guidelines may be downloaded at the study website (http://www.stop-study.com/index.php/publications/)
Task 4, 5, 6 were completed:
Survey specific modalities for informed consent procedures in each partner EU country, preparation of information sheets, training of study sites on GCP- informed consent procedures (in collaboration with WP 11).
A specific questionnaire was prepared in order to define the specific national provisions for clinical trials, the specific rules for obtaining informed consent from parents and assent from children and adolescents, the logistic structure of the Institutional Review Board/Ethic Committee (local/ hospital, regional, national) and the specific division of duties among central and local IRB/EC; specific information on national modalities for documenting investigator research experience, for defining the nature of observational(in interventional) studies and for national study registration were also collected.

Although many general rules on informed consent/ assent were similar all over Europe, specific national modalities were found at the moment of the survey (March 2011) for documenting investigator research experience, certifying certification for GCP and National registration of the clinical trials. Detailed definitions varied in different countries and some time (especially in Italy) also for individual EC. Following the indication of the survey, information sheets and informed consent forms for the new suicidality questionnaires have been developed. Specific ethical issues for the different protocols were extensively discussed between partners and with the member of the IIADMSB. Training on GCP (including ethical aspects) was performed on-line and some specific controversial issues discussed during the training sessions organized by WP 11.

Task 7: Applications for the IRB of each study site
A standard informed consent form, with specific versions for parents, children and adolescent and for specific studies (validation study; Risperidone/ Aripiprazole, Fluoxetine/CBT, Montelukast studies and controls) were prepared: site-specific, minor changes were implemented according to specific requests from local Ethic Committees (i.e. compensation for participation to the study, allowed in some counties, illegal in some others). Information sheets and informed consent were then submitted and approved by the national/ site IRB for the first for the validation study, than for all the specific medication/CBT studies and for control subjects.

Task 8, 9, 10 were completed and was centred on 'Qualitative research into the ethical issues involved in paediatric psychopharmacological research, experiences of taking part in paediatric psychopharmacology research.'

Conclusions
Although the majority of both adolescents and patients did not find it difficult to complete the questionnaires and stated they would like to participate in similar study again (about 50% of adolescents, 74% of parents), many clinician reported the need of many reminders to parents and patients in order to complete the scales and to stay involved in a long term study; patient and parent difficulties appeared related to the number and the length of the scales, rather than to the topic, suggesting the opportunity of refine the scales to a shorter version and, probably to provide an electronic reminder.

WP 12: Dissemination

Background
It is important to begin with asking the question 'What is dissemination?' Wilson et al. (2010) define 'dissemination' as: "a planned process that involves consideration of target audiences and the settings in which research findings are to be received and, where appropriate, communicating and interacting with wider policy and health service audiences in ways that will facilitate research uptake in decision-making processes and practice." The dissemination WP was involved in collecting information about the STOP project in terms of progress and results, under supervision of the study board. The WP team was also responsible for the further development and regular updating of the dissemination and exploitation strategy. Dissemination activities occurred before, during and after the completion of the study.

Overall objective
Primary objective
- Dissemination of project progress and results

Secondary objectives
- Coordination of the further development and regular updating of the dissemination and exploitation strategy.
- Generation and diffusion of information assets for investigators and participants.

- Identification of relevant target groups for dissemination of aims, methods and results of the STOP project and related topics (diagnosis, evidence-based practices, paediatric clinical trials)
- Communication with professionals, patient organizations and general public.
- Coordination of publication strategies.

Results

Dissemination procedures and material

The dissemination processes were defined by a strategic plan, validated during the STOP kick-off meeting. Our first activities were to collect foreground information about STOP topics, with a main focus on suicidality in children and adolescents, medication related suicidality. Our objectives were to target mental health professionals, researchers and policy makers but also parents and young people and to provide appropriate and up-to date knowledge and references. In parallel, we also participated in communication and training activities inside the STOP consortium.

This foreground information was disseminated through different means:

- the STOP study website: http://www.stop-study.com/
- STOP consortium meetings: training sessions, Steering Committee and General Assembly meetings
- STOP toolkit: project summary, flyers, posters
- Local scientific communication: professionals workshops, staff meetings
- International scientific communication: congresses and publications (detailed below)

The STOP study website was launched in May 2011 and was organised in two parts:

- The first part is accessible to the public and contains the foreground information, a summary of STOP objectives and main studies, a description of the STOP consortium with links to all participating organisations. A section for mental health professionals and researchers provides a literature review about suicidality, medication-related suicidality with references whereas the general public and families/young people will find appropriate and resource-oriented information about suicidality. A section was also designed that specifically focussing on suicide prevention and helpful attitudes towards children and adolescents with suicidal ideation or at-risk behaviour. Every WP leader contributed to this content by providing links to national resources for suicide-prevention. This public website also contains summaries of the scientific communication activities and publications. As more STOP publications are expected, the web-site will be updated regularly. The website content is available in five European languages: English, German, French, Dutch, and Italian. Communication between the STOP consortium and the general public was facilitated through an email address.
- The second (internal) part of the website is password protected and only accessible for the STOP consortium members. It contains confidential information, more specific dissemination material, minutes and presentations of the STOP consortium meetings, newsletters and training material. It also helped monitor tasks and activities per WP that was updated regularly.

Dissemination activities: first steps

During the preparation of the STOP main studies, the project was communicated to international and national scientific societies and health authorities/policy makers. In UK, the STOP procedures of monitoring and tracking suicidality over time served as a template for the NICE guidelines. From the beginning, the STOP study has received support from the ECNP through the ECNP Network initiative http://www.ecnp.eu/about-ecnp.aspx. Progress of STOP study has been reported during the yearly meetings of the ECNP Child and Adolescent Neuropsychopharmacology Network.

Scientific dissemination activities: international congresses

The foreground information and the objectives/methods of the STOP project were communicated at different international congresses.

1) 20th European Psychiatric Association (EPA) congress Prague 3-6 march 2012: Title of the Symposium:
Medication related suicidality in children and adolescents: assessment, information and ethics.
Chair: Dr Paramala Santosh, UK Co-Chair: Dr Ulrike Schulze, GERMANY

Presenter:

- Multidimensional assessment of suicidality in children and adolescents Josefina Castro-Fornieles, SPAIN

- Development of an online assessment tool for medication monitoring Paramala Santosh, UK
- Ethical issues in paediatric pharmacological trials Alessandro Zuddas, ITALY
- Medication related risks: a challenge for patient/family information Diane Purper-Ouakil, FRANCE

Summary: Medications having been related with medication related suicidality are used in children and adolescents who may have illness that itself predispose them to suicidal ideation or behaviour. There also is insufficient data available about the time-course of medication related suicidality and what happens to it over the long-term. Further, there is insufficient data available about medication related suicidality in paediatrics since there is evidence to suggest that paediatric populations may represent a vulnerable group, compared to adults. Therefore, development of specific assessment tools, able to distinguish medicated related from diseases related suicidality is a key issue for research and clinical practice. This symposium focused on new assessment tools for medication related suicidality and on the critical issues of ethics and information about medication risk/benefit ratio.

2) International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP) congress, Paris 24 July 2012. STOP symposium: Medication related suicidality in children and adolescents

Presenter:

- Detecting signals for medication related suicidality : N Iessa, M Murray, K Star, P Santosh, I Wong, UK
- Psychosocial factors associated with suicidality in children , C Arango SPAIN
- Medication related suicidality : early recognition and assessment, J Castro-Fornieles, I Flamarique, I Mendez, S Romero, SPAIN
- Antidepressants and suicidality : RW Dittmann, GERMANY

In this symposium first results from WP 2 were presented. These results originated from an analysis of Individual Case Harm Reports (ICHRs) in children aged 2–17 years (up to February 2010), extracted from a worldwide database of spontaneous reports of suspected adverse drug reactions, VigiBase, maintained by the Uppsala Monitoring Centre (UMC).

3) ECNP congress Vienna, 13-17 October 2012
A STOP communication was organised within a symposium of the ECNP-Network Initiative chaired by Jan K Buitelaar from the Netherlands and Alessandro Zuddas from Italy.
Suicide in children and adolescents treated – and not treated – with psychotropic drugs: myths and truths
Paramala J. Santosh, United Kingdom

4)15th International ESCAP congress July 2013–STOP symposium: Innovative approaches in the study of paediatric drug-related suicidality

Presenter:

- The Suicidality: Treatment Occurring in Paediatrics (STOP) studies – objectives and methods; Paramala J. Santosh, UK
- Pharmacogenomic studies in children and young people to elucidate biomarkers of suicidality ; Sarah Curran et al. UK
- Cross-cultural validation of the STOP suicidality scales, I Flamarique et al. SPAIN

During this congress, the results of the STOP validation study were presented. Four instruments were developed, two instruments for adolescents (the STOP-SAS and STOP-MS^3) and more simplified versions for children between 8 and 11. The STOP Side Effects Scale assesses the possible association of suicidality and medication side effects and the STOP Suicidality Scale assesses the different components of suicidality. The newly developed scales (The STOP scales) assess suicidality and its possible relation with medication side effects. The instruments for adolescents show high internal consistency and test-retest reliability like the Side effects scale for children. The suicidality scale for children shows good internal consistency, but low test-retest reliability. Countries analysed individually show similar results.

5) ECNP congress, Barcelona October 2013 – STOP poster communications

Presenter:

- Development and initial validation of a Medication Side-Effects Suicidality scale for children and adolescents, P Santosh et al.

- Development and initial validation of a Suicidality Scale for children and adolescents. I Flamarique et al.

Further scientific communication is planned for the main study results. European congresses and to specifically aim at the American public will be targeted by submitting a proposal to the congresses of the American Academy of Child and Adolescent Psychiatry.

Scientific dissemination activities: publications and publication plan

- Gassó P, Pagerols M, Flamarique I, Castro-Fornieles J, Rodriguez N, Mas S, Curran S, Aitchison K, Santosh P, Lafuente A; Stop Consortium. The effect of age on DNA concentration from whole saliva: implications for the standard isolation method. Am J Hum Biol. 2014 Nov-Dec;26(6):859-62. doi: 10.1002/ajhb.22593. Epub 2014 Jul 28. PubMed PMID: 25065578.
- Santosh P (2014): STOP Study aims to monitor suicidality. EU Research Vol 2014, Issue 1: 36-39.

A detailed publication plan has been defined during the last STOP steering committee meeting.

Conclusions
Suicidality is an important topic in individual mental health care and, more generally, a public health problem. Therefore, the STOP project results should be translated into evidence informed decision making at both levels: individual assessment and designing of a treatment plan and policy making. Our dissemination strategies targeted mental health professionals, general public and key decision makers. Dissemination activities have been implemented from the beginning of the STOP project, are still ongoing and will continue after the end of the main STOP project. This is expected as, once the main results are published, the STOP-data will be accessible to all participants for further analyses (once they are approved by the Coordinator). We are planning to respond to grants in order to continue the promotion and dissemination of our results through scientific publications (with a focus on open-access publications) and communications in scientific congresses. We will also target national events and media and update our website to keep the STOP community informed about upcoming STOP output.

Reference
Wilson PM, Petticrew M, Calnan MW, Nazareth I. (2010). Disseminating research findings: what should researchers do? A systematic scoping review of conceptual frameworks. Implement Sci. 22: 5:91.

4 The potential impact (including the socio-economic impact and the wider societal implications of the project so far) and the main dissemination activities and exploitation of results

4.1 Socio-economic impact and the wider societal implications of STOP

Suicidality in children and adolescents is a pressing health concern and has a deleterious far reaching impact not only on the individual concerned by also on their families. This overarching remit of this project was address the measurement of suicidality (psychopathology-related suicidality, and medication-related suicidality) and its bio-psychosocial mediators, in children and adolescents. It was important that increased risk in suicidal behaviour was assessed whilst controlling for potential confounding factors and measuring any bias. Current instruments only focus on assessing suicidality and inadequately measure confounding variables, with a focus on paper-based, clinician completed/assisted measures; which makes it difficult to use in large trials and in pharmacovigilance. The STOP project represents a coordinated effort to **develop HealthTracker™-based measures of suicidality in children and adolescents aged 8-18 years in different languages and across multiple countries in the European Union (EU) with physical conditions, mental conditions and healthy controls.** The HealthTracker™ based measures developed through this project can be made available to regulatory authorities, researchers, pharmaceutical companies, and medical and mental health professionals. The modules were developed in STOP with significant input from children and adolescents with and without suicidality, their parents, as well as clinicians, to ensure that the measure was appropriate and used for the reporting of suicidality by children and adolescents as part of a patient reported outcome measure (PROM) in three paediatric observational trials involving seven cohorts using atypical antipsychotics, antidepressants and Montelukast in order to demonstrate that the methodology can be used in both psychiatric as well as physical illness groups, as well as a healthy control group.

Properties of the HealthTracker™-based STOP Suite of Suicidality Measures (Suicidality Assessment Scale [SAS], Medication Suicidality Side-effects Scale [MS³], Terminating Medication Scale [TMS], Suicidality Resilience Scale [SRS] and the Suicidality Risk Factors Scale [SRFS])

To further demonstrate that the web-based HealthTracker™ can monitor change and report clinically meaningful information, the HealthTracker™ based STOP Suite of Suicidality Measures was administered in seven cohorts as part of three observational trials of children and adolescents aged between 8-18 years i.e. those taking atypical antipsychotics (Risperidone [cohort 1], Aripiprazole [cohort 2], WP7), with depression (treated with Fluoxetine [cohort 3], non-pharmacological/CBT [cohort 4], WP8), or with asthma or respiratory allergies (on Montelukast [cohort 5] or other medications [cohort 6]) as well as healthy controls (cohort 7). For these analyses, the total score was calculated by adding up the values of the response options for each scale, for example, 0 to 5 for adolescents, parents and clinicians and from 0 to 3 for children for the SAS scale. Where there was a combination score (i.e. frequency and severity of an item), these two scores were added together/2 to create one score for that item. The Mauchly's Test of Sphericity was used to for the assessment of sphericity. The Greenhouse-Geisser correction was used if the assumption of sphericity had been violated. Where relevant, a t-test was performed for post-hoc analyses (t-test with Bonferroni correction for multiple comparisons). Internal consistency was estimated using Cronbach's alpha coefficient. Pearson's correlation was used to assess the correlation between respondents and convergent validity between the SAS and the Columbia Suicide Severity Rating Scale (C-SSRS). Moreover, the sensitivity and specificity of the scales were also assessed using the receiver operating characteristic (ROC) analyses using the C-SSRS as the gold standard. Cut off scores, sensitivity, and specificity are also presented.

Overall Conclusion

The STOP project will have widespread implications and have a transformational impact in the way suicidality is monitored in children and adolescents. It has provided a comprehensive evaluation of suicidality monitoring because the HealthTracker™ based STOP Suite of Suicidality Measures developed on the HealthTracker™ platform has been validated during the course of the project and demonstrated that it can be used to gather comprehensive information on both psychopathology- and medication-related suicidality. It also developed methodology to measure biological variables using non-invasive or minimally-invasive methods, so that it can be routinely used in trials if necessary. Fundamentally, the STOP results have provided new knowledge on suicidality as an adverse drug reaction, which constitutes a major public health concern and will allow suicidality research in general to move significantly forward.

Overall, the STOP project has succeeded in:

- The development of HealthTracker™ based STOP measures of suicidality using the HealthTracker™ platform in children and adolescents aged 8-18 years in different languages and across multiple countries in the European Union (EU) with physical conditions, mental conditions and healthy controls.
- The development and validation of the HealthTracker™ based STOP Suite of Suicidality Measures that consist of STOP-Suicidality Assessment Scale (SAS), the STOP-Medication Suicidality Side-effects Scale (MS3), STOP Terminating Medication Scale (TMS), STOP Suicidality Resilience Scale (SRS) and the STOP Suicidality Risk Factors Scale (SRFS).
- Allowing longitudinal data modelling so that a predictive adolescent model of suicidal behaviour could be developed for the identification of specific items from the various HealthTracker™ based STOP Suite of Suicidality Measures that best predicts suicidal behaviours, leading to the development of the Suicidality Prediction and Optimising Treatment Scale (SPOTS): a single scale for pharmacovigilance.
- The development of a HealthTracker™ based tool for use as a stand-alone single scale (SPOTS) to be used for drug-safety monitoring (pharmacovigilance) whenever a new drug is introduced in children and adolescents (or for that matter in adults) so that medication related suicidality can be prospectively monitored.
- Stimulating innovation for HealthTracker™ based monitoring of suicidality research by ensuring close and productive interaction between groups across the EU.
- Allowing opportunities for education and training in HealthTracker™ based monitoring.

The pertinent findings from the HealthTracker™ based STOP Suite of Suicidality Measures consisting of STOP-Suicidality Assessment Scale (SAS), the STOP-Medication Suicidality Side-effects Scale (MS3), STOP Terminating Medication Scale (TMS), STOP Suicidality Resilience Scale (SRS) and the STOP Suicidality Risk Factors Scale (SRFS) are described below:

Suicidality Assessment Scale (SAS)

Psychometric Properties of the SAS scale

The Clinician, Adolescent and Parent versions of the SAS were based on 19 standardised items whilst the Child version of the SAS was based on 14 items. Very good internal consistency was found for clinicians (Cronbach's alpha: 0.950), adolescents (Cronbach's alpha: 0.962), parents (Cronbach's alpha: 0.944) and children (Cronbach's alpha: 0.915) versions. For the

assessment of convergent validity, the C-SSRS was used. A strong correlation was found between the SAS and the C-SSRS for clinicians (r: 0.899), adolescents (r: 0.753), parents (r: 0.593) and children (r: 0.698). Moreover, the overall ROC area was good for clinicians (0.973), adolescents (0.890), children (0.890) and parents (0.856) (see Table 4.1A).

Factor Analysis of the SAS

The Exploratory Factor Analysis for the clinicians' version showed a 3-factor model. Based on the pattern of symptom domain loading the 3 factors were named: (1) Suicidal ideations, (2) Suicidal Behaviours and (3) Plans and Preparations. This factor structure was confirmed in the Clinicians version of the SAS and is shown in Table 4.1B. The ROC curve for suicidal ideations (factor 1) was good for clinicians (0.968), adolescents (0.882) and parent (0.774) versions. Similarly, the ROC curve for plans and preparations (factor 2) was good for clinicians (0.705), adolescents (0.771) but poor for parent versions (0.586). For factor 3 (suicidal behaviours), the ROC area was good for clinicians (0.821), adolescents (0.797) and parent (0.702) versions.

Sensitivity, Specificity and Predictive Value of the SAS

Regarding the results from the ROC analysis, the accuracy of the clinicians' version to predict suicidal ideations, behaviours plans and preparations was good compared with the C-SSRS. With some exceptions, the accuracy of the adolescents, children and parent version was also good. The sensitivity and specificity results are also shown in Table 4.1C.

The general GLM analysis (ANOVA) was used to test the Adolescent, Child, Parent and Clinician versions of the scale to see if the versions scored differently. The ANOVA returned no significant results ($F_{[2]}$=0.018, p>0.05) in the version of the scale (Child, Parent and Clinician) but returned significant results in the Adolescent, Parent and Clinician version of the scale ($F_{[2]}$=5.863, p=0.003). To further explore the main effect of the Adolescent, Parent and Clinician version of the scale, a post-hoc analysis was performed (Bonferroni corrected t-test for multiple comparisons p<0.016), which returned significant results in the total scores of the compared versions of the scale Adolescent vs. Parent ($t_{[109]}$=2.649, p=0.009 [n=110]), Adolescent vs. Clinician ($t_{[225]}$=3.773, p<0.001 [n=226]) and Parent vs. Clinician ($t_{[285]}$=-3.789, p<0.001 [n=286]).

Medication Suicidality Side-effects Scale (MS^3)

The results showed that the originally planned MS^3 had to be split into two scales – the Medication Side-effect Suicidality Scale (MS^3) and the Terminating Medication Scale (TMS). The properties of these scales are described below:

Psychometric Properties of the MS^3

For the STOP MS^3 scale, the Clinician version of the scale based on 26 items showed very good internal consistency (Cronbach's alpha: 0.941), however for items 25 ("stopped due to side effects") and 26 ("medication made symptoms worse"), the corrected item correlations were <0.200. For this reason, these two items were separated out to form the TMS and the remaining 24 items of the MS^3 re-analysed. This 24 item scale also showed very good internal consistency (Cronbach's alpha: 0.943) and the corrected total item correlations were >0.200 for all the items.

For the 24-item scale, very good internal consistency was found for clinicians (Cronbach's alpha: 0.943), adolescents (Cronbach's alpha: 0.956) and parents (Cronbach's alpha: 0.949) versions. A poor correlation was found between the MS^3 scale and the C-SSRS for clinicians (r: 0.193), adolescents (r: 0.321), parents (r: 0.314) and children (r: 0.372). The ROC area was good for clinicians (0.609), adolescents (0.806) and parents (0.707).

Factor Analysis of the MS^3

The Exploratory Factor Analysis for the clinicians' version of the MS^3 showed a 2-factor model and based on the pattern of symptom domain loading the 2 factors were named: (1) 'Medication Induced Emotional Dyscontrol' and (2) 'Medication Induced Behavioural Dyscontrol.' This factor structure was confirmed in the Clinicians version of the MS^3 and is shown in Table 4.1D. The overall ROC Areas for the adolescent, parent and clinician version of the scales (Table 4.1E).Further ROC analyses for factors (1) and (2) showed that the ROC area for clinicians was reasonable but not as good as the adolescents and parents versions (see Table 4.1F).

The ANOVA showed significant results in the Adolescent, Parent and Clinician version of the scale ($F_{[2]}$=20.83, p<0.001). A post-hoc analysis (Bonferroni corrected t-test for multiple comparisons p<0.016) revealed significant differences in the total scores for the Adolescent vs. Parent ($t_{[305]}$=4.085, p<0.001 [n=306]) and Adolescent vs. Clinician ($t_{[327]}$=7.641, p<0.001 [n=328]) but not for the Parent vs. Clinician ($t_{[561]}$=0.034, p>0.05 [n=562]) versions of the scale.

Terminating Medication Scale (TMS)

Psychometric Properties of the TMS

Good internal consistency was found for clinicians (Cronbach's alpha: 0.755) but low internal consistency was shown for adolescents (Cronbach's alpha: 0.571) and parents (Cronbach's alpha: 0.509) versions. A poor correlation was found between the STOP-Terminating Medication Scale (STOP-TMS) and the C-SSRS for clinicians (r: 0.073), adolescents (r: 0.181) and parents (r: 0.148). The ROC area was modest for clinicians (0.552), adolescents (0.561) and parents (0.534).

Factor Analysis of the TMS

The Exploratory Factor Analysis for the clinicians' version of the TMS showed a 1-factor model (Table 4.1G). The ROC analysis showed that the ROC area was modest for all versions of the scale in that although the scales were high in specificity, they were rather weak in detecting the measure (see Table 4.1H).

GLM ANOVA showed a significant main effect in the Adolescent, Clinician and Parent version of the scale ($F_{[2]}$=4.988, p=0.007). The post-hoc analysis (Bonferroni corrected t-test for multiple comparisons p<0.016) showed significant differences in the total scores for the Adolescent vs. Clinician ($t_{[270]}$=4.044, p<0.001 [n=271]), Parent vs. Clinician ($t_{[463]}$=2.640, p=0.009 [n=464]) but not the Adolescent vs. Parent ($t_{[271]}$=-0.068, p>0.05 [n=272]) versions of the scale.

Risk and Resilience Scale (RRS)

These results indicated that the STOP RRS had to be split into the Suicidality Resilience Scale (STOP-SRS) and the Suicidality Risk Factors Scale (STOP-SRFS). The pertinent findings from these scales are described below.

Suicidality Resilience Scale (SRS)

The general linear model (GLM) analysis (ANOVA) showed no significant results ($F_{[2]}$=0.400, p>0.05) in the Adolescent (n=165), Parent (n=165) and Clinician (n=165) version of the scale.

Psychometric Properties of the SRS

The Clinician, Adolescent and Parent versions of the SRS were based on 9 standardised items. Good internal consistency was found for clinicians (Cronbach's alpha: 0.765), adolescents (Cronbach's alpha: 0.784) and parent (Cronbach's alpha: 0.817) versions. A weak correlation was found between the STOP SRS and the C-SSRS for clinicians (r: -0.009), adolescents (r: -0.162) and parents (r: 0.072). Moreover, the overall ROC area was modest for clinicians (0.559), adolescents (0.452) and parents (0.546) (see Table 4.1J for the overall ROC Areas).

Factor Analysis of the SRS

The Exploratory Factor Analysis for the clinicians' version showed a 2-factor model. Based on the pattern of symptom domain loading the 2 factors were named: (1) External Resilience Factors and (2) Internal Resilience Factors. This factor structure was confirmed in the Clinicians version and is shown in Table 4.1I.

Sensitivity, Specificity and Predictive Value of the SRS

Regarding the results from the ROC analysis, overall the accuracy of the adolescent, parent and clinician version to predict resilience was modest (see Table 4.1K). Moreover, factor 1 'External Resilience Factors' showed a better accuracy in predicting resilience in the parent and clinician version when compared to the adolescent version.

Suicidality Risk Factors Scale (SRFS)

Psychometric Properties of the SRFS

For the STOP-SRFS scale based on 13 items, fair internal consistency was found for clinicians (Cronbach's alpha: 0.673) whilst good internal consistency was seen for adolescents (Cronbach's alpha: 0.797) and parents (Cronbach's alpha: 0.790) versions. Moreover, whilst a modest correlation was found between the STOP-SRFS scale and the C-SSRS for clinicians (r: 0.629), it was poor for adolescents (r: 0.474) and parents (r: 0.358). The overall ROC area was good for clinicians (0.776) but modest for adolescents (0.682) and parents (0.640). See Table 4.1M for overall ROC Areas for the adolescent, parent and clinician version of the scales.

Factor Analysis of the SRFS

The Exploratory Factor Analysis for the clinicians' version of the SRFS showed a 4-factor model and based on the pattern of symptom domain loading the 4 factors were named as: (1) 'Depression', (2) 'Chronic stress', (3) Historical risk and (4) 'Bullying'

(see Table 4.1L). Further ROC analyses showed that the predictive value of factor 1 'Depression' was the highest for all versions of the scale (see Table 4.1N).

The ANOVA showed significant results in the Adolescent, Parent and Clinician version of the scale ($F_{[2]}$=3.992, p=0.019). A post-hoc analysis (Bonferroni corrected t-test for multiple comparisons p<0.016) revealed a significant difference in the total scores for the Adolescent vs. Parent ($t_{[191]}$=1.961, p=0.051 [n=192]) but not in the Parent vs. Clinician ($t_{[288]}$=-1.308, p>0.05) [n=289]) or Adolescent vs. Clinician ($t_{[223]}$=1.004, p>0.05 [n=224]) versions of the scale.

Suicidality Prediction and Optimizing Treatment Scale (SPOTS)

Collectively the HealthTracker™-based STOP Suite of Suicidality Measures consisting of the Suicidality Assessment Scale (SAS), Medication Suicidality Side-effects Scale (MS^3), Terminating Medication Scale (TMS), Suicidality Resilience Scale (SRS) and the Suicidality Risk Factors Scale (SRFS), allowed for prediction of the adolescent model of suicidal behaviour to be performed which lead to the identification of specific domains for suicidality that were developed into a single scale to predict the risk of suicidality in children and adolescents. This scale was called the Suicidality Prediction and Optimising Treatment Scale (SPOTS).

The adolescent suicidal behaviour prediction model was done on a split half sample that took into consideration the gender, the duration of the medication and age of the patient at the time of recruitment. These were imputed into the prediction model as covariate factors. This model was tested and validated in the other half of the sample (results to be described elsewhere).The adolescent split half model in cohorts 1, 2 3 and 4 (WP7+WP8) yielded an r^2 value of 0.459 based on 491 observations (n). For cohorts 1 and 2 (WP7), the r^2=0.433 (n=272) and for cohorts 3 and 4 (WP8) the r^2=0.764 (n=219). The remaining sample from the split-half procedure was used to estimate the psychometric properties of the new Suicidality Prediction and Optimizing Treatment Scale (SPOTS). These results showed very good internal consistency for the adolescent version of the SPOTS and a strong correlation between the SPOTS and the C-SSRS for clinicians and adolescents; however, the correlation was fair for parents. The Exploratory Factor Analysis for the adolescents' version showed a 5-factor model. Based on the pattern of symptom domain loading the 5 factors were named: (1) Suicidal Thoughts, (2) Medication Related Depressive Mood and Thinking, (3) Medication Related Somatic Symptoms, (4) Medication Related Mood Dysregulation and (5) Suicidality Related Stressors. The ROC area was the highest for the clinician version and good for the adolescent and parent versions of the scale.

Psychometric Properties of the SPOTS

Very good internal consistency was found for the adolescent (Cronbach's alpha: 0.926) version of the scale. For the assessment of convergent validity, the C-SSRS was used. A strong correlation was found between the SPOTS and the C-SSRS for clinicians (r: 0.801) and adolescents (r: 0.683), however, the correlation was modest for parents (r: 0.485). The overall ROC area was good for clinicians (0.912), adolescents (0.825) and parents (0.763).

Factor Analysis of the SPOTS

The Exploratory Factor Analysis for the adolescents' version showed a 5-factor model. Based on the pattern of symptom domain loading the 5 factors were named: (1) Suicidal Thoughts, (2) Medication Related Depressive Mood and Thinking, (3) Medication Related Somatic Symptoms, (4) Medication Related Mood Dysregulation and (5) Suicidality Related Stressors. This factor structure was confirmed in the adolescent version of the SPOTS and is shown in Table 4.1O. The ROC area was the highest for the clinician version and good for the adolescent and parent versions of the scale.

Sensitivity, Specificity and Predictive Value of the SPOTS

Regarding the results from the ROC analysis, the accuracy of the clinicians' version to predict the 5-factors was the highest when compared with the C-SSRS followed by the adolescent and parent versions of the scale. The sensitivity and specificity results for SPOTS are shown in Table 4.1P.

The general GLM analysis (ANOVA) was used to test the Adolescent, Parent and Clinician versions of the scale. The ANOVA returned a significant result in the Adolescent, Parent and Clinician version of the scale ($F_{[2]}$=29.30, p<0.001). To further explore the main effect of the Adolescent, Parent and Clinician version of the scale, a post-hoc analysis was performed (Bonferroni corrected t-test for multiple comparisons p<0.016), which returned significant results in the total scores of the compared versions of the scale Adolescent vs. Parent ($t_{[215]}$=6.803, p<0.001 [n=216]), Adolescent vs. Clinician ($t_{[229]}$=4.792, p<0.001 [n=230]) and Parent vs. Clinician ($t_{[370]}$=-3.436, p=0.001 [n=371]).

HealthTracker Ltd has submitted an enquiry to the MHRA to confirm the device classification of the STOP Drug-Safety scale (SPOTS). The device might be either Class 1 or Class IIa. The requirements for Class IIa are stricter, and dictate other steps such as ISO 13485 implementation and Notified Body involvement. These steps all precede a CE marking proposal. Once this

scoping exercise is complete (HealthTracker Ltd are currently employing consultants from the Emergo Group to assist with this) we will be able to fully detail what the implications for the next steps are. It is impossible to predict the amount of work and subsequent costs to reach definitive CE marking, until this initial piece of work is complete.

Cohorts 1 and 2 (WP7), General Linear Model – Repeated Measures ANOVAs

The GLM ANOVA (repeated measures ANOVA) and one-way ANOVA values for cohorts 1 and 2 (WP7) at baseline are presented in Table 4.1Q and Table 4.1R. The GLM repeated measures ANOVA showed that there was a significant within subject result for the adolescent, parent and clinician versions of the PONS scale. The one way ANOVA data showed that all STOP scales for the adolescent, parent and clinician versions showed statistically significant results (group: Risperidone, Aripiprazole and healthy control) (Table 4.1R).

Cohorts 3 and 4 (WP8), General Linear Model – Repeated Measures ANOVAs

The GLM ANOVA (repeated measures ANOVA) and one-way ANOVA values for WP8 are presented in Table 4.1S and Table 4.1T at baseline. The GLM repeated measures ANOVA showed that there was a significant within subject result for the adolescent, parent and clinician version for all the scales. Moreover, with the exception of the SAS and SRFS, a significant within subject interaction for the SRS, MS^3 and PONS scale was seen (Table 4.1S). There were no significant between subject results. One way ANOVA showed that except for the parent version of the SRS, all other STOP scales for the adolescent, parent and clinician versions showed statistically significant results (group: fluoxetine, CBT and healthy control) (Table 4.1T).

Cohorts 5 and 6 (WP9), General Linear Model – Repeated Measures ANOVAs

The GLM ANOVA (repeated measures ANOVA) and one-way ANOVA values for WP9 are presented in Table 4.1U and Table 4.1V at baseline. The GLM repeated measures ANOVA showed that there was a significant within subject result for the adolescent, parent and clinician version of the PONS scale for Montelukast and non-Montelukast (Table 4.1U). One way ANOVA did not show any significant differences for the individual scales (Table 4.1V).

Cohort 7 (healthy controls), General Linear Model – Repeated Measures ANOVAs

For healthy controls the GLM ANOVA (repeated measures ANOVA) values at baseline are shown in Table 4.1W. The GLM repeated measures ANOVA showed that there was a significant within subject result for the adolescent, parent and clinician versions of the SAS, MS^3 and PONS scale. There were no significant between subject results.

4.2 The main dissemination activities of STOP

The main dissemination activities of STOP were:

Posters:

P1 KCL: Development and Validation of a Patient Centred Outcome Measure – the Profile of Neuropsychiatric Symptoms (PONS) in children and adolescents. 24/06/2014, London, UK

P1 KCL: Development and Initial Validation of a Medication Side-Effect Suicidality Scale for Children and Adolescents. 05/10/2013, Barcelona, Spain

P10 FCRB: Development and initial validation of a Suicidality Scale for children and adolescents. 05/10/2013, Barcelona, Spain

P17 UA: Comparing ADME-related genes with various technologies. 22/05/2015, Alberta, Canada

Presentations:

P1 KCL: HealthTracker™: web-based monitoring of patient centred outcomes in routine practice. 19/09/2014, Cardiff, UK

P1 KCL: Suicidality in youth: monitoring and treatment. 18/10/2014, Berlin, Germany

P9 CIBERSAM: Conference at International Association of Child and Adolescent Psychiatry and Allied Professions (IACAPAP) World Congress. 24/07/2012, Paris, France

P10 FCRB: Medication Related Suicidality in Children and Adolescents: Assessment, information and ethics: Multidimensional Assessment of suicidality in children and adolescents. 03/03/2012, Prague, Czech Republic

P10 FCRB: Cross-cultural validation of the STOP suicidality scales. 06/07/2013, Dublin, Ireland

P17 UA: Establishing biological sampling methodology for pharmacogenomics in young people. 03/2012, New York, US

P17 UA: CYP2D6: Detecting New Structures for Clinical Practice. 14/05/2015, Toronto, Canada

Press Releases and Conferences:

P1 KCL: Suicide in children and adolescents. 16/10/2012, Vienna, Austria

P1 KCL: Suicide in children and adolescents. 14/10/2014, Berlin, Germany

Organisation of Conferences / Symposia:

P8 APHP: EPA STOP-Symposium. 03/2012, Prague, Czech Republic

P8 APHP: IACAPAP STOP-Symposium. 07/2012, Paris, France

Articles published in the popular press:

P1 KCL: STOP Study aims to monitor suicidality, 2014, EU Research Journal

Websites/Applications:

P8 APHP: Booklets: STOP study information. Paris, France

P15 concentris: Project website: www.stop-study.com

P19 CHU: Flyers for each work package, available at STOP intranet. Montpellier, France

4.3 Exploitation of results of STOP

The HealthTracker™ platform has allowed for the HealthTracker™ based STOP Suicidality Suite of Measures to be developed and subsequently validated - the STOP Suicidality Assessment Scale (SAS), the STOP Medication Suicidality Side-Effects Scale (MS3), the STOP Termination of Medication Scale (TMS); the STOP Suicidality Resilience Scale (SRS) and the STOP Suicidality Risk Factors Scale (SRFS). These newly validated scales can be used for Post-marketing Surveillance and Pharmacovigilance and allows for an improved method of suicidality monitoring and recording, which will result in better surveillance and risk assessment, and therefore, more effective management, intervention, treatment, and prevention of individuals at risk for suicide.

Apart from this, we have developed a simple to use scale, a post-marketing surveillance and pharmacovigilance tool, the **Suicidality Prediction and Optimising Treatment Scale** (**SPOTS**) which uses a HealthTracker™ platform based algorithm to predict the degree of risk for suicidal behaviour during treatment in mental health settings in children and adolescents. This IP will be exploited in due course.

This HealthTracker™ based Suite of Suicidality Measures can be procured by regulatory authorities, researchers, pharmaceutical companies for pharmacovigilance using existing agreements for Background and Foreground IP use, which will improve the detection and management of medication-related suicidality and reduce morbidity and mortality.

Manuscripts for publication are in preparation and will be finalised in coming months. This in combination with conferences will be a key way to disseminate the findings from the STOP project.

5 The address of the project public website, if applicable as well as relevant contact details

The address of the public website is: www.stop-study.com
The contact details of the scientific representative of the project's co-ordinator are:

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