PATIENCE

Individual Patient DATa Network Meta-AnalysIs of the Efficacy aNd aCceptability of ADHD mEdication

PROTOCOL for INDIVIDUAL PATIENT DATA REQUEST

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Protocol – Individual Patient Data

1. Plain English Summary – Research Proposal

1.1. Background

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent neurodevelopmental disorder which has been estimated to affect 5-7% of children and 2.5% of adults worldwide. It is characterised by inattention and/or hyperactivity-impulsivity, that lead to impairment in the family, classrooms, workplaces and social settings and can prevent individuals from maintaining relationships and reaching their full potential. A number of pharmacologic and non-pharmacologic treatments are available. A network meta-analysis (NMA) of published and unpublished data provided the most comprehensive evidence on the relative efficacy, safety and tolerability of pharmacological treatments across the lifespan at the group level.

NMA is a statistical method that uses data from multiple randomised controlled trials (RCTs) and aims to estimate the relative effects of all available treatments for a certain condition. Common applications of NMA use aggregate data and estimate average treatment effects, i.e., treatment effects at the group level. The analysis of aggregate data, although useful on its own, cannot estimate treatment effects for specific types of patients, i.e., it cannot account for important differences in characteristics of the patients that may significantly moderate treatment effects (e.g., previous exposure to medication, specific comorbidities and severity of symptoms). PATIENCE, an Individual Patient Data Network Meta-Analysis (IPD-NMA), has been designed to use data from individual participants recruited in RCTs of ADHD medications, to enable more detailed and flexible analyses to be performed than those based on aggregate data. This will provide evidence to inform future clinical guidelines, support personalised approaches in the treatment of ADHD, and identify areas for further research.

1.2. Aim

To collect and analyse individual patient data (IPD) from published and unpublished RCTs of FDA-approved pharmacological treatments for ADHD in children, adolescents, and/or adults.

1.3. Objectives

The main objectives of this project are to:

1. provide an updated evidence synthesis on the efficacy, acceptability and tolerability of pharmacological treatments for ADHD;
2. Use information on patient-level characteristic to estimate how individual characteristics impact on the efficacy and tolerability of ADHD medication.

1.4 Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS	Attention-Deficit/Hyperactivity Disorder Rating Scale
CSDR	Clinical Study Data Request
CGI-I	Clinical Global Impression – Improvement
DSM	Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, APA)
ICD	International Statistical Classification of Diseases and Related Health Problems (World Health Organization, WHO)
IPD	Individual Patient Data
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HKD	Hyperkinetic Disorder
NMA	Network Meta-Analysis
MedDRA	Medical Dictionary for Regulatory Activities
N/S	Not Specified
PATIENCE	Individual **P**atient D**AT**a Network Meta-Analys**I**s of the **E**fficacy aNd a**C**ceptability of ADHD m**E**dication
PERMP	Permenant Product Measure of Performance
PI	Principal Investigator
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
ROB	Risk of Bias
SKAMP	Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale
SNAP	The Swanson, Nolan, and Pelham Rating Scale

2. Research proposal

2.1. Background

2.1.1. Attention-Deficit/Hyperactivity Disorder (ADHD)

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder and one of the most common diagnoses in child and adolescent mental health services [1]. It has been estimated that the worldwide prevalence of ADHD is in the order of 5-7% in children [2] and 2.5% in adults [3]. ADHD is a heterogeneous disorder, primarily characterised by developmentally inappropriate inattention and/or hyperactivity-impulsivity to a degree that adversely affects schooling, work, and/or relationships. The disorder usually becomes apparent in early childhood [1] and, for approximately 70% of people, impairing symptoms continue into adulthood [4], disrupting the lives of patients and those around them.

2.1.2. Treatments commonly prescribed to treat ADHD

Treatment for ADHD includes pharmacological and non-pharmacological options. Pharmacological interventions recommended by clinical guidelines (e.g., [5, 6]) include psychostimulants (e.g., methylphenidate and amphetamines) and non-psychostimulant medications (e.g., atomoxetine and α2-agonists) [7]. Over the past few decades, prescriptions for these medications have increased significantly both in the USA [8] and in other countries [9]. The most comprehensive NMA at the aggregate level of the efficacy and safety of these medications found evidence to support the use of methylphenidate for children and adolescents and of amphetamines for adults as first choice for short-term treatment [10].

2.1.3. Rationale for Individual Patient Data Network Meta-analysis

For ADHD, as for many other disorders, clinicians, patients and parents/carers are faced with a range of possible medications to choose from. In the absence of evidence-based biomarkers and clinical predictors of response or adverse effects, currently treatment selection in the clinical practice often relies on trial-and-error [7]. This results in protracted periods of sub-optimal treatment until the drug that provides the optimum balance of efficacy and tolerability for an individual patient is identified.

The most robust empirical evidence for the effects of treatments comes from RCTs. The results of these can be statistically combined in pairwise Meta-Analyses (MAs) to estimate the relative effects of two drugs (or one drug and placebo). When a range of treatment options are available, the utility of pairwise comparisons from MAs for selection of treatment is limited. NMAs overcome this limitation by comparing multiple treatments simultaneously in a single analysis to produce estimates of relative effects among all interventions [11]. In addition to including data on treatment comparisons provided directly from RCTs, NMAs also incorporate indirect information, obtained by combining data from RCTs of different drugs evaluated against the same comparator.

NMAs facilitate initial treatment selection by providing estimates of the extent to which patients with a clinical condition are likely to benefit from and/or not be harmed by a particular medication, as compared to a reference treatment (e.g., active drug or placebo).

However, NMA results based on aggregate data only estimate the average treatment effects, i.e., at the group level. Individual Patient Data Network Meta-Analyses (IPD-NMAs) analyse patient-level rather that group-level data. This type of analysis also has the capacity to provide estimates of the effects of medication on subgroups of patients with specific characteristics, such as previous exposure to medications, severity of symptoms and comorbidities which could moderate the effects of medications [12]. Additionally, an IPD-NMA has other advantages as compared to aggregate data NMAs, such as the ability to standardise analyses across different studies, harmonise the definition of outcomes, offset inadequate reporting of individual studies, and allow more accurate assessment of study quality [13] [14].

2.1.4. Conducting Individual Patient Data Meta-analyses (IPD-NMAs)

Data for IPD-NMAs may be obtained from trial investigators and sponsors, including pharmaceutical companies, either directly or via data-sharing repositories and platforms. In addition to published data, the datasets may include information on unreported outcomes, allowing additional comparisons to be made. The data collected are first re-examined and verified, and any discrepancies found are checked with authors. As well as re-analyses of data reported in trial publications, additional analyses can be performed on data not reported in trial publications, new hypotheses can be tested and data from participants excluded from the original analyses can be included [15].

2.2. Impact

An IPD-NMA can help to inform guidelines, which in turn will have an impact on the treatment of ADHD, by enabling clinicians, patients and parents/carers to take patients' personal characteristics into account when selecting medications. The results will inform clinical treatment guidelines on the management of ADHD. Of note, Professor Cortese is a member of the European ADHD Guidelines Group, a working group of the European Network for Hyperkinetic Disorders (EUNETHYDIS), which will facilitate the translation of the findings in clinical guidance at the national and international level. PATIENCE will also identify areas for future research and may shed some light on factors that underpin the clinical heterogeneity observed in the way the disorder presents in different individuals.

2.3. Objectives and Outcomes

The overall objective of the IPD-NMA is the establishment of a hierarchy of the efficacy and acceptability/tolerability of the available pharmacological treatments for ADHD in sub-groups of children, adolescents or adults with particular clinical characteristics (see https://esm.ispm.unibe.ch/shinies/iCBT/ for an example). This will involve:

i. assessing pharmacological treatments in patients with ADHD, in terms of:
   - overall efficacy on severity of ADHD core symptoms;
   - tolerability (defined as dropouts due to adverse events);
   - acceptability (defined as dropouts due to any cause);
   - changes in body weight changes in blood pressure and in heart rate
   - individual adverse events

ii. exploring interactions between treatment effects and potential moderators, to identify predictors of individual response to medication.

iii. re-analysing data to reduce clinical heterogeneity and network inconsistency, by controlling for any patient-level moderators identified.

iv. using the data to conduct time-to-event analyses.

v. IPD may include additional information compared to aggregate data, meaning that better assessments of bias may be possible. Moreover, if a source of potential bias is identified, there may be ways to fix it. For example, a study may have used suboptimal ways of addressing missing data (LOCF). With IPD we can use more advanced methods, e.g., multiple imputations.

2.4. Rationale for Study Selection and Selection of Populations/Participants

The selection of studies for the IPD-NMA follows the same criteria as in our previously published an aggregate data NMA [16], with the addition of including the newly FDA approved ADHD medication – Viloxazine. The same study selection, inclusion and exclusion criteria are being used for this IPD NMA will be published in the study protocol.

2.4.1. Types of studies

Studies included in this IPD-NMA: Double-blind randomised controlled trials (parallel group or crossover). For crossover trials - data from the pre-crossover phase will be included, to avoid the risk of carry-over effects from one treatment period to the next [17].

Excluded studies include:

i. quasi-randomised trials, trials using Latin square randomisation, open-label or single-blind RCTs;

ii. N-of-1 trials;

iii. trials recruiting participants taking ADHD medication prior to entry if they did not complete an appropriate washout period prior to randomisation (see Appendix 1 for recommended washout periods for each medication);

iv. trials using enrichment designs, i.e., only including patients who responded to one of the trial medications either prior to trial entry or during a pre-randomisation run-in phase, regardless of any washout period;
v. Discontinuation trials

2.4.2. Types of participants

Participants will include children (aged ≥5 years and <12 years), adolescents (aged ≥12 years and <18 years) and/or adults (≥18 years) as inpatients or outpatients with a primary diagnosis of ADHD or Hyperkinetic Disorder (HKD), according to standardised diagnostic criteria, including DSM-III, DSM III-R, DSM-IV(TR), DSM-5, ICD-9, ICD-10 or ICD-11. No restriction will be made based on ADHD subtype/presentation, gender, IQ or socioeconomic status of participants. Trials in which some or all participants had a comorbid psychiatric or neurological disorder will be included provided that those disorders were not being treated with medication or pharmacotherapy during trial participation.

2.4.3. Types of interventions

We will include all RCTs including at least one arm comparing the following active agents (prescribed for oral administration) against each other or with placebo: Stimulants (methylphenidate, dexmethylphenidate and amphetamine derivatives including lisdexamfetamine); non-stimulants (including atomoxetine, clonidine, guanfacine, viloxazine). We will include all doses. Trials using concomitant pharmacotherapy for comorbid psychiatric or neurological disorders (e.g., antiepileptic drugs for epilepsy or mood stabilisers for bipolar disorder) because these medications could alter the effects of the intervention of interest.

2.5. Outcome measures for IPD analysis

Primary outcome

Observer-rated efficacy: the endpoint scores for the severity of core symptoms of ADHD (combined score of inattention, hyperactivity and impulsivity) measured on validated ADHD rating scales will be used. For adults, efficacy will be based on ratings by clinicians and, for children and adolescents, ratings by clinicians and teachers will be used.

In the first instance we aim to use the same rating scale for all studies. If studies do not report scores from the same rating scale, we will convert different scores into one single score from the same rating scale, ADHD-RS, as done by Furukawa et al [18]. In order to convert, we need studies reporting scores from different rating scales for the same outcome. If we are able to convert everything into ADHD-RS, we will synthesise data as a mean difference.

If we are not able to convert different scales into ADHD-RS, we will keep the original scales and will do the analysis using the standardized mean difference. We will use the following hierarchy:

1. ADHD-RS
2. SNAP;
3. Conner's rating scale (any version);
4. Other ADHD scales (e.g., SKAMP, PERMP).

Secondary outcomes

Tolerability: defined as the proportion of participants who left the trial for any side effect during the first 12 weeks of randomised treatment;

Acceptability: defined as the proportion of participants who left the trial for any reason during the first 12 weeks of randomised treatment;

Safety: number of patients with specific adverse events (which will be classified using the MedDRA system for medical terminology - https://www.meddra.org/)

Self-rated efficacy: by adults and parent ratings for children and adolescents of ADHD core symptoms on validated ADHD rating scales, and blood pressure, heart rate and weight.

2.6. Data Collection

From the included RCTs and using predefined templates, two reviewers will independently extract the relevant information about trial characteristics, patient characteristics, intervention details and clinical outcomes as shown in Table 1 (see below). The raw data can be provided in any convenient usable format (Excel, SPSS, Stata, CSV, etc).

2.6.1 Data Management

The Chief Investigator has overall responsibility for the management of PATIENCE data. The Data Manager will have day-to-day responsibility for management of the data. In terms of confidentiality, the data set will not contain any personal identifier of patients, such as names or phone numbers. No attempt will be made to identify or "link" patients on individual basis. All data will be stored on the secure Oxford University server and adhere to the following:

- The data will be stored on a password protected institutional network server (data will not be stored on portable computers, portable storage devices, institutions/personal websites or public clouds);
- The network perimeter will be fully protected by firewall systems to block access from outside of the institution;

- Where data is required to be used on a portable device for a limited time periods it will be encrypted and deleted from the device when no longer required;
- The data will be password-protected and only the research team will have access to them;
- The data will be destroyed once the research is completed;
- Researchers with assess to the data are trained on the importance of data security;
- Study sponsor will be informed of any data breach;
- Only the named individuals in the research team will have access to the data;

***Table 1:* Data items requested for individual participant data network meta-analysis**

General information	Demographic and baseline characteristics	Clinical characteristics	Outcomes
1. Publication status (i.e. full reference of the paper, if published, or link to the unpublished report) 2. Date of trial commencement (first patient in) 3. Date of trial completion (last patient last follow-up) 4. Countr(y)/ies 5. Recruiting centre(s)	1. Setting (such as primary care, hospitals, clinics) 2. Patient status (inpatient, outpatient) 3. Hospital/Clinic ID 4. Date of randomisation 5. Sex 6. Ethnicity 7. Marital status 8. Education 9. Employment status 10. Height 11. Weight 12. Age 13. Age of onset of illness 14. Length of illness 15. Baseline ADHD symptom score 16. Baseline quality of life and functioning score 17. Previous and/or ongoing secondary psychiatric disorder 18. Family history of ADHD 19. Laboratory values 20. Physical characteristics 21. Socioeconomic status 22. IQ	1. Treatment (ADHD medication, placebo, non-pharmacological as co-treatment); 2. Dose * target; * permitted range; * actual dose; * flexible or fixed dosing * titration schedule and timing (i.e. pre- or post-randomisation). 3. Concomitant medication and psychological therapies; 4. Prior treatments - previous exposure to ADHD medication and timing i.e., prior to or at baseline; 5. Any washout of previous ADHD medications; 6. Any medication initiated during the trial with reason and timing.	1. ADHD-RS and core symptom scores (clinicians, parents, teachers, self); 2. CGI scores; 3. Quality of life and functioning (scale); 4. Blood pressure; 5. Heart rate; 6. Weight; 7. Study discontinuation and reason (drop out before starting the treatment/lack of efficacy/ adverse events/others); 8. Adverse events and whether judged to be treatment related; 9. Serious adverse events and whether judged to be treatment related;

2.7. Statistical analysis

Overview

Our aim is to estimate the patient-specific effectiveness and safety of each drug, to facilitate a personalised choice of treatment. Our main hypothesis is that routinely collected patient-level covariates (such as disease and medication history, demographics, etc.) can be used to predict to some extent the effects of the various drugs on the outcomes of the individual patients, to guide a personalized choice of treatment. The overall target of our analysis is to estimate relative effects between all interventions with respect to [19] the endpoint ADHD symptom score, [20] the probability of dropping out of treatment and [21] the probability of specific side effects for a patient with certain characteristics after 12 weeks of treatment.

To maximize the power to detect modifications of the drug effects according to patient characteristics, we opt to synthesise all data that becomes available. Consequently, our sample size will be the maximum available, subject to the responses from data owners.

In cases of treatment switch during the randomised phase, patients will be analysed according to the drug they were initially allocated, i.e., following an intention-to-treat analysis.

Assessment of transitivity

Transitivity is the main underlying assumption of NMA [20]. This suggests that there are no systematic differences in the distribution of effect modifiers in the studies grouped by comparison. To check this assumption, we will group studies by comparison, and we will look at their characteristics. If studies are deemed to be sufficiently similar to be synthesised in an NMA, we will proceed with the analysis.

Missing data imputation

It is very often the case that for some patients we do not have complete information on all the covariates of interest, or the outcomes. Analysing only patients with complete records will reduce our statistical power and may bias results, when outcomes are not missing completely at random. To retain patients with missing data in our analyses, we will create 10 multiply imputed datasets, while taking into account the stratification of patients in studies. This will be based on the missing at random assumption. We will use all covariates and outcomes for our imputation models. For implementation, we will use the jomo package in R [22].

Aggregating IPD to carry out a MA and NMA

Using the IPD, in each multiply imputed dataset we will perform a pairwise MA after grouping studies comparing the same interventions, as well as NMAs. We will use the netmeta package in R [23]. We will assume random effects, and we will use a common heterogeneity parameter (τ) for all comparisons in the network. We will then

synthesize results from all multiply imputed datasets using Rubin's rules, and we will present them in league tables and forest plots.

Assessment of heterogeneity and inconsistency

We will assess the extent of heterogeneity by inspecting the estimate τ and comparing it with empirical distributions for binary outcomes [24]. We will check for inconsistency in the networks (i.e. the agreement between direct and indirect evidence) using a local approach ('back-calculation') as well as a global test ('design-by-treatment') [25, 26].

Assessment of small study effects and publication bias

Small study effects and publication bias might compromise the validity of our results. To assess these issues, we will create contour-enhanced funnel plots and perform Egger's test to check for asymmetry, after grouping active treatments [27].

Individual patient data network meta-analyses

We will employ a two stage IPD-NMA. At the first stage, we will analyse each study separately, using the 10 multiply imputed datasets [28]. We will fit a Bayesian model including linear interactions between treatment and a list of predefined suspected effect modifiers. These include: age, gender, weight, height, baseline ADHD score, comorbid psychiatric disorder and baseline quality of life score. For binary covariates we will use a binomial likelihood, or, if deemed possible according to data availability, we will do a time-to-event analysis. To avoid overfitting and aiming to have better generalizability of our model, we will use a Bayesian LASSO prior distribution for all treatment-covariate interactions [29]. Next, the posterior estimates from all multiply imputed datasets will be combined into a final posterior distribution [30]. Using this distribution, we will summarize the study-specific estimates for average treatment effect and treatment-covariate interactions as well as their variance-covariance matrix from each study. Finally, we will synthesize the study-specific point estimates and variance covariance matrices across the whole network assuming consistency, using multivariate normal distributions. As in the analysis of aggregate data, we will assume a common heterogeneity parameter across the whole network. The final output of this analysis will be estimates of relative effects and 95% Credible Intervals for all treatment comparisons, for all levels of the effect modifiers.

Presentation of results and prediction of patient-level treatment effects

To facilitate the uptake of our IPD NMA results, we will build an online tool (for an example see https://esm.ispm.unibe.ch/shinies/iCBT/), where the estimates of our models will be used in conjunction with input regarding baseline patient characteristics to estimate patient-level relative effects regarding all interventions in the network.

2.8. Publication Plan

Publication of the results from each phase of the project in peer-reviewed, scientific journals and dissemination of the findings to the general audience via patient and public engagement.

We will ensure that the data providers are notified and have the opportunity to view the results before publication.

3. Research Team Details

Lead Researcher

Name: Professor Andrea Cipriani

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1997 MD, University of Padua
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2018 "Academic Researcher of the Year", Royal College of Psychiatrists, UK
2020 Highly Cited Researcher, Clarivate/Web of Science
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As a clinical academic, Prof Cipriani's main research expertise is in the evaluation of treatments in psychiatry. He has published some methodologically innovative, highly influential systematic reviews and meta-analyses that have had a major impact on the treatment of mental disorders. In the past he has also carried out RCTs in psychopharmacology and investigated clinically relevant issues using observational study designs, including epidemiological studies about persistence with pharmacological treatment in patients with schizophrenia or mood disorders, prevalence of drug consumption, risk of serious adverse events (such as bleeding, thrombosis, suicide and deliberate self-harm) and implementation of treatment guidelines. Ten of his papers are among the highly cited papers in Web of Science and since 2009 he has published 6 articles in The Lancet: 5 network meta-analyses (4 as first and corresponding author, and 1 as second author) and 1 RCT.

In collaboration with world-leading methodologists Prof Cipriani has developed novel statistical techniques that facilitate the translation of evidence synthesis into practice. For example, he recently validated innovative methods to identify study and patient characteristics that have an impact on premature discontinuation in depression and

schizophrenia, and new models to jointly synthesize multiple correlated outcomes in networks of interventions.

With the Department of Mental Health at WHO (Geneva), he also co-authored a manual on psychopharmacology, which provides evidence-based information to guide and influence health care professionals in low- and middle-income countries (http://www.who.int/mental_health/management/psychotropic/en/). Now part of the WHO Gap Action Programme (http://www.who.int/mental_health/mhgap/en/), this manual is distributed as a reference source to assist general practitioners in using evidence-based medicines for mental disorders in routine clinical practice.
His publications have contributed to national and international guidelines. For instance, his network meta-analyses on antidepressants for major depression in adults (2009) and children and adolescents (2016) have been incorporated into clinical guidelines in the UK, the Netherlands, Germany, US, Canada and Australia. Another development in translational research capability is the clarification of "new" effects of "old" drugs (such as lithium for suicide prevention or calcium channel blockers in bipolar disorder), which are promoting innovation in clinical psychopharmacology. For instance, his recent systematic review on calcium channel antagonists (Cipriani et al., 2016), informed by GWAS findings, is driving drug discovery in bipolar research by generating renewed focus on these drugs as targets.

Since 2004, Prof Cipriani has published a total of 264 articles indexed in Scopus (h index: 40) in leading psychiatric, medical and statistical journals, such as *Lancet, British Medical Journal, PLoS Medicine, World Psychiatry, Annals of Internal Medicine, Canadian Medical Association Journal, BMC Medicine, JAMA Psychiatry, Lancet Psychiatry, Acta Psychiatrica Scandinavica, American Journal of Psychiatry, British Journal of Psychiatry, International Journal of Epidemiology, Journal of Clinical Psychiatry, Journal of Clinical Psychopharmacology, Psychological Medicine, Schizophrenia Bulletin, Statistics in Medicine, The Cochrane Library*.

Potential Conflict of Interest: AC has received research and consultancy fees from INCiPiT (Italian Network for Paediatric Trials), and Angelini Pharma

Researcher

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Prizes and professional recognition
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2019 Kramer-Pollnow-Prize for excellence in biological research in child and adolescent psychiatry, European Network of Hyperkinetic disorder (Eunethydis)

Samuele Cortese, MD, PhD is currently Professor of Child and Adolescent Psychiatry at the University of Southampton and Honorary Consultant Child and Adolescent Psychiatry for Solent NHS Trust. He is also Adjunct Professor with the New York University (NYU). Prof. Cortese's main research interest are around neurodevelopmental disorders, with a focus on ADHD. In his research, he uses advanced evidence synthesis methods to address clinically relevant questions. He has published more than 230 peer-review papers, including first author papers in prestigious journals such as the *New England Journal of Medicine*, *The Lancet Psychiatry* and the *American Journal of Psychiatry* (Scopus H Index:). He is Deputy Editor for the *Journal of the American Academy of Child and Adolescent Psychiatry* and sits on the editorial board of other 5 international journals. He is a member of the *European ADHD Guidelines Group*, as well as of the child and adolescent psychiatry faculty of the *European Collegium of Neuropsychopharmacology* (and of the *British Association of Psychopharmacology*-child and adolescent psychiatry module. In 2020, Prof. Cortese was included in the list of the world's most influential researchers of the past decade, demonstrated by the production of multiple highly-cited papers that rank in the top 1% by citations in the field of psychiatry/psychology in 2019 in Web of Science.

Potential Conflict of Interest: none

Senior Statistician

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Potential Conflict of Interest: AT has received research and consultancy fees from INCiPiT (Italian Network for Paediatric Trials), and Angelini Pharma

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Potential Conflict of Interest: None

4. Sources of funding

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