BMJ Open

Protocol for a cohort study of adolescent mental health service users with a nested cluster-randomised controlled trial to assess the clinical and cost effectiveness of managed transition in improving transitions from child to adult mental health services (The MILESTONE study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016055
Article Type:	Protocol
Date Submitted by the Author:	20-Jan-2017

Complete List of Authors:	Singh, Swaran; University of Warwick, Warwick Medical School Tuomainen, Helena; University of Warwick, Warwick Medical School De Girolamo, Giovanni; Psychiatric Epidemiology and Evaluation Unit, Saint John of God Clinical Research Center, Brescia, Italy Maras, Athanasios; Yulius Academy, Rotterdam, Netherlands; Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands Santosh , Paramala; King's College London , Child and Adolescent Psychiatry ; HealthTracker Ltd McNicholas, Fiona; University College Dublin School of Medicine and Medical Science; Geary Institute, University College Dublin, Dublin, Republic of Ireland Schulze, Ulrike; Universitatsklinikum Ulm Klinik fur Kinder- und Jugendpsychiatrie Psychotherapie Purper-Ouakil, Diane; Centre Hospitalier Regional Universitaire de Montpellier Tremmery, Sabine; Katholieke Universiteit Leuven, Department of Neurosciences, Child & Adolescent Psychiatry; Universitaire Ziekenhuizen Leuven, Department of Child and Adolescent Psychiatry Franić, Tomislav; Department of Psychiatry, Clinical Hospital Center Split Madan, Jason; University of Warwick, Warwick Medical School Paul, Moli; Coventry and Warwickshire Partnership NHS Trust; University of Warwick, Warwick Medical School Verhulst, Frank; Erasmus MC, Department of Child and Adolescent Psychiatry and Psychology; Kobenhavns Universitet, Department of Clinical Medicine Dieleman, Gwen; Erasmus MC, Department of Child and Adolescent Psychiatry and Psychology Warwick, Jane; University of Warwick Warwick Medical School, Warwick Clinical Trials Unit Wolke, Dieter; University of Warwick, Department of Psychology and Warwick Medical School Street, Cathy; University of Warwick, Warwick Medical School Daffern, Claire; University of Warwick, Warwick Medical School Tah, Priya ; University of Warwick, Warwick Medical School Griffin, James; University of Warwick, Warwick Medical School, Clinical Trials Unit

	Canaway, Alastair; University of Warwick, Warwick Medical School Signorini, Giulia; Psychiatric Epidemiology and Evaluation Unit, Saint John of God Clinical Research Center, Brescia, Italy Gerritsen, Suzanne; Erasmus MC, Department of Child and Adolescent Psychiatry and Psychology Adams, Laura; University of Plymouth, School of Psychology O'Hara, Lesley; University College Dublin, Department of Child and Adolescent Psychiatry Aslan, Sonja; Universitat Ulm, Department of Child and Adolescent Psychiatry/Psychotherapy Russet, Frédérick; Centre Hospitalier Regional Universitaire de Montpellier Davidović, Nikolina; Department of Psychiatry, Clinical Hospital Center Split Tuffrey, Amanda; University of Warwick, Warwick Medical School Wilson, Anna; University of Warwick, Warwick Medical School Gatherer, Charlotte; University of Warwick, Warwick Medical School Walker, Leanne; University of Warwick, Warwick Medical School
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Health services research
Keywords:	Child & adolescent psychiatry < PSYCHIATRY, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, EPIDEMIOLOGY

Protocol for a cohort study of adolescent mental health service users with a nested cluster-randomised controlled trial to assess the clinical and cost effectiveness of managed transition in improving transitions from child to adult mental health services (The MILESTONE study)

CORRESPONDING AUTHOR

Swaran P Singh
Mental Health and Wellbeing
Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry CV4 7AL
UK
S.P.Singh@warwick.ac.uk
+44 (0) 2476 574 530

JOINT FIRST AUTHOR

Helena Tuomainen, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK

Swaran P Singh and Helena Tuomainen contributed equally to this paper.

CO-AUTHORS

Giovanni De Girolamo, Psychiatric Epidemiology and Evaluation Unit, Saint John of God Clinical Research Center, Brescia, Italy
Athanasios Maras, Yulius Academy, Rotterdam, Netherlands; Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands
Paramala Santosh, Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK; Centre for Interventional Paediatric Psychopharmacology and Rare Diseases (CIPPRD), National and Specialist Child and Adolescent Mental Health Services, Maudsley Hospital, London, UK; HealthTracker Ltd, Gillingham, UK
Fiona McNicholas, Department of Child and Adolescent Psychiatry, University College Dublin School of Medicine and Medical Science, Dublin, Republic of Ireland; Geary Institute, University College Dublin, Dublin, Republic of Ireland; Department of Child Psychiatry, Our Lady's Hospital for Sick Children, Dublin, Republic of Ireland; Lucena Clinic SJOG, Dublin, Republic of Ireland
Ulrike Schulze, Department of Child and Adolescent Psychiatry/Psychotherapy, University of Ulm, Germany
Diane Purper-Ouakil, Centre Hospitalier Universitaire de Montpellier, Montpellier, France
Sabine Tremmery, Department of Neurosciences, Child & Adolescent Psychiatry, University of Leuven, Belgium; Department of Child & Adolescent Psychiatry, University Hospitals Leuven, Leuven, Belgium
Tomislav Franić, Department of Psychiatry, Clinical Hospital Center Split, Split, Croatia
Jason Madan, Warwick Medical School, University of Warwick, Coventry, UK

Moli Paul, Coventry and Warwickshire Partnership NHS Trust, UK; Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Frank C Verhulst, Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands; Department of Clinical Medicine, University of Copenhagen, Denmark
Gwen C Dieleman, Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands
Jane Warwick, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
Dieter Wolke, Department of Psychology, University of Warwick, UK; Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Cathy Street, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Claire Daffern, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
Priya Tah, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
James Griffin, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
Alastair Canaway, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
Giulia Signorini, Psychiatric Epidemiology and Evaluation Unit, Saint John of God Clinical Research Center, Brescia, Italy
Suzanne Gerritsen, Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands
Laura Adams, School of Psychology, Plymouth University, UK
Lesley O'Hara, Department of Child and Adolescent Psychiatry, UCD, Dublin, Republic of Ireland
Sonja Aslan, Department of Child and Adolescent Psychiatry/Psychotherapy, University of Ulm, Germany
Frédérick Russet, Centre Hospitalier Universitaire de Montpellier, Montpellier, France
Nikolina Davidović, Department of Psychiatry, Clinical Hospital Center Split, Split, Croatia
Amanda Tuffrey, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Anna Wilson, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Charlotte Gatherer, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Leanne Walker, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK

for the MILESTONE Consortium

WORDCOUNT

9271

KEYWORDS

Mental health, child and adolescent mental health services, transition, health services research, cluster randomised controlled trial, longitudinal cohort study, youth mental health, Europe

ABSTRACT

Introduction: Disruption of care during transition from Child and Adolescent Mental Health (CAMHS) to Adult Mental Health Services (AMHS) may adversely affect the health and wellbeing of service users. The MILESTONE study aims to evaluate the longitudinal course and outcomes of adolescents approaching transition boundary (TB) of their CAMHS and to determine the effectiveness of the model of managed transition in improving outcomes, compared to usual care.

Methods and analysis: A cohort study with a nested cluster randomised controlled trial. Recruited CAMHS randomised to provide either i) managed transition underpinned by the Transition Readiness and Appropriateness Measure (TRAM) or ii) usual care for young people reaching the transition boundary. Participants are young people within one year of reaching the TB of their CAMHS in eight European countries; one parent/carer and a CAMHS clinician for each recruited young person; and adult mental health clinician or other community based care provider, if young person transitions. Primary outcome is Health of the Nation Outcome Scale for Children and Adolescents (HoNOSCA) at 15 months post-intervention. Secondary outcomes include mental health, social and adult functioning, quality-adjusted life years and health and social care resource utilisation assessed at 9, 15 and 24 months. With a mean cluster size of 21, a total of 840 participants will be randomised 1:2 intervention to control. This will provide 89% power to detect a difference in HoNOSCA score of 0.30 standard deviations. An additional 210 recruits for the cohort study will ensure sufficient power for studying predictors, resulting in 1050 participants and an approximate 1:3 randomisation.

Ethics and dissemination: The study protocol was approved by the UK National Research Ethics Service (15/WM/0052) and equivalent ethics boards in participating countries. Results will be reported at conferences, in peer-reviewed publications, and to all relevant stakeholder groups.

Trial registration numbers: ISRCTN83240263; NCT03013595

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first ever methodologically robust trial to test whether a decision support and assessment tool can improve the mental health and social outcomes and functioning of transition age young people receiving care at Child and Adolescent Mental Health Services.
- Diverse health care settings in eight European countries are involved in the study.
- The cost-effectiveness of the intervention and research-related changes in health systems in terms of both expenditure and related health outcomes will be evaluated.
- A large, prospectively identified and robustly evaluated cohort of young people across several European countries is taking part in the study.
- There is a strong Patient and Public Involvement (PPI) embedded throughout the study.
- Due to the nature of the intervention it is not possible for clinicians or assessors to be blind to the allocation of clusters or of the service users within these clusters. To limit bias, several web-based service-user self-rated outcome measures will be used.
- Transition boundaries vary between and within countries.

INTRODUCTION

The MILESTONE (Managing the Link and Strengthening Transition from Child to Adult Mental Health Care) study focuses on the period when young people (YP) attending Child and Adolescent Mental Health Services (CAMHS) need to move on, or "transition" to, an adult mental health service (AMHS), if they still require ongoing care.

Adolescence is a high-risk period for psychological morbidity, and young adulthood is the period of onset of most of the serious mental disorders that disable or cause death in adult life.[1-4] The National Comorbidity Survey Replication in the USA found that 75% of people with a mental disorder have an age of onset younger than 24 years, 50% have an onset before 16.[1] However, only a small proportion of young people with mental health problems approaching adulthood, less than one in six, access services or receive appropriate care.[5 6]

There is international concern about young people who get 'lost' during their move from CAMHS to AMHS[7-15] and transition-related discontinuity of care is a major socioeconomic and societal challenge. In the UK, almost half of the service users reaching the transition boundary of their child and adolescent mental health service (CAMHS) do not go on to receive adult care.[7 16] The TRACK study found that less than 5% of patients undergoing CAMHS to AMHS transition experience continuity of care.[17] There is also a concern that despite recognition of ongoing mental health need, few young people are referred, with fewer than one third in one study.[18] Problems at the CAMHS-AMHS interface are accentuated by the fact that young people are simultaneously negotiating developmental and situational transitions, such as changes in housing and relationships and moving on to adult roles.[8 17] A lack of information about possible options, planning that takes too long and where no one professional takes charge to ensure decisions are acted upon, compound the problem.[19] Those who slip through the care net are likely to present to adult services at a subsequent time, with more severe and enduring mental health problems.[20-22] Disruption of care during transition adversely affects the health, wellbeing and potential of this vulnerable group,[23-

28] and negative transition experiences adversely impact the young person's future engagement with mental health services.

Intervening at the level of transition represents one of the most important ways we can facilitate not only recovery but also mental health promotion and mental illness prevention in adulthood. Ensuring sustained treatment through the transitional period is very likely to be cost-effective, since the presence of mental illness during childhood leads to ten times higher costs during adulthood.[29-31] However, there is currently no evidence for any effective model of transitional care or any interventions to reduce these individual and societal costs.[32]

Transitional care

Ideally, transition to adult mental health services should be a planned, orderly, purposeful and patient-centred process that ensures continuity of care, optimises health, minimises adverse events and ensures that the young person attains his/her maximum potential.[33-37] Good transitional care starts with preparing a service user to leave the child-centred health care setting and ends when that person is received in, and properly engaged with, the adult provider or an appropriate alternative, or is discharged from care in a planned and managed fashion.[38 39].

European research on transition from CAMHS to AMHS is sparse, with little information available on the quality of transition and transition experiences in different EU countries in relation to long term mental health outcomes. The organisation of CAMHS in the member states vary, including the age at which young people are transitioned to adult services, size and complexity, sources of funding, and service provision and care. There is some evidence though that transition is a problem across all EU states.[40 41]

Barriers to good transition have been mapped,[16 17] but the evidence of interventions for improving transitional care is scant. A recent systematic review of CAMHS to AMHS transition identified only three initiatives, all in the USA,[42] including a case management model, a transition support model and an outpatient transition programme. Although all three programmes showed

improved clinical and social outcomes for those with facilitated transition, none of these was a randomised trial and each model was deeply rooted within its own particular and specific healthcare context. There is no consensus as to who can be discharged on reaching the CAMHS transitional boundary, who should receive transitional care, and how this care should be delivered. Furthermore, it is not clear what outcomes should be measured to assess clinical and cost effectiveness of the model, what the outcomes of those who fall through the care gap are, and what the individual, organisational and societal costs of poor, inadequate or inappropriate transition are. A recent NICE review on transition from child to adult care across all specialities found that there was no robust evidence on models of transitional care.[32]

In the absence of a planned, purposeful and needs-based assessment of those who reach the boundary, clinical judgment on transition can be influenced by misperceptions of other services, time and resource constraints, poor communication between CAMHS-AMHS, and poor adherence to existing policies. Research has confirmed several information gathering biases in unstructured clinical judgements such as diagnostic biases, confirmation biases, ignoring conflicting information, and assumptions based on patient and service background.[43] A recent study found that feeding back structured assessment results to clinicians is leading to improved clinical decision making.[43]

Ideally all young people who reach a transition boundary would be assessed in a structured and standardised way to determine ongoing need for care. Those who need such care would make a transition to adult services in a planned and managed manner ensuring continuity of care across all domains. Those without ongoing need would be appropriately discharged. Despite the intuitive simplicity and clinical importance of such a structured decision process, a transition model incorporating this approach with regard to mentally ill patients has not been evaluated or reported in research or health practice literature, although its need has been articulated.[11 14]

The MILESTONE project

The five year MILESTONE project (February 2014 to January 2019) aims to improve the understanding of, and strengthen, CAMHS-AMHS transitional care across different healthcare systems in the EU. In a series of work packages, it will 1) map current services and transitional policies across EU; 2) develop and validate transition-specific outcomes measures; 3) conduct a longitudinal cohort study of transition process and outcomes across eight EU countries; 4) develop and test, in a cluster-randomised trial, the clinical and cost-effectiveness of an innovative transitional care model; 5) create clinical, organisational, policy and ethics guidelines for improving care and outcomes for transition age youth; and 6) develop and implement training packages for clinicians across EU. This paper presents the protocol for the work packages dealing with the longitudinal cohort study, the cluster randomised controlled trial and the economic evaluation of the trial, which combined constitute the MILESTONE study.

MILESTONE model of managed transition

The model of transitional care we have developed consists of an evidence-based decision-making process and managed transition, incorporating key principles of continuity of care: adequate information transfer, appropriate joint working, therapeutic and relational continuity, and engagement with adult services. This model includes:

1. The establishment and/or confirmation of shared understanding of criteria for good quality transitional care at the CAMHS-AMHS interface, and managed ending of care, taking into account clinicians' prior knowledge of good quality transition.
2. Systematic identification of all young people under CAMHS care who reach the transition boundary for their service.
3. Structured and standardised assessment of their mental health and social care needs using a bespoke Transition Readiness and Appropriateness Measure (TRAM), prior to reaching the transition boundary.
4. Feedback of TRAM results to relevant clinicians in both CAMHS and AMHS, users, and carers.

5. Structured and regular follow-up of all young people using Transition Outcome Measure (TROM) to assess whether those who needed care were appropriately engaged with adult services and those who had been discharged or referred to other services have no unmet needs following cessation of care.

Transition Readiness and Appropriateness Measure (TRAM) and the Transition Related Outcome Measure (TROM)

The Transition Readiness and Appropriateness Measure (TRAM) is a decision support and assessment tool using the HealthTracker™ platform. The Transition Related Outcome Measure (TROM) provides information on outcomes post-transition. The TRAM aims to identify a) high-risk, high-need cases for whom transition to AMHS is advisable and appropriate; b) those who can be appropriately discharged in a planned manner from CAMHS to a General Practitioner (GP); or c) transitioned to another community based service (such as social services, voluntary sector or other non-statutory agencies).

The TRAM and TROM were developed using existing literature, expert input and focus groups on developing and validating Patient Reported Outcome Measures (PROMS);[44] MILESTONE's group of young advisors also reviewed the scales and helped identify areas of duplication or unclear terms. These scales have been translated into Croatian, Dutch, Flemish, French, German, and Italian languages and provide a summary of all factors necessary to consider (including symptoms, functioning, risk and need for care) when making a transition decision and when assessing the outcomes of a transition. There are versions for young people pre-transition, young people post-transition, parents/carers and clinicians at CAMHS and AMHS which can be completed online, via the HealthTracker™ platform (https://www.healthtracker.co.uk/index.php/our-platform/), a web-based portal allowing measures to be completed remotely, which has been used in other EU FP7 projects [45].

The construct validity, content validity, inter-rater validity, test-retest validity, and sensitivity to change of TRAM and TROM were assessed in a sub-study between June 2015 and April 2016.

The TRAM score summary report presents the scores from the young person, parent/carer and clinician for each item with graphs visualising differences or similarities in scoring. The report contains items that are relevant to the clinician's transition decision (symptoms, risk factors and disruption experienced by the young person) and those that can facilitate a smooth transition.

AIMS AND OBJECTIVES

The overall aim of the nested cRCT is to determine the effectiveness and cost-effectiveness of the model of managed transition in improving the health and social outcomes of young people, and their transition to adult roles, as compared to treatment as usual, in eight participating EU countries. The specific objectives are

1. To test the hypothesis that the implementation of the model of managed transition in CAMHS at the transition boundary improves the mental health and social outcomes of young people and their transition to adult roles when they move on from CAMHS, as compared to usual care.
2. To conduct an economic evaluation of the model of managed transition compared with usual care.
3. To explore the views and experiences of health professionals and young people concerning the intervention.

The prospective cohort study will delineate the transition journey of a large number of young people across eight EU countries. The aims are

4. To evaluate the mental health, quality of life, and functioning of young people who attend CAMHS and reach the CAMHS/AMHS transition boundary;

5. To evaluate the longitudinal course of mental health, social and adult functioning outcomes of young people who reach the CAMHS/AMHS transition boundary and transition into young adulthood;

6. To compare the outcomes in those CAMHS users who transition with those who do not transition to AMHS.

METHODS AND ANALYSIS

Study design and management

A large cohort of young people approaching the CAMHS-AMHS transition boundary in eight EU countries will be recruited and a nested cluster randomised controlled trial (cRCT) in a randomly selected subset of clusters (CAMHS services) will be implemented. The study design is a modification of the Cohort Multiple Randomised Controlled Trial,[46] by virtue of allocation to the intervention by cluster randomisation, with each distinct CAMHS comprising a cluster. MILESTONE is a superiority trial; the aim being to show that managed transition is superior to usual care in improving patient reported outcomes. The study flow diagram is presented in Figure 1. The trial has economic and qualitative components, addressing objectives 2 and 3, respectively.

Figure 1 MILESTONE study flow diagram

The study is co-ordinated from the research office in the Mental Health and Wellbeing unit, Warwick Medical School, with Quality Assurance and Statistics from Warwick Clinical Trials Unit. The Study Co-ordinator is responsible for the day-to-day co-ordination and the Chief Investigator (CI) for clinical aspects. The study is managed by a trial management group (TMG), including work package leaders (i.e. country leads), and supported by MILESTONE research staff. The TMG speaks monthly by telephone conference chaired by the CI. The study conduct and progress is overseen by the MILESTONE Scientific Clinical and Ethical Advisory Board (SCEAB) comprising five international experts and four Patient and Public Involvement representatives. The SCEAB members are invited to the annual general meetings in order to monitor the progress of work, to assess the scientific quality

and to give feed-back to the Consortium members, but without a right to vote. The SCEAB will also review the main governance and any ethical issues which might require greater attention.

MILESTONE has strong Patient and Public Involvement (PPI) embedded throughout the project; young advisors, some with experience of transition in mental health services provided feedback on the protocol and study documents. Their ongoing role includes: attending and contributing to project steering committee meetings, designing the intervention leaflet and other promotional materials, and advising on recruitment and the engagement of young people. The first five PPI representatives have been from the UK; in the third year service users from other participating countries will be involved.

Setting and site selection

The study is currently running in Belgium, Croatia, France, Germany, Italy, the Netherlands, Republic of Ireland, and the United Kingdom. Recruitment of participants is underway in 52 CAMHS clusters that fit the inclusion criteria below (October 2015 – December 2016, with last inclusions in January 2017). Face-to-face meetings with clinical and managerial leads were arranged at those sites that expressed an interest and the study explained in detail. Signed site agreements or equivalent were obtained from participating sites prior to the start of the study.

Cluster level eligibility criteria

For a CAMHS to be eligible, it had to be a service delivering medical and psycho-social interventions for children and adolescents with mental health problems and disorders, and/or neuropsychiatric/developmental disorders (e.g. emotional/neurotic disorders; eating disorders; hyperkinetic disorder/ADHD; autism spectrum disorders); community-based, or provide outpatient or inpatient care; publicly or privately funded; must have a formal upper *age limit* (the transition boundary) for providing care to young people and; be responsible for transfer of care to an adult service for those who reach the transition boundary. Forensic services and highly specialised national services, which cater for rare/unusual disorders and/or serve a national population, such as

specialist clinics for rare metabolic disorders or long-term residential care for severe autism were excluded. Eligible services could vary in size and complexity, ranging from single psychiatrists or psychologists (e.g. Germany) or circumscribed teams to services with multiple teams and localities offering multidisciplinary care (e.g. UK).

Baseline service level data collection

Baseline service data was collected from the CAMHS manager or leading CAMHS clinician at all recruited CAMHS in the year preceding recruitment of study participants. The questionnaire covered: 1) Size (number of staff), structure and function of CAMHS; 2) Transition boundary of the service (i.e. age at expected transition); 3) The number and type of adult mental health services (AMHS) that operate within the CAMHS catchment area; 4) Current transition policy and practice; 5) Size of the catchment population. This information was used to establish the organisational structure of CAMHS and identify potential cross-over and/or movement of staff between teams or units so that distinct units (clusters) could be identified. If one or more CAMHS teams share the same core clinicians, then these were classified as one cluster, becoming the unit of allocation.

Upon leaving CAMHS care, young people may be referred on to AMHS or other another community based service (e.g. social services, voluntary sector or other non-statutory agencies offering support and therapeutic interventions for mental health needs), or discharged back to their GP. Community based services will be invited to participate in the study, and service level data will be collected once they are recruited.

Randomisation

As several countries only had three CAMHS clusters, this fixed the randomisation ratio at 1:2 and the randomisation was conducted in a two stage process: First, randomly selected triplets of clusters within each country were identified for inclusion in the cRCT. These three clusters were further randomised in a 1:2 ratio between intervention and control arms. The excess clusters (those not selected during the first stage for the cRCT) were used for the cohort study only to enhance

numbers. Overall, this two-stage process will equate approximately to a randomisation ratio of 1:3. All randomisation was conducted by the trial statistician using the statistical software Stata 14.[47]

The CAMHS were informed of their allocation after randomisation. The study personnel were also aware of the allocation as they are involved in delivering the intervention and assessing outcomes. The young people and their parents/carers, who are recruited after randomisation, will be informed of their allocation after they have consented to the study, yet only if they ask about this specifically [48].

Participant eligibility and recruitment

Young people

Individual recruitment targets were set for each CAMHS (cluster), based on local capacity, but with the constraint that in the cRCT there should be on average 21 participants per cluster. Databases of all participating CAMHS are scrutinised by CAMHS personnel to identify all young people approaching the service's transition boundary and meeting the inclusion criteria over a 15 month recruitment period (between October 2015 and December 2016).

Young people are eligible, if a) their age is within one year of reaching the transition boundary of their CAMHS during the trial recruitment period and, in exceptional cases, not more than 3 months older than the transition boundary, if a decision about transition has not yet been made; b) they have a mental disorder defined by DSM-IV-TR, DSM-5 or ICD 10/11, or they are under the regular care of CAMHS (if not yet diagnosed); c) they have an IQ ≥ 70 as ascertained by previous standardised assessment or diagnosed by clinician, or no indication of intellectual impairment; and d) they provide valid written informed consent, or assent, if below the legal age of consent. They will be ineligible if they a) are younger than a year before the transition boundary of their CAMHS; b) have a more severe intellectual impairment (IQ < 70) as ascertained by previous standardised assessment or diagnosed by clinician – if no data on intellectual functioning are available (because it has never been assessed) then care coordinators will be asked to make a clinical judgement on

intellectual impairment before baseline assessment takes place; c) are not able to (or expected not to be able to) complete the questionnaires due to severe physical disabilities or language problems, even with assistance from family members or a research assistant; d) are service users in a secure forensic institution; or e) don't provide valid written informed consent, or assent, if below the legal age of consent.

At each site, the clinicians of eligible young people will advise the research team of the ability/capacity of the young person to give informed, voluntary consent or assent. Young people will be introduced to the study (as appropriate, taking local ethical/legal conditions and best practice into consideration) either by a) a clinician or care coordinator, who will provide a study leaflet and/or briefing sheet and seek consent for the individual to be contacted by a MILESTONE researcher using a signed contact form; b) a letter signed by their care coordinator or clinician outlining the purpose of the study followed by a phone call by a CAMHS personnel if no response is received; or c) posters and/or leaflets displayed in the participating CAMHS sites, with contact details of the research team.

All young people who agree to be approached by a MILESTONE researcher will be individually contacted and provided with further information about the study; interested individuals are asked to sign a study consent form. Young people who are below the legal age of consent will be asked for their assent and signed consent is obtained from a parent/carer (or, in some countries, parents/carers, according to national medical ethics requirements).

Parents/carers

The information provided to young people will include separate information and consent forms for their parents/carers. After signing up to the study, the young person will be asked to name his/her primary care giver whom s/he would like to be involved. For young people under the legal age of consent, the parent/carer has to be the legal guardian of the young person. The aim will be to engage the same parent/carer throughout the whole study period. If the latter is not possible, then

the aim is to involve another parent/carer. If the young person doesn't live with his/her biological parent/s, then his/her carer will be involved. A carer may be the legal guardian or a partner or an older adult sibling, or another individual living with and/or providing regular support to the young person.

The parent/carer will be eligible if the young person consents to parent/carer participation and he/she provides a valid written informed consent. A parent/carer will be ineligible if he/she does not live with and/or provide regular support to the young person, and/or is not able to (or expected not to be able to) complete the questionnaires due to severe physical disabilities or language problems, even with assistance from family members or research assistant.

Young people who do not wish their parent/carer to be approached to participate in the study will have their wishes respected, regardless of their own capacity to consent. If a parent/carer is unwilling to participate, their wishes will be respected.

Clinicians/care providers

Clinicians/care providers will be contacted and provided with separate information sheets and consent forms. They are eligible if they are responsible for the main care for the young person at CAMHS (and AMHS or other relevant service provider, if referral is made) and provide a valid written informed consent.

Intervention

The CAMHS in the intervention arm will receive information on good quality managed transition and feedback the TRAM assessment in the form of a TRAM score summary report for each participating young person.

Information provision at CAMHS (AMHS)

A special meeting will be held between MILESTONE personnel and participating CAMHS in the intervention arm prior to service user recruitment to establish clinicians' existing knowledge and

current practice of transition, and to discuss optimal transition, using TRAM as a decision support tool, and managed ending of care. Each meeting will follow a prescribed structure. Additionally, written information on good quality transitional care will be provided to all clinicians in the intervention arm CAMHS teams. This will consist of presentation handouts and a leaflet on good quality transition designed by our young project advisors.

The AMHS linked with the CAMHS will be provided with similar information once the service has been recruited into the study.

Feedback of TRAM results

TRAM findings (TRAM score summary report) will be fed back to clinicians soon after the young person, parent/carer and CAMHS clinician have completed the baseline assessments.

1) The TRAM results will be communicated to the CAMHS clinician via an email, attaching the TRAM score summary report, and an offer made to explain the findings at a face-to-face meeting. If no response is received, the email will be followed up once only with a telephone call.
2) The CAMHS clinician is encouraged to communicate the TRAM findings to the young person and parent/carer.
3) The CAMHS clinician will decide whether or not to refer the young person to adult services.
4) If a referral is made, the CAMHS clinician should, if appropriate and with relevant permissions, send the TRAM score summary report along with the referral letter to the new adult service.
5) The AMHS clinician or other care provider will be offered a chance to discuss the TRAM findings with an appropriate member of the MILESTONE research team.

The aim of the TRAM score summary report is to support clinicians in their decision making regarding transition, communication with stakeholders and planning of the transition process;

hence it supports and is the basis of managed transition. A flowchart of the study intervention is depicted in Figure 2.

Figure 2 Flowchart of study intervention (Feedback of TRAM results) and follow-up assessments with young person

The control arm

Young people, parent/carers and clinicians in the control arm complete the same baseline assessments but the latter do not receive any additional training or feedback of TRAM scores (i.e. will continue providing usual care).

Outcome measures

Primary outcome measure

The primary outcome measure is the clinician-rated Health of the Nation Outcome Scale for Child and Adolescents (HoNOSCA),[49] which has 15 items scored on scale of 0-4, and covers the severity of the behaviour, impairments, symptoms and social functioning of children and young people with mental health problems. The clinical usefulness of the HoNOSCA has been validated and its sensitivity to change confirmed.[50 51]

Although the HoNOSCA is intended as a measure that is completed by a clinician who is also responsible for treatment of the client, the measure can also be completed by a mental health care professional not involved in the treatment using semi-structured interview.[52] In our study the measure will be completed by a trained MILESTONE Research Assistant by interviewing the young person and taking into account all other available sources of information (parent/carer, relevant clinician and the medical records) to ensure accuracy of data.

To ensure consistency and comparability, HoNOSCA is used throughout (rather than switching to HoNOS at age 18 years). The primary outcome endpoint for the cRCT is 15 months.

Secondary outcome measures

The secondary outcome measures are as indicated in Table 1. Two of them were developed specifically for the MIELSTONE study.

Table 1 Outcome measures

Study Instrument	Description
Health of the Nation Outcome Scale for Children and Adolescents (HoNOSCA)[53]	Used to assess the need for care based on a wide range of problems.
Transition Related Outcome Measure (TROM)[1]	Informs on quality of transition and changes in symptoms, risk factors and impairment due to transition. It has been developed based on the TRAM.
World Health Organization Quality of Life Brief Inventory (WHOQOL-BREF)[54 55]	Assesses quality of life, covering physical and psychological health, social relationships and current environment.
MILESTONE specific Client Service Receipt Inventory (CSRI)[56]	Focuses on the use of health and social services.
EuroQol health questionnaire (EQ-5D-5L)[57]	Assesses health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).
ASEBA: Youth Self Report (YSR)/Adult Self Report (ASR)/Child Behavior Checklist (CBCL)/Adult Behavior Checklist (ABCL)[58 59]	Suite of measures assessing dimensions of emotional and behavioural problems.
Ethics of Transitioning[1]	Assesses ethical challenges regarding the delivery of transitional care.
Independent Behaviour During Consultation Scale (IBDCS)[60]	Measures independent behaviour.
Barriers to Care[61]	Assesses practical (e.g. costs, time) and psychological barriers (e.g. fear to stigmatization) to care.
Bullying – adapted from Retrospective Bullying and Friendship Interview Schedule[62 63]	Assesses the experiences with bullying in different settings (e.g. school, at home, college).
Life Events[1]	Assesses significant live events such as accidents, deaths in the family and separation of parents/carers.
Brief Illness Perception Questionnaire (B-IPQ)[64 65]	Assesses the cognitive and emotional representation of illness, including consequences. The term 'illness' has been replaced with the term 'condition'.
On Your Own Feet: Transition Experience Scale (OYOF-TES)[66]	Focuses on specific experiences with the transition process and has two versions: one for Young People who transition to AMHS (or other types of adult care) and one for Young People discharged from CAMHS.
Specific Levels of Functioning Scale (SLOF)[67]	Assesses adult functioning of the Young Person from the Parent/Carer's perspective.
Clinical Global Impression Severity scale (CGI-S)[68]	Assesses the severity of the patient's illness at the time of assessment, relative to the clinician's past experiences.

[1]Developed specifically for the MILESTONE study

The Ethics of Transitioning questionnaire was developed based on the themes raised by a systematic literature review and focus groups and addresses the following research question: "What are the ethical challenges of ensuring delivery of transitional care to those who need it most against the risk of pathologising transient and self-limiting distress and dysfunction, which may be normal during adolescence?". It contains seven items rated on a five-point Likert scale, with one version to be completed prior to, and another after, transitioning.

The Life Events questionnaire is a dichotomous 13-item scale that is appropriate for both young people and adults, and focuses on significant life events, such as accidents, deaths in the family, and separation of parents/carers.

Data collection

Baseline data

Table 2 highlights the number of contacts with the participants, the time points of the various assessments, and the type of data to be collected from the young person, parent/carer and clinician.

Table 2 Study assessments for participants (transition scenario)

Contact	**1**	**2 (T1)**	**3 (T2)**	**4 (T3)**	**5 (T4)**
Contact Window (No. months ± No. months)		**Within 6m before TB*****	**9m (± 1m) after T1**	**15m (± 1m) after T1**	**24m (± 1m) after T1**
Inclusion/exclusion criteria	**YP P/C**				
Informed consent	**YP P/C**	**YP P/C C**	**(YP) (P/C) C**	**(YP) (P/C) (C)**	**(YP) (P/C) (C)**
Contact details	**YP P/C**	**YP P/C**	**YP P/C**	**YP P/C**	**YP P/C**
Sociodemographic & personal information		**YP P/C C**	**YP (C)**	**YP P/C (C)**	**YP P/C (C)**
Need for Care (HoNOSCA – SR) (HoNOSCA – Clinician report)		**YP RA (C;YP;P/C)**	**YP RA (C;YP;P/C)**	**YP RA (C;YP;P/C)**	**YP RA (C;YP;P/C)**
Transition readiness / Transition outcome (TRAM/TROM)		**YP P/C C**	**YP P/C C**	**YP P/C C**	**YP P/C C**
Referral and Transition Status (CAMHS clinician only)			**C**	**(C)**	**(C)**
Quality of Life (WHOQOL-BREF)		**YP**		**YP**	**YP**
Cost-effectiveness (EQ-5D-5L)		**YP**	**YP**	**YP**	**YP**
Service use (CSRI)		**YP**	**YP**	**YP**	**YP**
Emotional/behavioural problems (YP: YSR/ASR P/C: CBCL/ABCL)		**YP P/C**	**YP P/C**	**YP P/C**	**YP P/C**
Ethics of transitioning		**YP**		**YP**	
Independent behaviour** (IBDCS)		**YP**	**YP**	**YP**	**YP**
Barriers to Care (BtC)**			**YP**	**YP**	**YP**
Bullying		**YP**			**YP**
Life events		**YP**	**YP**	**YP**	**YP**
Illness perception (B-IPQ)		**YP**			**YP**
Transition experience & readiness (OYOF-TES)*			**YP P/C**	**(YP) (P/C)**	
Functioning & Impairment (SLOF)		**P/C**		**P/C**	**P/C**
Illness severity (CGIS)		**C**	**(C)**	**(C)**	**(C)**
Psychopathology (YP: DAWBA 5-17/18+ SR) P/C: DAWBA 5-17/18+ PR) C: Clinical diagnosis		**YP P/C C**	**(C)**	**(C)**	**YP P/C (C)**

TB = Transition boundary of service; YP = young person; P/C = parent/carer

C = clinician. T1: CAMHS clinician; if YP is transitioned after T1, then at T2-T4 the clinician is based at AMHS. If there is a delay in transitioning, the clinician at T2-T4 will still be based at CAMHS. Consent and sociodemographic data will be sought from the clinician only once. (C) = if YP is a mental health service user, then clinician will be asked for information.

RA = Research Assistant

SR = Self-report

PR = Parent-report

* = completed only once at the first assessment after transition

** = if the YP is a service user the IBDCS will be administered, if the YP is not a current service user, the BtC will be administered.

*** = in exceptional cases, the assessment can take place up to 12 months before or 3 months after the TB (e.g. if transitions regularly happen earlier in a service or a decision about transition hasn't yet been made.

The baseline assessment (T1) is undertaken after consent/assent has been given but before the delivery of the intervention, within 6 months before the transition boundary of the service or, in exceptional cases, within 12 months before or 3 months after the boundary (e.g. if transitions regularly happen earlier in a service or a decision about transition hasn't yet been made). Young people and their parents/carers are assessed at the clinic, or at an alternative location suitable for the young person, with both semi-structured interview (sociodemographic and personal information, and HoNOSCA) and online assessment. The sociodemographic and personal information questionnaire for young people and parent/carers collects general information about the young person and family, and the care the young person receives. The questionnaire covers also medical history and additional variables previously shown to contribute to continuity of mental health problems (for example, history of mental health problems and alcohol or drug abuse by parents). The last online assessment of T1 is the structured sections of the Development and Well-being Assessment (DAWBA),[69 70] which obtains information on mental health. Information from the assessment with the young person and parent/carer will be combined with a computer algorithm that provides an estimate of the probability of a certain individual diagnosis. Information on clinical diagnosis is obtained from clinician.

The length of the baseline assessment (YP) is approximately 1.5 – 2 hours. The participant can take a short break in between the online measures, and if required, complete them over multiple sessions. The research assistant is available to assist if there are any difficulties. The baseline assessment (T1) should be completed before the end of the recruitment period.

Follow-up data

Outcomes will be measured 9 months (T2), 15 months (T3) and 24 months (T4) after T1. The aim is to complete measures at T2 and T3 via telephone and online assessment, and at T4 via face-to-face contact with young people and their parents/carers, within a month (±) of the calculated assessment

time point (Table 2). Assessments with CAMHS or AMHS clinicians (or other service provider), which is dependent on transition status, follow the same schedule.

Evaluation of the study and intervention

The views and experiences of CAMHS clinicians in the intervention arm will be captured using a semi-structured questionnaire. All clinicians will be approached and those willing to engage will be interviewed over the telephone or face-to-face.

A sub-sample of young people taking part in the study will be invited to take part in focus groups at T4 from three participating countries: Ireland, UK and Croatia. The purpose of the focus groups will be to explore their experiences of leaving CAMHS, transition to AMHS if applicable, and views of mental health services, the aim being to establish whether young people have better health, educational and social outcomes, better quality of life and satisfaction with services if they: a) have experienced a managed transition from child to adult services at the transitional boundary or b) have experienced usual care (i.e. their transition to adult services, or their discharge from services, is via the usual procedure of their CAMHS clinic). It is hoped that, as part of MILESTONE's patient and public involvement activity, some of the young advisors, or other young people trained in facilitation skills by some of the research sites, may co-facilitate these focus groups.

Three audio-recorded focus groups will be held in each country with 9-12 young people in each group. Recruitment will be from the study participants with purposive sampling to include some young people who a) did not transition to adult services, b) who transitioned to adult services via usual care and c) who experienced managed transition.

Sample size

Assuming an average cluster size of 15 participants, an allocation ratio of 2:1 (control : intervention), a coefficient of variation of cluster size of 0.4 (cluster sizes ranging from approximately 5 to 30), and an intracluster correlation coefficient of 0.01, with 600 participants (195 intervention arm (13 clusters), 405 control arm (27 clusters)), the cRCT will have 89% power to detect a difference of 0.30

standard deviations in the primary outcome measure (HoNOSCA). To allow for 30% dropout, 21 participants will be recruited per cluster. Thus, for the cRCT the target sample size is 840 participants in total (273 intervention - 13 clusters of size 21; 567 control - 27 clusters of size 21). The randomisation will be stratified by country and the number and size of clusters dictated by local capacity. Excess clusters (those not required for the cRCT) will be allocated to the control arm and used in the analysis of the cohort study only to enhance numbers for sufficient power to study predictors for the longitudinal course and outcome of mental health during transition. Based on feasibility work to date we anticipate that there will be 10 such excess clusters (average size 21 before drop outs). The recruitment target for the cohort study is therefore 777 participants (567 from the control arm of the cRCT plus 210), and the total recruitment target is 1050 (840 plus 210).

Retention of study participants

To ensure that contact is not lost with any members of the study population during the follow-up period and that data are as complete as possible, MILESTONE has paid considerable attention to its engagement and retention strategies, drawing extensively on the advice and experiences of its young advisors to create a special “Bonding Plan”. Participants may be contacted using several methods of communication (post/phone/email); contact details of all participants, including GP and CAMHS clinician details, will be recorded in a “keeping in touch” form; data will be collected in several different ways (face-to-face, online, phone); and each contact, or contact attempt, made with participants will be recorded in a bespoke contact log. There are multiple contact points between study assessments, where the participants can advise of any changes to their contact details. The Bonding plan activities vary by country taking local ethical and cultural requirements into consideration, and include items such as thank you cards and newsletters and small thank you gifts, such as multi retail gift vouchers or book tokens. Reasonable travel expenses will be reimbursed for young people and their parents/carers.

Losses to follow up

Due to the characteristics of the study population group (young people, highly mobile, in the process of moving on to higher education, training or work), we have allowed for a 30% drop out rate.

Withdrawal of young people from the study

All participants will remain in the study and follow-up data will be sought unless consent for participation in data collection is explicitly withdrawn.

Data analysis

A detailed Statistical Analysis Plan, which will include specific methods of analysis for each outcome variable, will be drawn up by the study statisticians before any analysis is started, and will be reviewed and approved by the Trial Management Group.

A sensitivity analyses using multiple imputation will be conducted to explore the potential impact of missing data.

Cohort study

Baseline, longitudinal course, and outcome data at T4 will be analysed. Trajectories of mental health, subjective need for care and quality of life will be determined using mixed growth models and related to whether transitions from CAMHS to AMHS took place.

Data will be analysed to predict and characterise those with better primary and secondary outcomes. Functional, clinical and quality of life outcomes will be assessed in those CAMHS users who transition with those who do not transition to AMHS.

cRCT

Basic descriptive methods will be used to present the data on study participants, trial conduct, clinical outcomes and safety (in total and for each study group separately). The primary outcome will be HoNOSCA score at T3 and we will test the hypothesis that there is no difference in this between the managed transition and standard care arms over the study period using a multilevel model with

random effects to account for clustering and repeated measures, and adjustment for design factors (country and size of service). Where appropriate, a similar approach will be applied to the analysis of secondary outcomes. All analyses will be on an intention to treat basis.

Economic evaluation

Health economic data collection

To conduct the economic evaluation of the trial, information on health care usage, social care usage/social costs and intervention costs will be captured. Additionally, participant health-related quality of life, and HONOSCA score will be recorded.

Resource use data collection

Health and social care resource utilisation will be estimated using the MILESTONE specific Client Service Receipt Inventory (CSRI), which draws on a CSRI used previously to estimate mental health care costs in the UK,[56] but has been substantially revised for use in MILESTONE. It includes questions regarding not only health care usage, but also relating to social and judicial resource use, and these questions are tailored for each participating country to reflect local services. Young people complete the measure at all four time points. For the purpose of economic evaluation, interviews will also be conducted to ascertain the staff workload and additional resources required for patient care and decision-making related to service users passing through the transition boundary. CAMHS/AMHS in intervention sites will be asked, at end of the study, for specific details of the impact of the managed transition intervention in terms of the number of staff involved in transition, their workload, and additional service resources required. A sub-sample of members of staff will be involved in this part of the study.

The intervention costs associated with managed transition include the cost of implementing, as well as the delivery of the intervention. Questionnaires have been distributed to researchers in each country to ascertain the resources required to set up the intervention, whilst Excel logbooks capture the time spent by clinicians completing the TRAM. Likewise, the time spent by the University of

Warwick preparing the TRAM report is logged within an Excel database and clinician questionnaires will be used to capture the impact of the intervention on resource use.

Outcomes for economic evaluation

The two primary outcomes for the economic evaluation are quality adjusted life years (QALYs) and HONOSCA score.[49 50] Health-related quality of life (HRQL) will be measured using the EQ-5D-5L[57] and index scores[71] will be applied to calculate QALYs to determine the impact of the intervention on HRQL. Changes in QALYs and HONOSCA score between the two trial arms will be examined in conjunction with the costs to examine the cost-effectiveness of the intervention on mental health.

Economic evaluation: analysis

General principles of the economic analysis

Intention to treat: As recommended by best practice,[72] an intention to treat (ITT) framework will be adopted. That is, for each individual within the trial, the analysis will be conducted according to which arm they were randomised.

Perspective: The base-case analysis will adopt a healthcare and personal social services (PSS) perspective in accordance with NICE recommendations.[72] However, given the widespread acknowledgement of the wider costs of mental health, a societal perspective will be adopted as a secondary analysis.

Time horizon: The base-case analysis will be a trial based analysis and therefore consider just the years followed up within the trial. Given the complexity of the trial, the potential for long term decision modelling and extrapolation will be informed by a systematic review of the methods used within existing mental health literature. Long run extrapolation will therefore be considered in light of this.

Discounting: All costs and outcomes that occur after the first year of the trial will be discounted at 3.5%.

Missing data: Typically, within any economic evaluation of an RCT, there will be some missing data. This may be for a number of reasons, and a certain degree of attrition is to be expected during follow up. Should missing data be prevalent, the health economics analysis will address missing data through the use of multiple imputation.

Clustering: The hierarchical nature of the data needs to be addressed within multiple imputation procedures and within the analysis framework. To do this, random effects approaches will be used.

Uncertainty: The uncertainty around the results will be assessed through probabilistic sensitivity analysis and the generation of cost-effectiveness acceptability curves (CEACs).

Calculating costs for economic evaluation

Data on staff time and other resources in the transition process will be obtained at each location, and costed using appropriate sources of unit cost data (e.g. for the UK, standard unit cost sources include the NHS reference costs and the Unit Costs of Health and Social Care report published annually by the Personal Social Services Research Unit at the University of Kent). This will result in location-specific estimates of the direct costs involved in implementing the managed transition process.

Outcomes for economic evaluation

The primary economic analysis will be a cost utility analysis. The EQ-5D-5L measure allows the calculation of QALYs. QALYs will be calculated for each child within the trial using the area under the curve method. The trapezium rule will be used to calculate the area under the curve and thus calculate QALYs. An underlying assumption of this methodology is that there is a linear line between each utility value at each follow up. When analysing incremental QALYs between trial arms, it is important to adjust for baseline differences in utility.[73] In addition to controlling for baseline

utility, it is important to account for the hierarchical nature the outcome data. The base-case analysis of effectiveness will therefore use methods that incorporate a random-effects regression model controlling for baseline health status and accounting for clustering. EQ-5D-5L tariffs for each participating country, where available, will be used to allow for country-specific economic analyses. The cost-effectiveness of the intervention over the duration of the trial will be examined, and decision uncertainty assessed using probabilistic sensitivity analysis and scenario analysis.

Data management

Online data collection

All measures apart from DAWBA will be completed using HealthTracker™, which allows measures to be completed remotely using developmentally appropriate interfaces and subjects to skip modules if they do not score on screening questions for that module, thereby reducing the burden to participants. Each questionnaire has been optimised for the screen, based on feedback from service users and providers. HealthTracker™ automatically generates random participant (service user, parent, and clinician) ID numbers and passwords when the participant is entered onto the system. HealthTracker™ will store participant's month and year of birth. All other data will be anonymised.

The DAWBA will be completed using the website http://dawba.net and anonymised scores (identified and linked using the unique DAWBA ID) transferred to a centrally held secure database that has been developed at Warwick Medical School to store information that is not collected by HealthTracker™. This will include participant name, unique study ID, HealthTracker™ and DAWBA IDs, contact details, information linking participants (for example, young person to CAMHS clinician) and service level information. This database will be maintained locally at sites with access password controlled and strictly limited to MILESTONE personnel to ensure confidentiality. No personally identifiable information relating to participants will leave the local site. Only the unique identifiers, linking information (using identifiers) and service level data will be shared with Warwick Medical School.

Paper-copies of measures are only used as a last resort, or if preferred by the participant. All MILESTONE personnel will receive training on the HealthTracker™ platform and other systems for data collection prior to the study beginning.

Data transfer

All transfers of study data will be informed by and comply with the European Parliament and the Council of Europe's Directive 95/46/EC on protection of individuals with reference to the handling of personal data and on the free flow of such information between EU countries.

To ensure the security and integrity of data during such transfer an appropriate documented standard procedure will be established and followed without exception. Any study data that is to be transferred between research sites will be anonymised prior to transfer.

Data Storage

All essential documentation and trial records will be stored by Warwick Medical School and participating local sites in conformance with the applicable regulatory requirements with access to stored information restricted to authorised personnel.

Data access and quality assurance

In all partner countries, local research ethics committee requirements and national and EU law will underpin the collection, recording, sharing and secure storage of person identifiable data.

Personal information about potential and enrolled participants will be collected, shared, and maintained in a manner, which protects their confidentiality before, during and after the trial. All researchers working on the MILESTONE Study will be experienced in undertaking research in a way that maintains the privacy and confidentiality of study participants but which balances these demands against the needs to ensure that participants are not at risk. Names or addresses of participants will not be disclosed to anyone other than the staff involved in running the trial.

Data will only be accessible by authorised personnel and made available to relevant bodies for audit purposes only.

At the end of the MILESTONE project, analysis datasets will be made available following University of Warwick's Research Data Management Policy which ensures that data produced through the University's research activities is registered, stored, made accessible for use and reuse as appropriate, managed over time and/or disposed of, according to legal, ethical, funder requirements and good practice.(http://www2.warwick.ac.uk/services/rss/researchgovernance_ethics/research_code_of_practice/datacollection_retention/research_data_mgt_policy/)

Archiving

Data from this study will be retained intact in an appropriate format and storage facility for a minimum of 10 years in the UK in line with the Medical Research Council's guidelines on Personal Information in Medical Research; other countries will follow their relevant guidelines. (http://www.mrc.ac.uk/documents/pdf/personal-information-in-medical-research/)

Monitoring

UK sites will be monitored by Warwick Medical School during the first few weeks after recruitment of their first participant. Monitoring will include compliance to the protocol, quality of data collection, storage of documentation and will require monitors to have access to relevant participant notes/charts and trial documentation. Each overseas party will be responsible for monitoring their sites according to local procedures.

Adverse event management

Adverse events as a direct consequence of the intervention are unlikely. At each study assessment, participant will be asked whether any adverse events (bad or unfavourable medical occurrence) have occurred since the last time point. This includes events from the first trial-related activity after the participant has signed the consent form until the end point of the trial as defined in the protocol.

Any worsening of concomitant illness or new illness will be recorded as adverse events at each visit. If the event is classified as a Serious Adverse (SAE) event, an SAE form will be completed and the Principal Investigators (PIs) of each country will report all SAEs immediately to the trial coordinating centre at Warwick Medical School. The trial CI will determine whether SAEs require reporting to the trial sponsor or SCEAB.

ETHICS AND DISSEMINATION

Ethics and R&D governance

The study has been approved by the National Research Ethics Service in the UK (West Midlands: South Birmingham Research Ethics committee, Ref. no. 15/WM/0052) and by research ethics committees of all partaking countries. Regional and site-specific approvals have been obtained from NHS Research and Development offices in the UK and from other similar bodies in the other countries. The study is registered with the ISRCTN trial registry (ISRCTN83240263) (http://www.isrctn.com/ISRCTN83240263?q=MILESTONE&filters=&sort=&offset=3&totalResults=21&page=1&pageSize=10&searchType=basic-search) and ClinicalTrials.com (ADD REGISTRATION NUMBER).

The ethical conduct of the study will be monitored throughout by the MILESTONE Ethics work package.

Service users

We are involving a potentially vulnerable population in research: adolescent mental health service users who, in the main, will be over the age of 16, but in areas where the transition boundary is 16 years they will be under the age of legal consent (i.e. 15 years old). In some countries the age of legal consent is 18.

Despite best efforts, vulnerable people, either by virtue of being young and/or with mental health difficulties, are often omitted from research studies because of concerns regarding informed consent. The researchers in this study acknowledge these concerns and risks but also recognise the

importance of including individuals with enduring mental health difficulties in the study to better inform practice. The Council of Europe strongly promotes the participation of children in decisions affecting them. Young people will also have rights as service users, to expect appropriate and good quality services.

The participant information sheets and consent/assent forms will make explicit the voluntary nature of young people's involvement. Even if the parent/carer gives consent but a young person refuses, that young person will not be included in the study. The young person's consent will be sought before follow-up assessments (verbal consent for telephone interviews), consent being implicit when they log on to give responses online. The forms will also seek permission to delay data collection until a later point should a young person become unwell or due to some other pressing circumstances, as long as transition doesn't take place in the meantime, and to liaise with a young person's clinician and parent/carer should such a delay be deemed necessary. The forms will explain the various safeguards in place, namely to liaise with a young person's clinician and/or family if required and the resulting impact on confidentiality.

In order to minimise any distress to young people taking part in face-to-face interviews, wherever possible these will be organised in venues that are known to the young person and will be scheduled at times when there will be familiar staff or family members or carers on hand to offer support should a young person become upset during any data collection processes.

In the event that during an interview or other data collection session, a MILESTONE researcher identifies any situation where a young person is thought to be at risk of abuse or neglect, or that young person discloses information that raises concern about the young person's safety, then a detailed risk management plan will be followed, which stipulates that the child protection policies and procedures applicable to that country will be adhered to. This is likely to involve close liaison by the researcher and the MILESTONE lead for that study site, with the young person's clinician and/or the nominated child protection leads within the mental health service attended by the young

person. Also, young people consenting to the study will be asked to nominate, and provide contact details for, a health/care professional (for example, GP or CAMHS clinician) who we may contact should any adverse event arise. This safeguard will be made explicit in the study information leaflets, and at all data collection time points, so young people are aware of the impact on confidentiality during the process of data collection.

Training

All research assistants have participated in training sessions addressing Good Clinical Practice (GCP), transition practices, rating procedures, compliance, TRAM feedback, and communication with young people, families and clinicians. The study has been presented to all participating CAMHS teams and additional meetings have been held to implement the specific transition procedures in the intervention clusters.

Dissemination

The MILESTONE project has a work package that focuses on dissemination. Partnerships and networks with target bodies will be strategically developed to support both short- and long-term dissemination of the MILESTONE study and other project findings. External dissemination will target the scientific community, but also the general public, lay and patients' associations, health care authorities and care givers, scientific societies and professional boards, students, policy makers, and the pharmaceutical industry. Particular attention will be paid to the information needs of the various target audiences, and that they are addressed in the appropriate language and format.

The results of the MILESTONE study will be made available in the first instance to the clinicians of CAMHS and AMHS partaking in the study, and then to the scientific community at large via publications in scientific journals, presentations at meetings, the MILESTONE web site (http://milestone-transitionstudy.eu), press releases, and leaflets.

CONCLUSION

The continuity of adolescent psychopathology into adulthood means that transition to AMHS is necessary for many. However, there are real gaps in mental health care provision at this crucial stage, and those who experience transition frequently describe it as disruptive. The MILESTONE study is the first ever methodologically robust trial to test whether a decision support and assessment tool, the TRAM, can improve the mental health and social outcomes and functioning of transition age young people receiving CAMHS care. Young people in eight European countries are partaking in the trial; their longitudinal course of mental health, social and adult functioning outcomes are also evaluated as part of a longitudinal cohort study. The MILESTONE study has crucial input from young advisors, some with experience of transition in mental health services.

MILESTONE CONSORTIUM – MEMBERS AND PARTNER INSTITUTIONS

Swaran Singh, Helena Tuomainen, Jason Madan, Moli Paul, Cathy Street, Dieter Wolke, Jane Warwick, Priya Tah, Alastair Canaway, James Griffin, Rebecca Appleton, Amanda Tuffrey, Anna Wilson, Charlotte Gatherer, Leanne Walker, Jude Taylor (University of Warwick, UK); Giovanni de Girolamo, Giulia Signorini, Alessandro Ferrari, Elisa Gheza, Cecilia Ferrari, Laura Rivolta, Flavia Levi, Maria Cataldo, Lidia Manenti, Giorgia Morini, Adriana Pastore, Cecilia Toselli, Pamela Varvara (Saint John of God Clinical Research Center, Italy); Paramala Santosh, Kate Lievesley, Laura Adams, Jatinder Singh (Kings College London, UK); Diane Purper-Ouakil, Frédérick Russet, Virginie Maurice, Véronique Humbertclaude (Centre Hospitalier Universitaire de Montpellier, France); Athanasios Maras, Larissa van Bodegom, Mathilde Overbeek, Esther Kooymans (Yulius Academy, Netherlands); Ulrike Schulze, Jörg M Fegert, Sonja Aslan, Melanie Saam, Ulrike Breuninger, Renate Schepker, Michele Noterdaeme (University of Ulm, Germany); Sabine Tremmery, Veronique de Roeck (Katholieke Universiteit Leuven, Belgium); Fiona McNicholas, Lesley O'Hara, Rachael McKenna (University College Dublin, Republic of Ireland); Tomislav Franić, Nikolina Davidović (University Hospital Split, Croatia); Federico Fiori (HealthTracker Ltd, UK); Frank Verhulst, Gwen C Dieleman,

Suzanne Gerritsen (Erasmus Medical Centre, Netherlands); Andrea Wohner (concentris research management GmbH, Germany)

ACKNOWLEDGEMENTS

We are very grateful for the CAMHS and AMHS services and research teams who are collaborating in this study in the eight European countries. We also extend thanks to all the participating service users and their parents/carers. We are also grateful for the members of the MILESTONE Scientific Clinical and Ethical Advisory Board (SCEAB) - Norman Sartorius, Pat McGorry, Maryann Davis, Mario Maj, and Adriana Mihai – and for Tanveer Sandhu, Philippa Coleman for reviewing the protocol. We would also like to thank members of the wider MILESTONE Consortium for their contribution. We extend a special thanks to Andrea Wohner, our project manager based at concentris research management gmbh, Fürstenfeldbruck, Germany, for excellent project management and delivery.

AUTHORS' CONTRIBUTIONS

SPS is the chief investigator who conceived the original study design and obtained funding, together with AM, GdG, PS, JM, FM, DPO, ST, US, TF, CS, MP, DW, FV, and GD. HT is the study coordinator who prepared the first draft of the protocol and this manuscript, and is joint first author with SPS. JW and AC contributed to the manuscript. JW is the senior trial statistician who led the calculation of the sample size; JG will undertake the statistical analysis under her direction. JM designed the health economic component and AC will undertake the health economics analysis under his direction. CD is the quality assurance manager. PT, SG, GS, LA, FR, SA, LOH, and ND are research assistants and helped set up the study in their countries and gain local ethical approvals. The UK young advisors, AT, AW, CG, and LW, reviewed the proposed study scales (including the likely time required for completion, to assess for possible burden on study participants), participated in the design of the intervention leaflet and reviewed all study information material before submission to ethics. All authors critically reviewed the protocol and the manuscript, and gave approval for the publication.

FUNDING

The MILESTONE project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602442. This paper reflects only the authors' views and the European Union is not liable for any use that may be made of the information contained therein. The funding body has had no role in the study design, in the writing of the protocol or in the decision to submit the paper for publication.

COMPETING INTERESTS

Paramala Santosh is the director and shareholder of HealthTracker. Frank Verhulst publishes the Dutch translations of ASEBA from which he receives remuneration.

REFERENCES

1. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62(6):617-27.
2. McGorry P. The specialist youth mental health model: strengthening the weakest link in the public mental health system. *Med J Aust* 2007;187(7):s53-s56.
3. McGorry P. Transition to adulthood: the critical period for pre-emptive, disease-modifying care for schizophrenia and related disorders. *Schizophr Bull* 2011;37(3):524-30.
4. Pottick KJ, Bilder S, Vander Stoep A, et al. US patterns of mental health service utilization for transition-age youth and young adults. *J Behav Health Serv Res* 2008;35(4):373-89.
5. Kataoka SH, Zhang L, Wells KB. Unmet need for mental health care among U.S. children: variation by ethnicity and insurance status. *Am J Psychiatry* 2002;159(9):1548-55.
6. Offord DR, Boyle MH, Fleming JE, et al. Ontario Child Health Study. Summary of selected results. *Can J Psychiatry* 1989;34(6):483-91.
7. Singh SP, Paul M, Ford T, et al. Transitions of care from child and adolescent mental health services to adult mental health services (TRACK study): a study of protocols in Greater London. *BMC Health Serv Res* 2008;8(135):1-7.
8. Singh SP, Paul M, Ford T, et al. Process, outcome and experience of transition from child to adult mental healthcare: multiperspective study. *Br J Psychiatry* 2010;197(4):305-12.
9. Davis M, Geller JL, Hunt B. Within-state availability of transition-to-adulthood services for youths with serious mental health conditions. *Psychiatr Serv* 2006;57(11):1594-99.
10. Davis M, Vander Stoep A. The transition to adulthood for youth who have serious emotional disturbance: Developmental transition and young adult outcomes. *J Ment Health Adm* 1997;24(4):400-27.
11. Royal College of Nursing. Adolescent transition care. London: RCN Publications, 2004.
12. Royal College of Paediatrics and Child Health. Bridging the gaps: healthcare for adolescents. Secondary Bridging the gaps: healthcare for adolescents 2003.
13. Royal College of Physicians of Edinburgh Transition Steering Group. Think transition: developing the essential link between paediatric and adult care. Edinburgh: Royal College of Physicians of Edinburgh, 2008.

14. Royal College of Psychiatrists. Building and sustaining specialist child and adolescent mental health services: council report CR137. London: Royal College of Psychiatrists, 2006.
15. Davis M, Sondheimer DL. State child mental health efforts to support youth in transition to adulthood. *J Behav Health Serv Res* 2005;32(1):27-42.
16. Paul M, Ford T, Kramer T, et al. Transfers and transitions between child and adult mental health services. *Br J Psychiatry Suppl* 2013;54:s36-40.
17. Hovish K, Weaver T, Islam Z, et al. Transition experiences of mental health service users, parents, and professionals in the United Kingdom: a qualitative study. *Psychiatr Rehabil J* 2012;35(3):251-7.
18. McNicholas F, Adamson M, McNamara N, et al. Who is in the transition gap? Transition from CAMHS to AMHS in the Republic of Ireland. *Ir J Psychol Med* 2015;32(01):61-69.
19. Wilson A, Tuffrey A, McKenzie C, et al. After the flood: young people's perspectives on transition. *Lancet Psychiatry* 2015;2(5):376-78.
20. Davis M. Addressing the needs of youth in transition to adulthood. *Adm Policy Ment Health* 2003;30(6):495-509.
21. Department of Health. Continuity of care for people with severe mental illness? London: Department of Health, 2003.
22. Vostanis S, Richards V. Transition services for 16-19 year olds. Leicester: Leicester University, 2002.
23. Department for Children Schools and Families, Department of Health. A transition guide for all services: key information for professionals about the transition process for disabled young people. Secondary A transition guide for all services: key information for professionals about the transition process for disabled young people 2007.
24. Department for Children Schools and Families, Department of Health. Transition: moving on well. A good practice guide for health professionals and their partners on transition planning for young people with complex health needs or a disability. London: Department of Health, 2008.
25. Forbes A, While A, Ullman R, et al. A multi-method review to identify components of practice which may promote continuity in the transition from child to adult care for young people with chronic illness or disability. Report for the National Coordinating Centre for NHS Service Delivery and Organisation R & D (NCCSDO): The Florence Nightingale School of Nursing and Midwifery, King's College, London, UK, 2002.
26. Kennedy A, Sloman F, Douglass JA, et al. Young people with chronic illness: the approach to transition. *Intern Med J* 2007;37(8):555 - 60.
27. Kennedy P, Pugh R, Millar E. Towards managing the whole system of care and improving continuity of care. *Psychiatr Bull* 2005;29(7):252-54.
28. Whaley AL. Racism in the provision of mental health services; a social cognitive analysis. *Am J Orthopsychiatry* 1998;68:47-57.
29. Suhrcke M, Pillas D, Selai C. Economic aspects of mental health in children and adolescents. . Social Cohesion for Mental Wellbeing among adolescents: WHO, 2008:43-64.
30. Petrou S, Johnson S, Wolke D, et al. Economic costs and preference-based health-related quality of life outcomes associated with childhood psychiatric disorders. *Br J Psychiatry* 2010;197(5):395-404.
31. Copeland WE, Wolke D, Shanahan L, et al. Adult Functional Outcomes of Common Childhood Psychiatric Problems: A Prospective, Longitudinal Study. *JAMA psychiatry* 2015;72(9):892-9.
32. National Institute For Health and Care Excellence. Transition from children's to adults' services for young people using health or social care services. NICE guideline: Full version. London: NICE, 2016.
33. Blum R, Garell D, Hodgman C, et al. Transition from child-centered to adult health-care systems for adolescents with chronic conditions: a position paper for the Society of Adolescent Medicine. *J Adolesc Health* 1993;14:570–76.

34. McDonagh JE. Growing up ready for emerging adulthood: an evidence base for professionals involved in transitional care for young people with chronic illness and/or disabilities. Cambridge: Eastern Region Public Health Observatory, 2006.
35. McDonagh JE, Kelly DA. Transiting care of the pediatric recipient to adult care givers. *Pediatr Clin North Am* 2003;50:1561-83.
36. McDonagh JE, Viner R. Lost in transition? Between paediatric and adult services. *British Medical Journal* 2006;332:435-36.
37. Singh SP, Anderson B, Liabo K, et al. Supporting young people in their transition to adults' services: summary of NICE guidance. *BMJ* 2016;353:i2225.
38. Coleman EA, Berenson RA. Lost in transition: challenges and opportunities for improving the quality of transition of care. *Ann Intern Med* 2004;141(7):533-36.
39. Singh SP, Tuomainen H. Transition from child to adult mental health services: needs, barriers, experiences and new models of care. *World Psychiatry* 2015;14(3):358-61.
40. Brittlebank A, Hermans M, Bhugra D, et al. Training in psychiatry throughout Europe. *Eur Arch Psychiatry Clin Neurosci* 2016;266(2):155-64.
41. Schandrin A, Capdevielle D, Boulenger J-P, et al. Transition from child to adult mental health services: a French retrospective survey. *The Journal of Mental Health Training, Education and Practice* 2016;11(5):286-93.
42. Paul M, Street C, Wheeler N, et al. Transition to adult services for young people with mental health needs: A systematic review. *Clin Child Psychol Psychiatry* 2014.
43. Aebi M, Kuhn C, Metzke C, et al. The use of the devlopment and well-being assessment (DAWBA) in clinical practice: a randomized trial. *Eur Child Adolesc Psychiatry* 2012;21:559-67.
44. Nelson EC, Eftimovska E, Lind C, et al. Patient reported outcome measures in practice. *Bmj* 2015;350:g7818.
45. Flamarique I, Santosh P, Zuddas A, et al. Development and psychometric properties of the Suicidality: Treatment Occurring in Paediatrics (STOP) Suicidality Assessment Scale (STOP-SAS) in children and adolescents. *BMC Pediatr* 2016;16(1):213.
46. Relton C, Torgerson D, O'Cathain A, et al. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. *BMJ* 2010;340:c1066.
47. Stata Statistical Software: Release 14 [program]. College Station, TX: StataCorp LP, 2015.
48. Hayes RJ, Moulton LH. Cluster randomised trials. Interdisciplinary Statistics Series: Chapman & Hall/CRC, 2009.
49. Gowers SG, Harrington RC, Whitton A, et al. Brief scale for measuring the outcomes of emotional and behavioural disorders in children. Health of the Nation Outcome Scales for children and Adolescents (HoNOSCA). *Br J Psychiatry* 1999;174:413-6.
50. Garralda ME, Yates P, Higginson I. Child and adolescent mental health service use: HoNOSCA as an outcome measure. *Br J Psychiatry* 2000;177(1):52-58.
51. Pirkis JE, Burgess PM, Kirk PK, et al. A review of the psychometric properties of the Health of the Nation Outcome Scales (HoNOS) family of measures. *Health Qual Life Outcomes* 2005;3:76.
52. Demartini B, Petrochilos P, Edwards MJ, et al. Multidisciplinary inpatient programme for functional neurological symptoms: a prospective study assessing efficacy and predictors of good outcome. *J Neurol Neurosurg Psychiatry* 2014;85(8):e3.
53. Gowers S, Levine W, Bailey-Rogers S, et al. Use of a routine, self-report outcome measure (HoNOSCA-SR) in two adolescent mental health services. Health of the Nation Outcome Scale for Children and Adolescents. *Br J Psychiatry* 2002;180:266-9.
54. Skevington SM, Sartorius N, Amir M. Developing methods for assessing quality of life in different cultural settings. The history of the WHOQOL instruments. *Soc Psychiatry Psychiatr Epidemiol* 2004;39(1):1-8.
55. Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res* 2004;13(2):299-310.

56. Chisholm D, Knapp MR, Knudsen HC, et al. Client Socio-Demographic and Service Receipt Inventory--European Version: development of an instrument for international research. EPSILON Study 5. European Psychiatric Services: Inputs Linked to Outcome Domains and Needs. *Br J Psychiatry Suppl* 2000(39):s28-33.
57. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36.
58. Achenbach T, Rescorla L. Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families, 2001.
59. Achenbach T, Rescorla L. Manual for the ASEBA Adult Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families, 2003.
60. van Staa A. Unraveling triadic communication in hospital consultations with adolescents with chronic conditions: the added value of mixed methods research. *Patient Educ Couns* 2011;82(3):455-64.
61. Vanheusden K, Mulder CL, van der Ende J, et al. Young adults face major barriers to seeking help from mental health services. *Patient Educ Couns* 2008;73(1):97-104.
62. Wolke D, Sapouna M. Big men feeling small: childhood bullying experience, muscle dysmorphia and other mental health problems in bodybuilders. *Psychol Sport Exerc* 2008;9(5):595-604.
63. Tippett N, Wolke D, Platt L. Ethnicity and bullying involvement in a national UK youth sample. *J Adolesc* 2013;36(4):639-49.
64. Broadbent E, Petrie KJ, Main J, et al. The brief illness perception questionnaire. *J Psychosom Res* 2006;60(6):631-7.
65. Løchting I, Garratt A, Storheim K, et al. Evaluation of the Brief Illness Perception Questionnaire in Sub-Acute and Chronic Low Back Pain Patients: Data Quality, Reliability and Validity. *J Pain Relief* 2013;2(122).
66. van Staa A, Sattoe JN. Young Adults' Experiences and Satisfaction With the Transfer of Care. *J Adolesc Health* 2014.
67. Mucci A, Rucci P, Rocca P, et al. The Specific Level of Functioning Scale: Construct validity, internal consistency and factor structure in a large Italian sample of people with schizophrenia living in the community. *Schizophr Res* 2014;159(1):144-50.
68. Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: U.S. Department of Health, Education, and Welfare, 1976.
69. Goodman R, Ford T, Richards H, et al. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry* 2000;41(5):645-55.
70. Goodman A, Heiervang E, Collishaw S, et al. The 'DAWBA bands' as an ordered-categorical measure of child mental health: description and validation in British and Norwegian samples. *Soc Psychiatry Psychiatr Epidemiol* 2011;46(6):521-32.
71. Devlin N, Shah K, Feng Y, et al. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. OHE Research Paper 16/01. London: Office of Health Economics, 2016.
72. National Institute For Health and Care Excellence. Guide to the methods of technology appraisal 2013. London: NICE, 2013.
73. Manca A, Palmer S. Handling missing data in patient-level cost-effectiveness analysis alongside randomised clinical trials. *Appl Health Econ Health Policy* 2005;4(2):65-75.

FIGURES

Figure 1 MILESTONE study flow diagram

Figure 2 Flowchart of study intervention (Feedback of TRAM results) and follow-up assessments with young person

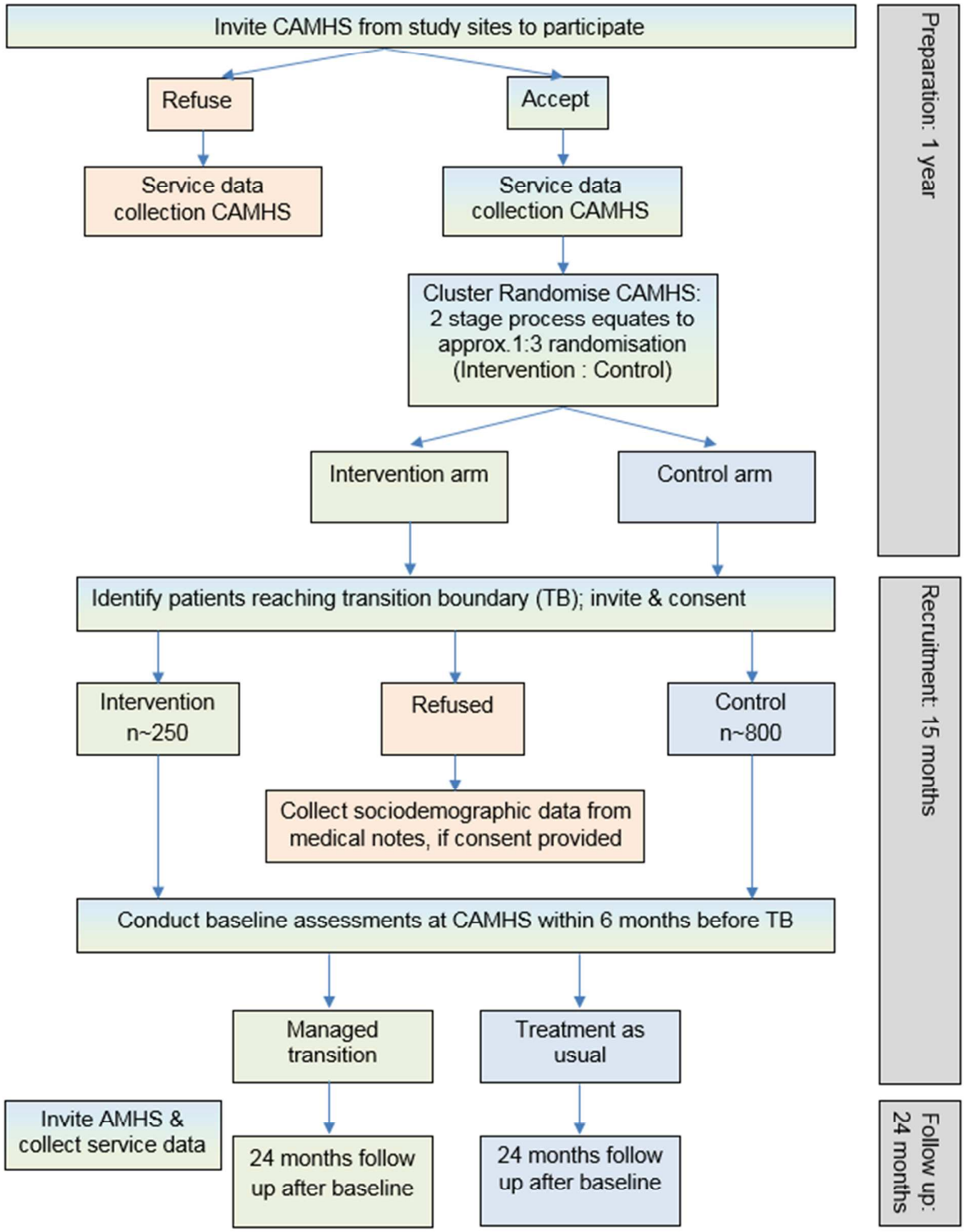

Figure 1 MILESTONE study flow diagram

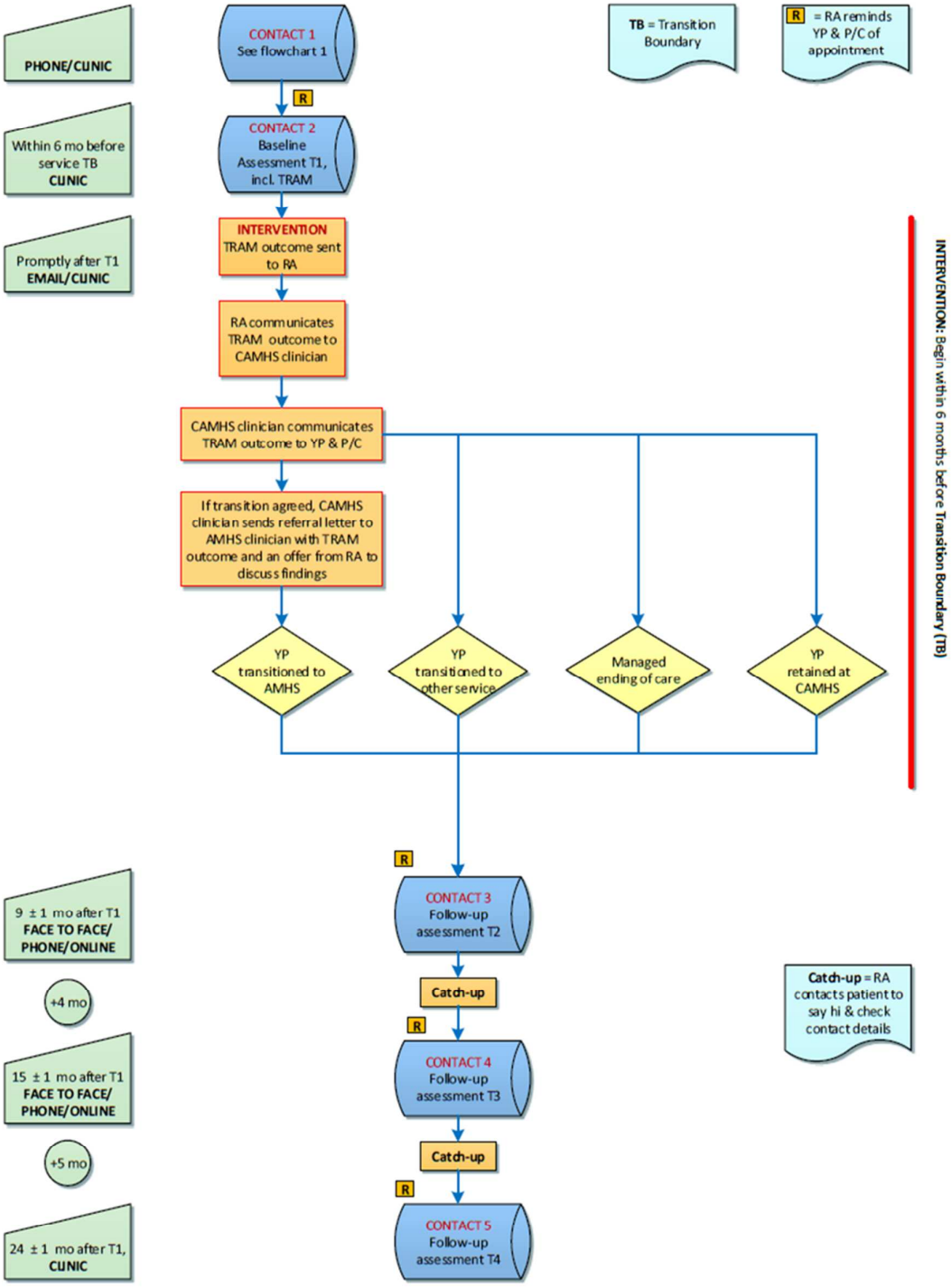

Figure 2 Flowchart of study intervention (Feedback of TRAM results) and follow-up assessments with young person

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5 - 10
	2b	Specific objectives or hypotheses	10
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	11, 13
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a (protocol)
Participants	4a	Eligibility criteria for participants	14-16
	4b	Settings and locations where the data were collected	12-13
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	16-18
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	18-22
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a (protocol)
Sample size	7a	How sample size was determined	23-24
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	13
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	13
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	n/a (cRCT)
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	13-15
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	13

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	25-26
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	27-29
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n/a (protocol)
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n/a (protocol)
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	36

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Protocol for a cohort study of adolescent mental health service users with a nested cluster-randomised controlled trial to assess the clinical and cost effectiveness of managed transition in improving transitions from child to adult mental health services (The MILESTONE study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016055.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Jun-2017
Complete List of Authors:	Singh, Swaran; University of Warwick, Warwick Medical School Tuomainen, Helena; University of Warwick, Warwick Medical School De Girolamo, Giovanni; Psychiatric Epidemiology and Evaluation Unit, Saint John of God Clinical Research Center, Brescia, Italy Maras, Athanasios; Yulius Academy, Rotterdam, Netherlands; Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands Santosh , Paramala; King's College London , Child and Adolescent Psychiatry ; HealthTracker Ltd McNicholas, Fiona; University College Dublin School of Medicine and Medical Science; Geary Institute, University College Dublin, Dublin, Republic of Ireland Schulze, Ulrike; Universitatsklinikum Ulm Klinik fur Kinder- und Jugendpsychiatrie Psychotherapie Purper-Ouakil, Diane; Centre Hospitalier Regional Universitaire de Montpellier Tremmery, Sabine; Katholieke Universiteit Leuven, Department of Neurosciences, Child & Adolescent Psychiatry; Universitaire Ziekenhuizen Leuven, Department of Child and Adolescent Psychiatry Franić, Tomislav; Department of Psychiatry, Clinical Hospital Center Split Madan, Jason; University of Warwick, Warwick Medical School Paul, Moli; Coventry and Warwickshire Partnership NHS Trust; University of Warwick, Warwick Medical School Verhulst, Frank; Erasmus MC, Department of Child and Adolescent Psychiatry and Psychology; Kobenhavns Universitet, Department of Clinical Medicine Dieleman, Gwen; Erasmus MC, Department of Child and Adolescent Psychiatry and Psychology Warwick, Jane; University of Warwick Warwick Medical School, Warwick Clinical Trials Unit Wolke, Dieter; University of Warwick, Department of Psychology and Warwick Medical School Street, Cathy; University of Warwick, Warwick Medical School Daffern, Claire; University of Warwick, Warwick Medical School Tah, Priya ; University of Warwick, Warwick Medical School Griffin, James; University of Warwick, Warwick Medical School, Clinical Trials Unit

	Canaway, Alastair; University of Warwick, Warwick Medical School Signorini, Giulia; Psychiatric Epidemiology and Evaluation Unit, Saint John of God Clinical Research Center, Brescia, Italy Gerritsen, Suzanne; Erasmus MC, Department of Child and Adolescent Psychiatry and Psychology Adams, Laura; University of Plymouth, School of Psychology O'Hara, Lesley; University College Dublin, Department of Child and Adolescent Psychiatry Aslan, Sonja; Universitat Ulm, Department of Child and Adolescent Psychiatry/Psychotherapy Russet, Frédérick; Centre Hospitalier Regional Universitaire de Montpellier Davidović, Nikolina; Department of Psychiatry, Clinical Hospital Center Split Tuffrey, Amanda; University of Warwick, Warwick Medical School Wilson, Anna; University of Warwick, Warwick Medical School Gatherer, Charlotte; University of Warwick, Warwick Medical School Walker, Leanne; University of Warwick, Warwick Medical School
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Health services research
Keywords:	Child & adolescent psychiatry < PSYCHIATRY, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, EPIDEMIOLOGY

Protocol for a cohort study of adolescent mental health service users with a nested cluster-randomised controlled trial to assess the clinical and cost effectiveness of managed transition in improving transitions from child to adult mental health services (The MILESTONE study)

CORRESPONDING AUTHOR

Swaran P Singh
Mental Health and Wellbeing
Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry CV4 7AL
UK
S.P.Singh@warwick.ac.uk
+44 (0) 2476 574 530

JOINT FIRST AUTHOR

Helena Tuomainen, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK

Swaran P Singh and Helena Tuomainen contributed equally to this paper.

CO-AUTHORS

Giovanni De Girolamo, Psychiatric Epidemiology and Evaluation Unit, Saint John of God Clinical Research Center, Brescia, Italy
Athanasios Maras, Yulius Academy, Rotterdam, Netherlands; Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands
Paramala Santosh, Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK; Centre for Interventional Paediatric Psychopharmacology and Rare Diseases (CIPPRD), National and Specialist Child and Adolescent Mental Health Services, Maudsley Hospital, London, UK; HealthTracker Ltd, Gillingham, UK
Fiona McNicholas, Department of Child and Adolescent Psychiatry, University College Dublin School of Medicine and Medical Science, Dublin, Republic of Ireland; Geary Institute, University College Dublin, Dublin, Republic of Ireland; Department of Child Psychiatry, Our Lady's Hospital for Sick Children, Dublin, Republic of Ireland; Lucena Clinic SJOG, Dublin, Republic of Ireland
Ulrike Schulze, Department of Child and Adolescent Psychiatry/Psychotherapy, University of Ulm, Germany
Diane Purper-Ouakil, Centre Hospitalier Universitaire de Montpellier, Montpellier, France
Sabine Tremmery, Department of Neurosciences, Child & Adolescent Psychiatry, University of Leuven, Belgium; Department of Child & Adolescent Psychiatry, University Hospitals Leuven, Leuven, Belgium
Tomislav Franić, Department of Psychiatry, Clinical Hospital Center Split, Split, Croatia
Jason Madan, Warwick Medical School, University of Warwick, Coventry, UK

Moli Paul, Coventry and Warwickshire Partnership NHS Trust, UK; Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Frank C Verhulst, Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands; Department of Clinical Medicine, University of Copenhagen, Denmark
Gwen C Dieleman, Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands
Jane Warwick, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
Dieter Wolke, Department of Psychology, University of Warwick, UK; Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Cathy Street, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Claire Daffern, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
Priya Tah, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
James Griffin, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
Alastair Canaway, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
Giulia Signorini, Psychiatric Epidemiology and Evaluation Unit, Saint John of God Clinical Research Center, Brescia, Italy
Suzanne Gerritsen, Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands
Laura Adams, School of Psychology, Plymouth University, UK
Lesley O'Hara, Department of Child and Adolescent Psychiatry, UCD, Dublin, Republic of Ireland
Sonja Aslan, Department of Child and Adolescent Psychiatry/Psychotherapy, University of Ulm, Germany
Frédérick Russet, Centre Hospitalier Universitaire de Montpellier, Montpellier, France
Nikolina Davidović, Department of Psychiatry, Clinical Hospital Center Split, Split, Croatia
Amanda Tuffrey, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Anna Wilson, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Charlotte Gatherer, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Leanne Walker, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK

for the MILESTONE Consortium

WORDCOUNT

10906 (excludes references)

KEYWORDS

Mental health, child and adolescent mental health services, transition, health services research, cluster randomised controlled trial, longitudinal cohort study, youth mental health, Europe

ABSTRACT

Introduction: Disruption of care during transition from Child and Adolescent Mental Health (CAMHS) to Adult Mental Health Services (AMHS) may adversely affect the health and wellbeing of service users. The MILESTONE study aims to evaluate the longitudinal course and outcomes of adolescents approaching transition boundary (TB) of their CAMHS and to determine the effectiveness of the model of managed transition in improving outcomes, compared to usual care.

Methods and analysis: A cohort study with a nested cluster randomised controlled trial. Recruited CAMHS randomised to provide either i) managed transition underpinned by the Transition Readiness and Appropriateness Measure (TRAM) or ii) usual care for young people reaching the transition boundary. Participants are young people within one year of reaching the TB of their CAMHS in eight European countries; one parent/carer and a CAMHS clinician for each recruited young person; and adult mental health clinician or other community based care provider, if young person transitions. Primary outcome is Health of the Nation Outcome Scale for Children and Adolescents (HoNOSCA) measuring health and social functioning at 15 months post-intervention. Secondary outcomes include mental health, quality of life, transition experience, and health care usage assessed at 9, 15 and 24 months post-intervention. With a mean cluster size of 21, a total of 840 participants randomised 1:2 intervention to control is required. This provides 89% power to detect a difference in HoNOSCA score of 0.30 standard deviations. The addition of 210 recruits for the cohort study ensures sufficient power for studying predictors, resulting in 1050 participants and an approximate 1:3 randomisation.

Ethics and dissemination: The study protocol was approved by the UK National Research Ethics Service (15/WM/0052) and equivalent ethics boards in participating countries. Results will be reported at conferences, in peer-reviewed publications, and to all relevant stakeholder groups.

Trial registration numbers: ISRCTN83240263; NCT03013595

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first ever methodologically robust trial to test whether a decision support and assessment tool can improve the mental health and social outcomes and functioning of transition age young people receiving care at Child and Adolescent Mental Health Services.
- A large, prospectively identified and robustly evaluated cohort of young people across several European countries with diverse health care systems is taking part in the study.
- The cost-effectiveness of the intervention and research-related changes in health systems in terms of both expenditure and related health outcomes will be evaluated.
- There is a strong Patient and Public Involvement (PPI) at all stages of the study.
- Due to the nature of the intervention it is not possible for clinicians or assessors to be blind to the allocation of clusters or of the service users within these clusters.

INTRODUCTION

The MILESTONE (Managing the Link and Strengthening Transition from Child to Adult Mental Health Care) study focuses on the period when young people (YP) attending Child and Adolescent Mental Health Services (CAMHS) need to move on, or "transition" to, an adult mental health service (AMHS), if they still require ongoing care.

Adolescence is a high-risk period for psychological morbidity, and young adulthood is the period during which most of the serious mental disorders that disable or cause death in adult life have their onset.[1-4] The National Comorbidity Survey Replication in the USA found that 75% of people with a mental disorder have an age of onset younger than 24 years, 50% have an onset before 16.[1] However, only a small proportion of young people with mental health problems approaching adulthood, less than one in six, access services or receive appropriate care.[5 6]

There is international concern about young people who get 'lost' during their move from CAMHS to AMHS[7-15] and transition-related discontinuity of care is a major socioeconomic and societal challenge. In the UK, almost half of the service users reaching the transition boundary of their child and adolescent mental health service (CAMHS) do not go on to receive adult care.[7 16] The TRACK study found that less than 5% of patients undergoing CAMHS to AMHS transition experience continuity of care.[17] There is also a concern that despite recognition of ongoing mental health need, few young people are referred, with fewer than one third in one study.[18] Continuity of care is hampered by a multitude of reasons, including differences between adult and child models of care; differing referral criteria; lack of a planned, purposeful and needs-based assessment of those who reach the boundary; communication and information transfer problems between services caused partly by different beliefs, attitudes, mutual misperceptions and lack of understanding of different service structures; lack of shared protocols/manuals for transition; lack of shared client planning between child and adult systems; young people's level of maturity and understanding; and

adolescent and/or family resistance to transition.[19-21]. Furthermore, transition may differ widely across different regions and countries due to lack of or different procedures.

Problems at the CAMHS-AMHS interface are accentuated by the fact that young people are simultaneously negotiating developmental and situational transitions, such as changes in housing and relationships and moving on to adult roles.[8 17] A lack of information about possible options, planning that takes too long and where no one professional takes charge to ensure decisions are acted upon, compound the problem.[22] Those who slip through the care net are likely to present to adult services at a subsequent time, with more severe and enduring mental health problems.[23-25] Disruption of care during transition adversely affects the health, wellbeing and potential of this vulnerable group,[26-31] and negative transition experiences adversely impact the young person's future engagement with mental health services.[32]

Intervening at the level of transition represents one of the most important ways we can facilitate not only recovery but also mental health promotion and mental illness prevention in adulthood. Ensuring sustained treatment through the transitional period is very likely to be cost-effective, since the presence of mental illness during childhood leads to ten times higher costs during adulthood.[33-35] However, there is currently no evidence for any effective model of appropriate transitional mental health care or any interventions to reduce these individual and societal costs.[36]

Transitional care

Ideally, transition to adult mental health services should be a planned, orderly, purposeful and patient-centred process that ensures continuity of care, optimises health, minimises adverse events and ensures that the young person attains his/her maximum potential.[37-41] Good transitional care starts with preparing a service user to leave the child-centred health care setting and ends when that person is received in, and properly engaged with, the adult provider or an appropriate alternative, or is discharged from care in a planned and managed fashion.[42 43].

European research on transition from CAMHS to AMHS is sparse, with little information available on the quality of transition and transition experiences in different EU countries in relation to long term mental health outcomes. The organisation of CAMHS in the member states vary, including the age at which young people are transitioned to adult services, size and complexity, sources of funding, and service provision and care. There is some evidence though that transition is a problem across all EU states.[44-46]

Barriers to good transition have been mapped,[16 17] but the evidence of interventions for improving transitional care is scant. A recent systematic review of CAMHS to AMHS transition identified only three initiatives, all in the USA,[20] including a case management model, a transition support model and an outpatient transition programme. Although all three programmes showed improved clinical and social outcomes for those with facilitated transition, none of these was a randomised trial and each model was deeply rooted within its own particular and specific healthcare context. There is no consensus as to who can be discharged on reaching the CAMHS transitional boundary, who should receive transitional care, and how this care should be delivered. Furthermore, it is not clear what outcomes should be measured to assess clinical and cost effectiveness of the model, what the outcomes of those who fall through the care gap are, and what the individual, organisational and societal costs of poor, inadequate or inappropriate transition are. A recent NICE review on transition from child to adult care across all specialities found that there was no robust evidence on models of transitional care.[36]

In the absence of a planned, purposeful and needs-based assessment of those who reach the boundary, clinical judgment on transition can be influenced by misperceptions of other services, time and resource constraints, poor communication between CAMHS-AMHS, and poor adherence to existing policies.[19] Research has confirmed several information gathering biases in unstructured clinical judgements such as diagnostic biases, confirmation biases, ignoring conflicting information,

and assumptions based on patient and service background.[47] A recent study found that feeding back structured assessment results to clinicians is leading to improved clinical decision making.[47]

Ideally all young people who reach a transition boundary would be assessed in a structured and standardised way to determine ongoing need for care. Those who need such care would make a transition to adult services in a planned and managed manner ensuring continuity of care across all domains. Those without ongoing need would be appropriately discharged. Despite the intuitive simplicity and clinical importance of such a structured decision process, a transition model incorporating this approach with regard to mentally ill patients has not been evaluated or reported in research or health practice literature, although its need has been articulated.[11 14]

The MILESTONE project

The five year MILESTONE project (February 2014 to January 2019) aims to improve the understanding of, and strengthen, CAMHS-AMHS transitional care across different healthcare systems in the EU. In a series of work packages, it will 1) map current services and transitional policies across the EU; 2) develop and validate transition-specific outcomes measures; 3) conduct a longitudinal cohort study of transition process and outcomes across eight EU countries; 4) develop and test, in a cluster-randomised trial, the clinical and cost-effectiveness of an innovative transitional care model; 5) create clinical, organisational, policy and ethics guidelines for improving care and outcomes for transition age youth; and 6) develop and implement training packages for clinicians across the EU. This paper presents the protocol (v2.2) for the work packages dealing with the longitudinal cohort study, the cluster randomised controlled trial and the economic evaluation of the trial, which combined constitute the MILESTONE study.

MILESTONE model of managed transition

The model of transitional care we have developed consists of an evidence-based decision-making process and managed transition, incorporating key principles of continuity of care: adequate information transfer, appropriate joint working, therapeutic and relational continuity, and

engagement with adult services.[48 49] The model of managed transition can be seen as one of the cornerstones of a planned and purposeful transition process and can lead to more effective joint working between services. It addresses the need to involve young people and parent/carers in the planning process, tailor transition support to individual needs, identify barriers to smooth transition and act on these, plan transition in a timely fashion, produce a succinct medical summary of the service user, and improve information transfer and communication with adult providers.[36] The model includes:

1. The establishment and/or confirmation of shared understanding of criteria for good quality transitional care at the CAMHS-AMHS interface, and managed ending of care, taking into account clinicians' prior knowledge of good quality transition.
2. Systematic identification of all young people under CAMHS care who reach the transition boundary for their service.
3. Structured and standardised assessment of their mental health and social care needs using a bespoke Transition Readiness and Appropriateness Measure (TRAM), completed by the young person, their parent/carer if available and CAMHS clinician prior to, ideally six months before, the transition boundary.
4. Feedback of TRAM results from all parties in a short, clearly presented report to relevant clinicians in CAMHS, allowing clinicians to identify areas in which attention should be focused to ease a young person's path to transition.
5. Using the findings from the TRAM report to focus communication with service users and carers on issues surrounding end of care at CAMHS and potential transition to AMHS or other community based service.
6. Incorporation of critical information by clinician to young person's care or transition plan, and designing goals for critical items that are achievable.
7. Sending the TRAM findings, along with a referral letter, to the new adult service, if a referral to AMHS is made.

8. Structured and regular follow-up of all young people using Transition Outcome Measure (TROM) to assess whether those who needed care were appropriately engaged with adult services and those who had been discharged or referred to other services have no unmet needs following cessation of care.

Transition Readiness and Appropriateness Measure (TRAM) and the Transition Related Outcome Measure (TROM)

The Transition Readiness and Appropriateness Measure (TRAM), a decision support and assessment tool, uses the HealthTracker™ platform. The measure, together with the linked findings report, have been designed to help the clinician identify a) high-risk, high-need cases for whom transition to AMHS is advisable and appropriate; b) those who can be appropriately discharged in a planned manner from CAMHS to a General Practitioner (GP); or c) transitioned to another community based service (such as social services, voluntary sector or other non-statutory agencies). Obviously, the clinicians will need to take their local service provision into account when making the decisions. The Transition Related Outcome Measure (TROM) provides information on outcomes post-transition, and on the transition process and experience.

The TRAM and TROM were developed using existing literature, expert input and focus groups on developing and validating Patient Reported Outcome Measures (PROMS);[50 51] MILESTONE's group of young advisors also reviewed the scales and helped identify areas of duplication or unclear terms. These scales have been translated into Croatian, Dutch, Flemish, French, German, and Italian languages and provide a summary of all factors necessary to consider (including symptoms, functioning, risk and need for care) when making a transition decision and when assessing the outcomes of a transition. There are versions for young people pre-transition, young people post-transition, parents/carers and clinicians at CAMHS and AMHS which can be completed online, via the HealthTracker™ platform (https://www.healthtracker.co.uk/index.php/our-platform/), a web-based portal allowing measures to be completed remotely, which has been used in other EU FP7 projects [52].

TRAM and TROM contain 20 questions common to both scales for all participants; further eight questions are relevant only to the clinician versions and nine only to the young person and parent/carer. All participant versions of TRAM contain 15 additional questions that are not in TROM, yet to allow comparison of results over time, most of the domains present in TRAM are also present in TROM, with versions for AMHS and CAMHS clinicians and different follow-up time points.

The construct validity, content validity, inter-rater validity, test-retest validity, and sensitivity to change of TRAM and TROM were assessed in a sub-study between June 2015 and April 2016.

The "TRAM score summary report" presents the scores from the young person, parent/carer and clinician for each item, with graphs visualising differences or similarities in scoring. The report contains items that are relevant to the clinician's transition decision (symptoms, risk factors and disruption experienced by the young person) and those that can facilitate a smooth transition. It displays all information in a user-friendly, relevant and accessible format, helping identify young people requiring further care and allowing key facts to be easily transferred to care plans and referrals. It should complement a much more comprehensive evaluation, with the ultimate decision about transition being the outcome of a process involving key stakeholders.

HealthTracker Ltd will optimize the TRAM on the HealthTracker™ platform based on decision making algorithms derived from the study. If appropriately funded, this will be made available to serve as the platform for optimization of transitions to adult mental health in the EU.

AIMS AND OBJECTIVES

The overall aim of the nested cRCT is to determine the effectiveness and cost-effectiveness of the model of managed transition in improving the health and social outcomes of young people, and their transition to adult roles, as compared to treatment as usual, in eight participating EU countries. The specific objectives are

1. To test the hypothesis that the implementation of the model of managed transition in CAMHS at the transition boundary improves the mental health and social outcomes of young people and their transition to adult roles when they move on from CAMHS, as compared to usual care.

2. To conduct an economic evaluation of the model of managed transition compared with usual care.

3. To explore the views and experiences of health professionals and young people concerning the intervention.

The prospective cohort study will delineate the transition journey of a large number of young people across eight EU countries. The aims are

4. To evaluate the mental health, quality of life, and functioning of young people who attend CAMHS and reach the CAMHS/AMHS transition boundary;

5. To evaluate the longitudinal course of mental health, social and adult functioning outcomes of young people who reach the CAMHS/AMHS transition boundary and transition into young adulthood;

6. To compare the outcomes in those young people who transition with those who do not transition to AMHS (i.e. remain in CAMHS, are discharged or referred to other care).

METHODS AND ANALYSIS

Study design and management

A large cohort of young people approaching the CAMHS-AMHS transition boundary in eight EU countries will be recruited and a nested cluster randomised controlled trial (cRCT) in a randomly selected subset of clusters (CAMHS services) will be implemented. The study design is a modification of the Cohort Multiple Randomised Controlled Trial,[53] by virtue of allocation to the intervention by cluster randomisation, with each distinct CAMHS comprising a cluster. The control arm clusters from

the cRCT together with additional excess clusters form the longitudinal cohort study, with a follow-up period of 24 months. The cRCT is a superiority trial; the aim is to show that managed transition is superior to usual care in improving patient reported outcomes. Usual care varies by CAMHS and may or may not include transitioning planning. The primary outcome endpoint is 15 months. The study flow diagram is presented in Figure 1. All arms of the study undergo the same data collection. The trial has economic and qualitative components, addressing objectives 2 and 3, respectively. Detailed Statistical Analysis Plans have been developed for both the cRCT and longitudinal cohort study. Final versions will be signed off prior to commencement of the analysis and made available on the study website.

Figure 1 MILESTONE study flow diagram

The study is sponsored by the University of Warwick and co-ordinated from the research office in the Mental Health and Wellbeing unit, Warwick Medical School, with Quality Assurance and Statistics from Warwick Clinical Trials Unit. The Study Coordinator is responsible for the day-to-day coordination and the Chief Investigator (CI) for clinical aspects. The study is managed by a trial management group (TMG), including work package leaders (i.e. country leads), and supported by MILESTONE research staff. The TMG speaks monthly by telephone conference chaired by the CI. The study conduct and progress is overseen by the independent MILESTONE Scientific, Clinical and Ethical Advisory Board (SCEAB) comprising five international experts and four Patient and Public Involvement representatives. The SCEAB members are invited to the annual general meetings in order to monitor the progress of work, to assess the scientific quality and to give feed-back to the Consortium members, but without a right to vote. The SCEAB will also review the main governance and any ethical issues which might require greater attention.

MILESTONE has strong Patient and Public Involvement (PPI) embedded throughout the project; young advisors, some with experience of transition in mental health services provided feedback on the protocol and study documents. Their ongoing role includes: attending and contributing to

project steering committee meetings, designing the intervention leaflet and other promotional materials, and advising on recruitment and the engagement of young people. The first five PPI representatives have been from the UK; in the third year service users from other participating countries will be involved.

Setting and site selection

The study is currently running in Belgium, Croatia, France, Germany, Italy, the Netherlands, Republic of Ireland, and the United Kingdom. Recruitment of participants is underway in 52 CAMHS clusters that fit the inclusion criteria below (October 2015 – December 2016, with last inclusions in January 2017). Face-to-face meetings with clinical and managerial leads were arranged at those sites that expressed an interest and the study explained in detail. Signed site agreements or equivalent were obtained from participating sites prior to the start of the study. The majority of sites received no funding from the EU grant (no 602442) for taking part in the study. However, two German recruiting sites received payments under subcontract to facilitate recruitment.

In most countries, other than the UK, there is no umbrella organisation to facilitate collaboration between AMHS and CAMHS. Furthermore, a single CAMHS may be linked with numerous AMHS (inpatient services, clinics, teams and individuals), making it difficult for AMHS clinicians to be engaged from the start, particularly given our limited resources. Also, we were not able to predict which AMHS would be involved, as this is dependent on transition decisions.

Cluster level eligibility criteria

For a CAMHS to be eligible, it had to be a service delivering medical and psycho-social interventions for children and adolescents with mental health problems and disorders, and/or neuropsychiatric/developmental disorders (e.g. emotional/neurotic disorders; eating disorders; hyperkinetic disorder/ADHD; autism spectrum disorders); community-based, or provide outpatient or inpatient care; publicly or privately funded; must have a formal upper *age limit* (the transition boundary) for providing care to young people and; be responsible for transfer of care to an adult

service for those who reach the transition boundary. Forensic services and highly specialised national services, which cater for rare/unusual disorders and/or serve a national population, such as specialist clinics for rare metabolic disorders or long-term residential care for severe autism were excluded. Eligible services could vary in size and complexity, ranging from single psychiatrists or psychologists (e.g. Germany) or circumscribed teams to services with multiple teams and localities offering multidisciplinary care (e.g. UK).

Baseline service level data collection

Baseline service data was collected from the CAMHS manager or leading CAMHS clinician at all recruited CAMHS in the year preceding recruitment of study participants. The questionnaire covered: 1) Size (number of staff), structure and function of CAMHS; 2) Transition boundary of the service (i.e. age at expected transition); 3) The number and type of adult mental health services (AMHS) that operate within the CAMHS catchment area; 4) Current transition policy and practice; 5) Size of the catchment population. This information was used to establish the organisational structure of CAMHS and identify potential cross-over and/or movement of staff between teams or units so that distinct units (clusters) could be identified. If one or more CAMHS teams share the same core clinicians, then these were classified as one cluster, becoming the unit of allocation.

The data revealed that the CAMHS-AMHS transition boundary for most countries was 18 years, i.e. the age of majority. In the UK, Belgium and France there was more variation, the boundary ranging from 15 to 18 years. We also discovered that some services in Belgium, France, the Netherlands and Germany adopt a more flexible approach to the boundary, and in these situations we agreed a nominal boundary (18 years), which reflects the age at which transitions most commonly occur and, in most instances, is also the official TB.

Upon leaving CAMHS care, young people may be referred on to AMHS or another community based service (e.g. social services, voluntary sector or other non-statutory agencies offering support and therapeutic interventions for mental health needs), or discharged back to their GP. AMHS and

community based services will be invited to participate in the study, and service level data will be collected once they are recruited.

Randomisation

As several countries only had three CAMHS clusters, this fixed the randomisation ratio at 1:2 and the randomisation was conducted in a two stage process: First, randomly selected triplets of clusters within each country were identified for inclusion in the cRCT. These three clusters were further randomised in a 1:2 ratio between intervention and control arms. The excess clusters (those not selected during the first stage for the cRCT) were used for the cohort study only to enhance numbers. Overall, this two-stage process equates approximately to a randomisation ratio of 1:3. All randomisation was conducted by the trial statistician using the statistical software Stata 14.[54]

The CAMHS were informed of their allocation after randomisation. The study personnel were also aware of the allocation as they are involved in delivering the intervention and assessing outcomes. The young people and their parents/carers, who are recruited after randomisation, are informed of their allocation after they have consented to the study, yet only if they ask about this specifically [55].

Participant eligibility and recruitment

Young people

Individual recruitment targets were set for each CAMHS (cluster), based on local capacity, but with the constraint that in the cRCT there should be on average 21 participants per cluster. Databases of all participating CAMHS are scrutinised by CAMHS personnel to identify all young people approaching the service's transition boundary and meeting the inclusion criteria over a 15 month recruitment period (between October 2015 and December 2016).

Young people are eligible, if a) their age is within one year of reaching the transition boundary of their CAMHS during the trial recruitment period and, in exceptional cases, not more than 3 months older than the transition boundary, if a decision about transition has not yet been made; b) they

have a mental disorder defined by DSM-IV-TR, DSM-5 or ICD 10/11, or they are under the regular care of CAMHS (attended at least one appointment, if not yet diagnosed); c) they have an IQ ≥ 70 as ascertained by previous standardised assessment or diagnosed by clinician, or no indication of intellectual impairment; and d) they provide valid written informed consent, or assent, if below the legal age of consent (in England this age is 16, in all other participating countries 18). They are ineligible if they a) are younger than a year before the transition boundary of their CAMHS; b) have a more severe intellectual impairment (IQ < 70) as ascertained by previous standardised assessment or diagnosed by clinician – if no data on intellectual functioning are available (because it has never been assessed) then care coordinators are asked to make a clinical judgement on intellectual impairment before baseline assessment takes place; c) are not able to (or expected not to be able to) complete the questionnaires due to severe physical disabilities or language problems, even with assistance from family members or a research assistant; d) are service users in a secure forensic institution; or e) don't provide valid written informed consent, or assent, if below the legal age of consent.

At each site, the clinicians of eligible young people advise the research team of the ability/capacity of the young person to give informed, voluntary consent or assent. Young people are introduced to the study (as appropriate, taking local ethical/legal conditions and best practice into consideration) either by a) a clinician or care coordinator, who provide a study leaflet and/or briefing sheet and seek consent for the individual to be contacted by a MILESTONE research assistant using a signed contact form; b) a letter signed by their care coordinator or clinician outlining the purpose of the study followed by a phone call by a CAMHS personnel if no response is received; or c) posters and/or leaflets displayed in the participating CAMHS sites, with contact details of the research team.

All young people who agree to be approached by a MILESTONE researcher are individually contacted and provided with further information about the study; interested individuals are asked to sign a study consent form. Young people who are below the legal age of consent are asked for their assent

and signed consent is obtained from a parent/carer (or, in some countries, parents/carers, according to national medical ethics requirements).

A compensatory inclusion process has been factored in; if one country is unable to meet its recruitment target, another country is allowed to over-recruit.

Parents/carers

The information provided to young people include separate information and consent forms for their parents/carers. After signing up to the study, the young person is asked to name his/her primary care giver whom s/he would like to be involved. For young people under the legal age of consent, the parent/carer has to be the legal guardian of the young person. The aim is to engage the same parent/carer throughout the whole study period. If the latter is not possible, then the aim is to involve another parent/carer. If the young person doesn't live with his/her biological parent/s, then his/her carer is involved. A carer may be the legal guardian or a partner or an older adult sibling, or another individual living with and/or providing regular support to the young person.

The parent/carer is eligible if the young person consents to parent/carer participation and he/she provides a valid written informed consent. A parent/carer is ineligible if he/she does not live with and/or provide regular support to the young person, and/or is not able to (or expected not to be able to) complete the questionnaires due to severe physical disabilities or language problems, even with assistance from family members or research assistant.

Young people who do not wish their parent/carer to be approached to participate in the study have their wishes respected, regardless of their own capacity to consent. If a parent/carer is unwilling to participate, their wishes are respected.

Clinicians/care providers

Clinicians/care providers are contacted and provided with separate information sheets and consent forms. They are eligible if they are responsible for the main care for the young person at CAMHS (and AMHS or other relevant service provider, if referral is made) and provide a valid written informed consent.

Intervention

The CAMHS in the intervention arm receive information on good quality managed transition and feedback from the TRAM assessment in the form of a TRAM score summary report for each participating young person.

Information provision at CAMHS

A special meeting is held between MILESTONE personnel and participating CAMHS in the intervention arm prior to service user recruitment to establish clinicians' existing knowledge and current practice of transition, and to discuss optimal transition, using TRAM as a decision support tool, and managed ending of care. Each meeting follows a prescribed structure. Additionally, written information on good quality transitional care is provided to all clinicians in the intervention arm CAMHS teams. This consists of presentation handouts and a leaflet on good quality transition designed by our young project advisors.

Feedback of TRAM results

The aim is to conduct the TRAM assessment approximately six months prior to the transition boundary. The TRAM findings (TRAM score summary report) are fed back to clinicians soon after the young person, parent/carer and CAMHS clinician have completed the baseline assessments.

1) The TRAM results are communicated to the CAMHS clinician in a secure fashion via an email, attaching the TRAM score summary report (which contains no identifiable information), and an offer is made to explain the findings at a face-to-face meeting. If no response is received, the email is followed up once only with a telephone call.

2) The CAMHS clinician is encouraged to communicate the TRAM findings to the young person and parent/carer, and incorporate critical information to young person's care or transition plan, and design goals for critical items that are achievable.
3) The CAMHS clinician decides whether or not to refer the young person to adult services.
4) If a referral is made, the CAMHS clinician is asked, if appropriate and with relevant permissions, to send the TRAM score summary report along with the referral letter to the new adult service.
5) The AMHS clinician or other care provider is offered a chance to discuss the TRAM findings with an appropriate member of the MILESTONE research team.

The aim of the TRAM score summary report is to support clinicians in their decision making regarding transition, communication with stakeholders and planning of the transition process. A flowchart of the study intervention is depicted in Figure 2.

Figure 2 Flowchart of study intervention (Feedback of TRAM results) and follow-up assessments with young person

The control arm

Young people, parent/carers and clinicians in the control arm complete the same baseline assessments but the latter do not receive any additional training or feedback of TRAM scores, i.e. continue providing usual care, which may or may not include transition planning.

Outcome measures

Primary outcome measure

The primary outcome measure is the clinician-rated Health of the Nation Outcome Scale for Child and Adolescents (HoNOSCA),[56] which has 15 items scored on scale of 0-4, and covers the severity of the behaviour, impairments, symptoms and social functioning of children and young people with mental health problems. The clinical usefulness of the HoNOSCA has been validated and its sensitivity to change confirmed.[57 58]

Although the HoNOSCA is intended as a measure that is completed by a clinician who is also responsible for treatment of the client, the measure can also be completed by a mental health care professional not involved in the treatment using semi-structured interview.[59] In our study the measure is completed by a trained MILESTONE Research Assistant by interviewing the young person and taking into account all other available sources of information (parent/carer, relevant clinician and the medical records) to ensure accuracy of data.

To ensure consistency and comparability, HoNOSCA is used throughout (rather than switching to HoNOS at age 18 years). The primary outcome endpoint for the cRCT is 15 months.

Secondary outcome measures

The secondary outcome measures are as indicated in Table 1. Apart from the TROM, two others were developed specifically for the MILESTONE study.

Table 1 Outcome measures

Study Instrument	Description
Health of the Nation Outcome Scale for Children and Adolescents (HoNOSCA)[60]	Used to assess the need for care based on a wide range of problems (behaviour, impairment, symptoms and social functioning).
Transition Related Outcome Measure (TROM)[1]	Informs on quality of transition and changes in symptoms, risk factors and impairment due to transition. It has been developed based on the TRAM.
World Health Organization Quality of Life Brief Inventory (WHOQOL-BREF)[61 62]	Assesses quality of life, covering physical and psychological health, social relationships and current environment.
MILESTONE specific Client Service Receipt Inventory (CSRI)[63]	Focuses on the use of health and social services, and medication use.
EuroQol health questionnaire (EQ-5D-5L)[64]	Assesses health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).
ASEBA: Youth Self Report (YSR)/Adult Self Report (ASR)/Child Behavior Checklist (CBCL)/Adult Behavior Checklist (ABCL)[65 66]	Suite of measures assessing dimensions of emotional and behavioural problems.
Ethics of Transitioning[1]	Assesses ethical challenges regarding the delivery of transitional care.
Independent Behaviour During Consultation Scale (IBDCS)[67]	Measures independent behaviour.
Barriers to Care[68]	Assesses practical (e.g. costs, time) and psychological barriers (e.g. fear to stigmatization) to care.
Bullying – adapted from Retrospective Bullying and Friendship Interview Schedule[69 70]	Assesses the experiences with bullying in different settings (e.g. school, at home, college).
Life Events[1]	Assesses significant live events such as accidents, deaths in the family, separation of parents/carers, and parent/carer losing jobs.
Brief Illness Perception Questionnaire (B-IPQ)[71 72]	Assesses the cognitive and emotional representation of illness, including consequences. The term 'illness' has been replaced with the term 'condition'.
On Your Own Feet: Transition Experience Scale (OYOF-TES)[73]	Focuses on specific experiences with the transition process and has two versions: one for Young People who transition to AMHS (or other types of adult care) and one for Young People discharged from CAMHS.
Specific Levels of Functioning Scale (SLOF)[74]	Assesses adult functioning of the Young Person from the Parent/Carer's perspective.
Clinical Global Impression Severity scale (CGI-S)[75]	Assesses the severity of the patient's illness at the time of assessment, relative to the clinician's past experiences.

[1]Developed specifically for the MILESTONE study

The Ethics of Transitioning questionnaire was developed based on the themes raised by a systematic literature review and focus groups and addresses the following research question: "What are the ethical challenges of ensuring delivery of transitional care to those who need it most against the risk of pathologising transient and self-limiting distress and dysfunction, which may be normal during adolescence?". It contains seven items rated on a five-point Likert scale, with one version to be completed prior to, and another after, transitioning.

The Life Events questionnaire is a dichotomous 13-item scale that is appropriate for both young people and adults, and focuses on significant life events, such as accidents, deaths in the family, and separation of parents/carers.

Data collection

Data collection is the same in the intervention, control and cohort arms of the study.

Baseline data

Table 2 highlights the number of contacts with the participants, the time points of the various assessments, and the type of data to be collected from the young person, parent/carer and clinician.

Table 2 Study assessments for participants (transition scenario)

Contact	**1**	**2 (T1)**	**3 (T2)**	**4 (T3)**	**5 (T4)**
Contact Window (No. months ± No. months)		**Within 6m before TB*****	**9m (± 1m) after T1**	**15m (± 1m) after T1**	**24m (± 1m) after T1**
Inclusion/exclusion criteria	**YP P/C**				
Informed consent	**YP P/C**	**YP P/C C**	**(YP) (P/C) C**	**(YP) (P/C) (C)**	**(YP) (P/C) (C)**
Contact details	**YP P/C**	**YP P/C**	**YP P/C**	**YP P/C**	**YP P/C**
Sociodemographic & personal information		**YP P/C C**	**YP (C)**	**YP P/C (C)**	**YP P/C (C)**
Need for Care (HoNOSCA – SR) (HoNOSCA – Clinician report)		**YP RA (C;YP;P/C)**	**YP RA (C;YP;P/C)**	**YP RA (C;YP;P/C)**	**YP RA (C;YP;P/C)**
Transition readiness / Transition outcome (TRAM/TROM)		**YP P/C C**	**YP P/C C**	**YP P/C C**	**YP P/C C**
Referral and Transition Status (CAMHS clinician only)			**C**	**(C)**	**(C)**
Quality of Life (WHOQOL-BREF)		**YP**		**YP**	**YP**
Cost-effectiveness (EQ-5D-5L)		**YP**	**YP**	**YP**	**YP**
Service use (CSRI)		**YP**	**YP**	**YP**	**YP**
Emotional/behavioural problems (YP: YSR/ASR P/C: CBCL/ABCL)		**YP P/C**	**YP P/C**	**YP P/C**	**YP P/C**
Ethics of transitioning		**YP**		**YP**	
Independent behaviour** (IBDCS)		**YP**	**YP**	**YP**	**YP**
Barriers to Care (BtC)**			**YP**	**YP**	**YP**
Bullying		**YP**			**YP**
Life events		**YP**	**YP**	**YP**	**YP**
Illness perception (B-IPQ)		**YP**			**YP**
Transition experience & readiness (OYOF-TES)*			**YP P/C**	**(YP) (P/C)**	**(YP) (P/C)**
Functioning & Impairment (SLOF)		**P/C**		**P/C**	**P/C**
Illness severity (CGIS)		**C**	**(C)**	**(C)**	**(C)**
Psychopathology (YP: DAWBA 5-17/18+ SR) P/C: DAWBA 5-17/18+ PR) C: Clinical diagnosis		**YP P/C C**	**(C)**	**(C)**	**YP P/C (C)**

TB = Transition boundary of service; YP = young person; P/C = parent/carer

C = clinician. T1: CAMHS clinician; if YP is transitioned after T1, then at T2-T4 the clinician is based at AMHS. If there is a delay in transitioning, the clinician at T2-T4 will still be based at CAMHS. Consent and sociodemographic data is sought from the clinician only once. (C) = if YP is a mental health service user, then clinician is asked for information.

RA = Research Assistant

SR = Self-report

PR = Parent-report

* = completed only once at the first assessment after transition

** = if the YP is a service user the IBDCS is administered, if the YP is not a current service user, the BtC is administered.

*** = in exceptional cases, the assessment can take place up to 12 months before or 3 months after the TB (e.g. if transitions regularly happen earlier in a service or a decision about transition hasn't yet been made.

The baseline assessment (T1) is undertaken after consent/assent has been given but before the delivery of the intervention, within 6 months before the transition boundary of the service or, in exceptional cases, within 12 months before or 3 months after the boundary (e.g. if transitions regularly happen earlier in a service or a decision about transition hasn't yet been made). Young people and their parents/carers are assessed at the clinic, or at an alternative location suitable for the young person, with both semi-structured interview (sociodemographic and personal information, and HoNOSCA) and online assessment. The sociodemographic and personal information questionnaire for young people and parent/carers collects general information about the young person and family, and the care the young person receives. The questionnaire covers also medical history and additional variables previously shown to contribute to continuity of mental health problems (for example, history of mental health problems and alcohol or drug abuse by parents). The last online assessment of T1 is the structured sections of the Development and Well-being Assessment (DAWBA),[76 77] which obtains information on mental health. Information from the assessment with the young person and parent/carer will be combined with a computer algorithm that provides an estimate of the probability of a certain individual diagnosis. Information on clinical diagnosis is obtained from the clinician.

The length of the baseline assessment (YP) is approximately 1.5 – 2 hours. The participant can take a short break in between the online measures, and if required, complete them over multiple sessions. The research assistant is available to assist if there are any difficulties. The baseline assessment (T1) should be completed before the end of the recruitment period.

Follow-up data

Outcomes are measured 9 months (T2), 15 months (T3) and 24 months (T4) after T1. The aim is to complete measures at T2 and T3 via telephone and online assessment, and at T4 via face-to-face contact with young people and their parents/carers, within a month (±) of the calculated assessment

time point (Table 2). Assessments with CAMHS or AMHS clinicians (or other service provider), which is dependent on transition status, follow the same schedule.

Evaluation of the intervention and experiences of young people regarding services

The views and experiences of CAMHS clinicians in the intervention arm are captured using a semi-structured questionnaire. All clinicians are approached and those willing to engage are interviewed over the telephone or face-to-face.

A sub-sample of young people taking part in the study will be invited to take part in focus groups at T4 from three participating countries: Ireland, UK and Croatia. The purpose of the focus groups will be to explore their experiences of leaving CAMHS, transition to AMHS if applicable, and views of mental health services, the aim being to establish whether young people have better health, educational and social outcomes, better quality of life and satisfaction with services if they: a) have experienced a managed transition from child to adult services at the transitional boundary or b) have experienced usual care (i.e. their transition to adult services, or their discharge from services, is via the usual procedure of their CAMHS clinic). It is hoped that, as part of MILESTONE's patient and public involvement activity, some of the young advisors, or other young people trained in facilitation skills by some of the research sites, may co-facilitate these focus groups.

Three audio-recorded focus groups will be held in each country with 9-12 young people in each group. Recruitment will be from the study participants with purposive sampling to include some young people who a) did not transition to adult services, b) who transitioned to adult services via usual care and c) who experienced managed transition.

Sample size

Assuming an average cluster size of 15 participants, an allocation ratio of 2:1 (control : intervention), a coefficient of variation of cluster size of 0.4 (cluster sizes ranging from approximately 5 to 30), and an intracluster correlation coefficient of 0.01, with 600 participants (195 intervention arm [13 clusters], 405 control arm [27 clusters]), the cRCT has 89% power to detect a difference of 0.30

standard deviations in the primary outcome measure (HoNOSCA). To allow for 30% dropout, the required average cluster size is 21 participants. Thus, for the cRCT the target sample size is 840 participants in total (273 intervention - 13 clusters of size 21; 567 control - 27 clusters of size 21). The randomisation was stratified by country, with the number and size of clusters dictated by local capacity. Excess clusters (those not required for the cRCT) were allocated to the control arm and will be used in the analysis of the cohort study only to enhance numbers for sufficient power to study predictors for the longitudinal course and outcome of mental health during transition. There are 10 such excess clusters (average size 21 before drop outs). The recruitment target for the cohort study is therefore 777 participants (567 from the control arm of the cRCT plus 210), and the total recruitment target is 1050 (840 plus 210).

Retention of study participants

To ensure that contact is not lost with any members of the study population during the follow-up period and that data are as complete as possible, MILESTONE has paid considerable attention to its engagement and retention strategies, drawing extensively on the advice and experiences of its young advisors to create a special "Bonding Plan". Participants may be contacted using several methods of communication (post/phone/email); contact details of all participants, including GP and CAMHS clinician details, are recorded in a "keeping in touch" form; data is collected in several different ways (face-to-face, online, phone); and each contact, or contact attempt, made with participants is recorded in a bespoke contact log. There are multiple contact points between study assessments, where the participants can advise of any changes to their contact details. The Bonding plan activities vary by country taking local ethical and cultural requirements into consideration. Items include thank you cards, newsletters, gift vouchers and a chance to win a prize in a lottery. The value of gift vouchers provided after assessments range from £10-£20 or similar equivalent in Euros. In Italy and Croatia, the research ethics committees did not allow providing any gifts after the individual assessment time points. Reasonable travel expenses are reimbursed for young people and their parents/carers.

Losses to follow up

Due to the characteristics of the study population group (young people, highly mobile, in the process of moving on to higher education, training or work), we have allowed for a 30% drop out rate.

Withdrawal of young people from the study

All participants remain in the study and follow-up data is sought unless consent for participation in data collection is explicitly withdrawn.

Data analysis

Detailed Statistical Analysis Plans, which include specific methods of analysis for each outcome variable, have been developed individually for both studies, and final versions will be reviewed and approved by the Trial Management Group and made available on the study website (http://www.milestone-transitionstudy.eu/).

A sensitivity analyses using multiple imputation will be conducted to explore the potential impact of missing data.

cRCT

Basic descriptive methods will be used to present the data on study participants, trial conduct, clinical outcomes and safety (in total and for each study group separately). The primary outcome will be HoNOSCA score at T3 and we will test the hypothesis that there is no difference in this between the managed transition and standard care arms over the study period using a multilevel model with random effects to account for clustering and repeated measures, and adjustment for design factors (country and size of service). Where appropriate, a similar approach will be applied to the analysis of secondary outcomes. All analyses will be on an intention to treat basis.

Cohort study

Baseline, longitudinal course, and outcome data at T4 will be analysed. Trajectories of mental health, subjective need for care and quality of life will be determined using mixed growth models and related to whether transitions from CAMHS to AMHS took place.

Data will be analysed to predict and characterise those with higher primary and secondary outcome scores. Functional, clinical and quality of life outcomes will be assessed in those CAMHS users who transition with those who do not transition to AMHS.Economic evaluation

Health economic data collection

To conduct the economic evaluation of the trial, information on health care usage, social care usage/social costs and intervention costs will be captured. Additionally, participant health-related quality of life, and HONOSCA score will be recorded.

Resource use data collection

Health and social care resource utilisation for both trial arms will be estimated using the MILESTONE specific Client Service Receipt Inventory (CSRI), which draws on a CSRI used previously to estimate mental health care costs in the UK,[63] but has been substantially revised for use in MILESTONE. It includes questions regarding not only health care usage, but also relating to social and judicial resource use, and these questions are tailored for each participating country to reflect local services. Young people complete the measure at all four time points. For the purpose of economic evaluation, a questionnaire on the burden and impact of TRAM will be completed by all clinicians within the cRCT. This will assess how much extra burden is placed upon staff involved within the transition process due to the intervention compared to usual care.

The intervention costs associated with managed transition include the cost of implementing, as well as the delivery of the intervention. Questionnaires have been distributed to researchers in each country to ascertain the resources required to set up the intervention, whilst Excel logbooks capture

the time spent by clinicians completing the TRAM. Likewise, the time spent by the University of Warwick preparing the TRAM report is logged within an Excel database and clinician questionnaires will be used to capture the impact of the intervention on resource use.

Outcomes for economic evaluation

The two primary outcomes for the economic evaluation are quality adjusted life years (QALYs) and HONOSCA score.[56 57] Health-related quality of life (HRQL) will be measured using the EQ-5D-5L[64] and index scores[78] will be applied to calculate QALYs to determine the impact of the intervention on HRQL. Changes in QALYs and HONOSCA score between the two trial arms will be examined in conjunction with the costs to examine the cost-effectiveness of the intervention on mental health.

Economic evaluation: analysis

General principles of the economic analysis

Intention to treat: As recommended by best practice,[79] an intention to treat (ITT) framework will be adopted. That is, for each individual within the trial, the analysis will be conducted according to which arm they were randomised.

Perspective: The base-case analysis will adopt a healthcare and personal social services (PSS) perspective in accordance with NICE recommendations.[79] However, given the widespread acknowledgement of the wider costs of mental health,[80] a societal perspective will be adopted as a secondary analysis. Societal costs will include: social care, productivity, and criminal justice system contacts.

Time horizon: The base-case analysis will be a trial based analysis and therefore consider just the years followed up within the trial. Given the complexity of the trial, the potential for long term decision modelling and extrapolation will be informed by a systematic review of the methods used within existing mental health literature. Long run extrapolation will therefore be considered in light of this.

Discounting: As recommended by NICE,[79] all costs and outcomes that occur after the first year of the trial will be discounted at 3.5%.

Missing data: Typically, within any economic evaluation of an RCT, there will be some missing data.[81] This may be for a number of reasons, and a certain degree of attrition is to be expected during follow up. Should missing data be prevalent, the health economics analysis will address missing data through the use of multiple imputation.[81]

Clustering: The hierarchical nature of the data needs to be addressed within multiple imputation procedures and within the analysis framework. To do this, random effects approaches will be used.[82]

Uncertainty: The uncertainty around the results will be assessed through sensitivity analyses and the generation of cost-effectiveness acceptability curves (CEACs).[83]

Calculating costs for economic evaluation

Data on staff time and other resources in the transition process will be obtained at each location, and costed using appropriate sources of unit cost data (e.g. for the UK, standard unit cost sources include the NHS reference costs and the Unit Costs of Health and Social Care report published annually by the Personal Social Services Research Unit at the University of Kent). This will result in location-specific estimates of the direct costs involved in implementing the managed transition process.

Outcomes for economic evaluation

The primary economic analysis will be a cost utility analysis. The EQ-5D-5L measure allows the calculation of QALYs. QALYs will be calculated for each child within the trial using the area under the curve method. The trapezium rule will be used to calculate the area under the curve and thus calculate QALYs. An underlying assumption of this methodology is that there is a linear line between each utility value at each follow up. When analysing incremental QALYs between trial arms, it is

important to adjust for baseline differences in utility.[84] In addition to controlling for baseline utility, it is important to account for the hierarchical nature the outcome data.[82] The base-case analysis of effectiveness will therefore use methods that incorporate a random-effects regression model controlling for baseline health status and accounting for clustering.[82] EQ-5D-5L tariffs for each participating country, where available, will be used to allow for country-specific economic analyses. The cost-effectiveness of the intervention over the duration of the trial will be examined, and decision uncertainty assessed using probabilistic sensitivity analysis and scenario analysis.

Data management

Online data collection

All measures apart from DAWBA are completed using HealthTracker™, which allows measures to be completed remotely using developmentally appropriate interfaces and subjects to skip modules if they do not score on screening questions for that module, thereby reducing the burden to participants. Each questionnaire has been optimised for the screen, based on feedback from service users and providers. HealthTracker™ automatically generates random participant (service user, parent, and clinician) ID numbers and passwords when the participant is entered onto the system. HealthTracker™ stores participant's month and year of birth. All other data is anonymised.

The DAWBA is completed using the website http://dawba.net and anonymised scores (identified and linked using the unique DAWBA ID) transferred to a bespoke form on the HealthTracker™ system. A secure database developed at Warwick Medical School stores information that is not collected by HealthTracker™. This includes participant name, unique study ID, HealthTracker™ and DAWBA IDs, contact details, information linking participants (for example, young person to CAMHS clinician) and service level information. This database is maintained locally at sites with access password controlled and strictly limited to MILESTONE personnel to ensure confidentiality. No personally identifiable information relating to participants leaves the local site. Only the unique

identifiers, linking information (using identifiers) and service level data is shared with Warwick Medical School.

Paper-copies of measures are only used as a last resort, or if preferred by the participant. All MILESTONE researchers have received training on the HealthTracker™ platform and other systems for data collection prior to the study beginning.

Data transfer

All transfers of study data are informed by and comply with the European Parliament and the Council of Europe's Directive 95/46/EC on protection of individuals with reference to the handling of personal data and on the free flow of such information between EU countries.

To ensure the security and integrity of data during such transfer an appropriate documented standard procedure has been established and is followed without exception. Any study data that is to be transferred between research sites is anonymised prior to transfer.

Data Storage

All essential documentation and trial records is stored by Warwick Medical School and participating local sites in conformance with the applicable regulatory requirements with access to stored information restricted to authorised personnel.

Data access and quality assurance

In all partner countries, local research ethics committee requirements and national and EU law underpin the collection, recording, sharing and secure storage of person identifiable data.

Personal information about potential and enrolled participants are collected, shared, and maintained in a manner, which protects their confidentiality before, during and after the trial. All researchers working on the MILESTONE Study are experienced in undertaking research in a way that maintains the privacy and confidentiality of study participants but which balances these demands

against the needs to ensure that participants are not at risk. Names or addresses of participants are not disclosed to anyone other than the staff involved in running the trial.

Data is only accessible by authorised personnel and made available to relevant bodies for audit purposes only.

At the end of the MILESTONE project, analysis datasets will be made available following University of Warwick's Research Data Management Policy which ensures that data produced through the University's research activities is registered, stored, made accessible for use and reuse as appropriate, managed over time and/or disposed of, according to legal, ethical, funder requirements and good practice.(http://www2.warwick.ac.uk/services/rss/researchgovernance_ethics/research_code_of_practice/datacollection_retention/research_data_mgt_policy/)

Archiving

Data from this study will be retained intact in an appropriate format and storage facility for a minimum of 10 years in the UK in line with the Medical Research Council's guidelines on Personal Information in Medical Research; other countries will follow their relevant guidelines. (http://www.mrc.ac.uk/documents/pdf/personal-information-in-medical-research/)

Monitoring

UK sites are monitored by Warwick Medical School. Monitoring includes compliance to the protocol, quality of data collection, storage of documentation and requires monitors to have access to relevant participant notes/charts and trial documentation. Each overseas party is responsible for monitoring their sites according to local procedures.

Adverse event management

A young person experiencing adverse events as a direct consequence of the intervention are unlikely, as the intervention is as aimed at the clinician. At each study assessment, the young person is asked whether any adverse events (bad or unfavourable medical occurrence) have occurred since

the last time point. This includes events from the first trial-related activity after the participant has signed the consent form until the end point of the trial as defined in the protocol. Any worsening of concomitant illness or new illness is recorded as adverse events at each visit. If the event is classified as a Serious Adverse (SAE) event, an SAE form is completed and the Principal Investigators (PIs) of each country report all SAEs immediately to the trial coordinating centre at Warwick Medical School. The trial CI determines whether SAEs require reporting to the trial sponsor or SCEAB.

ETHICS AND DISSEMINATION

Ethics and R&D governance

The study has been approved by the National Research Ethics Service in the UK (West Midlands: South Birmingham Research Ethics committee, Ref. no. 15/WM/0052) and by research ethics committees of all partaking countries. Regional and site-specific approvals have been obtained from NHS Research and Development offices in the UK and from other similar bodies in the other countries. The study is registered with the ISRCTN trial registry (ISRCTN83240263) (http://www.isrctn.com/ISRCTN83240263?q=MILESTONE&filters=&sort=&offset=3&totalResults=21&page=1&pageSize=10&searchType=basic-search) and ClinicalTrials.com (NCT03013595) https://clinicaltrials.gov/ct2/show/NCT03013595?term=NCT03013595&rank=1.

The ethical conduct of the study is monitored throughout by the MILESTONE Ethics work package.

Service users

We are involving a potentially vulnerable population in research: adolescent mental health service users who, in the main, are over the age of 16, but in areas where the transition boundary is 16 years (some parts of England) or 16.5 years (some parts of France) they are 15 years. In England, the legal age of consent is 16, in all other participating countries it is 18.

Despite best efforts, vulnerable people, either by virtue of being young and/or with mental health difficulties, are often omitted from research studies because of concerns regarding informed consent.[85 86] The researchers in this study acknowledge these concerns and risks but also

recognise the importance of including individuals with enduring mental health difficulties in the study to better inform practice. The Council of Europe strongly promotes the participation of children in decisions affecting them.[87] Young people will also have rights as service users, to expect appropriate and good quality services.

The participant information sheets and consent/assent forms make explicit the voluntary nature of young people's involvement. Even if the parent/carer gives consent but a young person refuses, that young person is not included in the study. The young person's consent is sought before follow-up assessments (verbal consent for telephone interviews), consent being implicit when they log on to give responses online. The forms also seek permission to delay data collection until a later point should a young person become unwell or due to some other pressing circumstances, as long as transition doesn't take place in the meantime, and to liaise with a young person's clinician and parent/carer should such a delay be deemed necessary. The forms explain the various safeguards in place, namely to liaise with a young person's clinician and/or family if required and the resulting impact on confidentiality.

In order to minimise any distress to young people taking part in face-to-face interviews, wherever possible these are organised in venues that are known to the young person and are scheduled at times when there are familiar staff or family members or carers on hand to offer support should a young person become upset during any data collection processes.

In the event that during an interview or other data collection session, a MILESTONE researcher identifies any situation where a young person is thought to be at risk of abuse or neglect, or that young person discloses information that raises concern about the young person's safety, then a detailed risk management plan is followed, which stipulates that the child protection policies and procedures applicable to that country are adhered to. This is likely to involve close liaison by the researcher and the MILESTONE lead for that study site, with the young person's clinician and/or the nominated child protection leads within the mental health service attended by the young person.

Also, young people consenting to the study are asked to nominate, and provide contact details for, a health/care professional (for example, GP or CAMHS clinician) who we may contact should any adverse event arise. This safeguard is made explicit in the study information leaflets, and at all data collection time points, so young people are aware of the impact on confidentiality during the process of data collection.

Training

All research assistants have participated in training sessions addressing Good Clinical Practice (GCP), transition practices, rating procedures, compliance, TRAM feedback, and communication with young people, families and clinicians. A special focus of the training has been the primary outcome measure, the clinician-rated HoNOSCA, completed by research assistants. The training has included ratings and discussions of clinical vignettes and how to conduct the HoNOSCA interview.[88] The study has been presented to all participating CAMHS teams and additional meetings have been held to implement the specific transition procedures in the intervention clusters.

Dissemination

The MILESTONE project has a work package that focuses on dissemination. Partnerships and networks with target bodies will be strategically developed to support both short- and long-term dissemination of the MILESTONE study and other project findings. External dissemination will target the scientific community, but also the general public, lay and patients' associations, health care authorities and care givers, scientific societies and professional boards, students, policy makers, and the pharmaceutical industry. Particular attention will be paid to the information needs of the various target audiences, and that they are addressed in the appropriate language and format.

The results of the MILESTONE study will be made available in the first instance to the clinicians of CAMHS and AMHS partaking in the study, and then to the scientific community at large via publications in scientific journals, presentations at meetings, the MILESTONE web site (http://milestone-transitionstudy.eu), press releases, and leaflets.

CONCLUSION

The continuity of adolescent psychopathology into adulthood means that transition to AMHS is necessary for many. However, there are real gaps in mental health care provision at this crucial stage, and those who experience transition frequently describe it as disruptive. The MILESTONE study is the first ever methodologically robust trial to test whether a decision support and assessment tool, the TRAM, can improve the mental health and social outcomes and functioning of transition age young people receiving CAMHS care. Young people in eight European countries are partaking in the trial; their longitudinal course of mental health, social and adult functioning outcomes are also evaluated as part of a longitudinal cohort study. The MILESTONE study has crucial input from young advisors, some with experience of transition in mental health services.

MILESTONE CONSORTIUM – CURRENT MEMBERS AND PARTNER INSTITUTIONS

Swaran Singh, Helena Tuomainen, Jason Madan, Moli Paul, Cathy Street, Dieter Wolke, Jane Warwick, Priya Tah, Alastair Canaway, James Griffin, Rebecca Appleton, Amanda Tuffrey, Anna Wilson, Charlotte Gatherer, Leanne Walker, Jude Taylor (University of Warwick, UK); Giovanni de Girolamo, Giulia Signorini, Alessandro Ferrari, Elisa Gheza, Cecilia Ferrari, Laura Rivolta, Flavia Levi, Maria Cataldo, Lidia Manenti, Giorgia Morini, Adriana Pastore, Cecilia Toselli, Pamela Varvara (Saint John of God Clinical Research Center, Italy); Paramala Santosh, Ilyas Sagar-Ouriaghli, Natalie Heaney , Jatinder Singh (Kings College London, UK); Diane Purper-Ouakil, Frédérick Russet, Virginie Maurice, Véronique Humbertclaude (Centre Hospitalier Universitaire de Montpellier, France); Athanasios Maras, Larissa van Bodegom, Mathilde Overbeek (Yulius Academy, Netherlands); Ulrike Schulze, Jörg M Fegert, Melanie Saam, Ulrike Breuninger, Renate Schepker, Michele Noterdaeme (University of Ulm, Germany); Sabine Tremmery, Gaëlle Hendrickx (Katholieke Universiteit Leuven, Belgium); Fiona McNicholas, Aleksandra Gronostaj (University College Dublin, Republic of Ireland); Tomislav Franić, Nikolina Davidović (University Hospital Split, Croatia); Kate Lievesley, Federico Fiori (HealthTracker Ltd, UK); Frank Verhulst, Gwen C Dieleman, Suzanne Gerritsen (Erasmus Medical Centre, Netherlands); Andrea Wohner (concentris research management GmbH, Germany).

ACKNOWLEDGEMENTS

We are very grateful for the CAMHS and AMHS services and research teams who are collaborating in this study in the eight European countries. We also extend thanks to all the participating service users and their parents/carers. We are also grateful for the members of the MILESTONE Scientific Clinical and Ethical Advisory Board (SCEAB) - Norman Sartorius, Pat McGorry, Maryann Davis, Mario Maj, and Adriana Mihai – and for Tanveer Sandhu, Philippa Coleman for reviewing the protocol. We would also like to thank members of the wider MILESTONE Consortium for their contribution. We extend a special thanks to Andrea Wohner, our project manager based at concentris research management gmbh, Fürstenfeldbruck, Germany, for excellent project management and delivery.

AUTHORS' CONTRIBUTIONS

SPS is the chief investigator who conceived the original study design and obtained funding, together with AM, GdG, PS, JM, FM, DPO, ST, US, TF, CS, MP, DW, FV, and GD. HT is the study coordinator who prepared the first draft and subsequent versions of the protocol and this manuscript, and is joint first author with SPS. JW and AC contributed to the manuscript. JW is the senior trial statistician who led the calculation of the sample size; JG will undertake the statistical analysis under her direction. JM designed the health economic component and AC will undertake the health economics analysis under his direction. CD is the quality assurance manager. PT, SG, GS, LA, FR, SA, LOH, and ND are research assistants and helped set up the study in their countries and gain local ethical approvals. The UK young advisors, AT, AW, CG, and LW, reviewed the proposed study scales (including the likely time required for completion, to assess for possible burden on study participants), participated in the design of the intervention leaflet and reviewed all study information material before submission to ethics. All authors critically reviewed the protocol and the manuscript, and gave approval for the publication.

FUNDING

The MILESTONE project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602442. This paper reflects only the authors' views and the European Union is not liable for any use that may be made of the information contained therein. The funding body has had no role in the study design, in the writing of the protocol or in the decision to submit the paper for publication.

COMPETING INTERESTS

Paramala Santosh is the director and shareholder of HealthTracker Ltd. Frank Verhulst publishes the Dutch translations of ASEBA from which he receives remuneration.

REFERENCES

1. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62(6):617-27.
2. McGorry P. The specialist youth mental health model: strengthening the weakest link in the public mental health system. *Med J Aust* 2007;187(7):s53-s56.
3. McGorry P. Transition to adulthood: the critical period for pre-emptive, disease-modifying care for schizophrenia and related disorders. *Schizophr Bull* 2011;37(3):524-30.
4. Pottick KJ, Bilder S, Vander Stoep A, et al. US patterns of mental health service utilization for transition-age youth and young adults. *J Behav Health Serv Res* 2008;35(4):373-89.
5. Kataoka SH, Zhang L, Wells KB. Unmet need for mental health care among U.S. children: variation by ethnicity and insurance status. *Am J Psychiatry* 2002;159(9):1548-55.
6. Offord DR, Boyle MH, Fleming JE, et al. Ontario Child Health Study. Summary of selected results. *Can J Psychiatry* 1989;34(6):483-91.
7. Singh SP, Paul M, Ford T, et al. Transitions of care from child and adolescent mental health services to adult mental health services (TRACK study): a study of protocols in Greater London. *BMC Health Serv Res* 2008;8(135):1-7.
8. Singh SP, Paul M, Ford T, et al. Process, outcome and experience of transition from child to adult mental healthcare: multiperspective study. *Br J Psychiatry* 2010;197(4):305-12.
9. Davis M, Geller JL, Hunt B. Within-state availability of transition-to-adulthood services for youths with serious mental health conditions. *Psychiatr Serv* 2006;57(11):1594-99.
10. Davis M, Vander Stoep A. The transition to adulthood for youth who have serious emotional disturbance: Developmental transition and young adult outcomes. *J Ment Health Adm* 1997;24(4):400-27.
11. Royal College of Nursing. Adolescent transition care. London: RCN Publications, 2004.
12. Royal College of Paediatrics and Child Health. Bridging the gaps: healthcare for adolescents. Secondary Bridging the gaps: healthcare for adolescents 2003. www.rcpsych.ac.uk.
13. Royal College of Physicians of Edinburgh Transition Steering Group. Think transition: developing the essential link between paediatric and adult care. Edinburgh: Royal College of Physicians of Edinburgh, 2008.

14. Royal College of Psychiatrists. Building and sustaining specialist child and adolescent mental health services: council report CR137. London: Royal College of Psychiatrists, 2006.
15. Davis M, Sondheimer DL. State child mental health efforts to support youth in transition to adulthood. *J Behav Health Serv Res* 2005;32(1):27-42.
16. Paul M, Ford T, Kramer T, et al. Transfers and transitions between child and adult mental health services. *Br J Psychiatry Suppl* 2013;54:s36-40.
17. Hovish K, Weaver T, Islam Z, et al. Transition experiences of mental health service users, parents, and professionals in the United Kingdom: a qualitative study. *Psychiatr Rehabil J* 2012;35(3):251-7.
18. McNicholas F, Adamson M, McNamara N, et al. Who is in the transition gap? Transition from CAMHS to AMHS in the Republic of Ireland. *Ir J Psychol Med* 2015;32(01):61-69.
19. McLaren S, Belling R, Paul M, et al. 'Talking a different language': an exploration of the influence of organizational cultures and working practices on transition from child to adult mental health services. *BMC Health Serv Res* 2013;13(1):254.
20. Paul M, Street C, Wheeler N, et al. Transition to adult services for young people with mental health needs: A systematic review. *Clin Child Psychol Psychiatry* 2014.
21. Singh S, P., Paul M, Islam Z, et al. Transition from CAMHS to Adult Mental Health Services (TRACK): A Study of Service Organisation, Policies, Process and User and Carer Perspectives. Report for the National Institute for Health Research Service Delivery and Organisation programme (SDO Project 08/1613/117), 2010.
22. Wilson A, Tuffrey A, McKenzie C, et al. After the flood: young people's perspectives on transition. *Lancet Psychiatry* 2015;2(5):376-78.
23. Davis M. Addressing the needs of youth in transition to adulthood. *Adm Policy Ment Health* 2003;30(6):495-509.
24. Department of Health. Continuity of care for people with severe mental illness? London: Department of Health, 2003.
25. Vostanis S, Richards V. Transition services for 16-19 year olds. Leicester: Leicester University, 2002.
26. Department for Children Schools and Families, Department of Health. A transition guide for all services: key information for professionals about the transition process for disabled young people. Secondary A transition guide for all services: key information for professionals about the transition process for disabled young people 2007. http://www.everychildmatters.gov.uk/_files/TransitionGuide.pdf.
27. Department for Children Schools and Families, Department of Health. Transition: moving on well. A good practice guide for health professionals and their partners on transition planning for young people with complex health needs or a disability. London: Department of Health, 2008.
28. Forbes A, While A, Ullman R, et al. A multi-method review to identify components of practice which may promote continuity in the transition from child to adult care for young people with chronic illness or disability. Report for the National Coordinating Centre for NHS Service Delivery and Organisation R & D (NCCSDO): The Florence Nightingale School of Nursing and Midwifery, King's College, London, UK, 2002.
29. Kennedy A, Sloman F, Douglass JA, et al. Young people with chronic illness: the approach to transition. *Intern Med J* 2007;37(8):555 - 60.
30. Kennedy P, Pugh R, Millar E. Towards managing the whole system of care and improving continuity of care. *Psychiatr Bull* 2005;29(7):252-54.
31. Whaley AL. Racism in the provision of mental health services; a social cognitive analysis. *Am J Orthopsychiatry* 1998;68:47-57.
32. Singh SP. Transition of care from child to adult mental health services: the great divide. *Current opinion in psychiatry* 2009;22(4):386-90.

33. Suhrcke M, Pillas D, Selai C. Economic aspects of mental health in children and adolescents. . Social Cohesion for Mental Wellbeing among adolescents: WHO, 2008:43-64.
34. Petrou S, Johnson S, Wolke D, et al. Economic costs and preference-based health-related quality of life outcomes associated with childhood psychiatric disorders. *Br J Psychiatry* 2010;197(5):395-404.
35. Copeland WE, Wolke D, Shanahan L, et al. Adult Functional Outcomes of Common Childhood Psychiatric Problems: A Prospective, Longitudinal Study. *JAMA psychiatry* 2015;72(9):892-9.
36. National Institute For Health and Care Excellence. Transition from children's to adults' services for young people using health or social care services. NICE guideline: Full version. London: NICE, 2016.
37. Blum R, Garell D, Hodgman C, et al. Transition from child-centered to adult health-care systems for adolescents with chronic conditions: a position paper for the Society of Adolescent Medicine. *Journal of Adolescent Health* 1993;14:570–76.
38. McDonagh JE. Growing up ready for emerging adulthood: an evidence base for professionals involved in transitional care for young people with chronic illness and/or disabilities. Cambridge: Eastern Region Public Health Observatory, 2006.
39. McDonagh JE, Kelly DA. Transiting care of the pediatric recipient to adult care givers. *Pediatric Clinic of North America* 2003;50:1561-83.
40. McDonagh JE, Viner R. Lost in transition? Between paediatric and adult services. *British Medical Journal* 2006;332:435-36.
41. Singh SP, Anderson B, Liabo K, et al. Supporting young people in their transition to adults' services: summary of NICE guidance. *Bmj* 2016;353:i2225.
42. Coleman EA, Berenson RA. Lost in transition: challenges and opportunities for improving the quality of transition of care. *Annals of Internal Medicine* 2004;141(7):533-36.
43. Singh SP, Tuomainen H. Transition from child to adult mental health services: needs, barriers, experiences and new models of care. *World Psychiatry* 2015;14(3):358-61.
44. Brittlebank A, Hermans M, Bhugra D, et al. Training in psychiatry throughout Europe. *Eur Arch Psychiatry Clin Neurosci* 2016;266(2):155-64.
45. Schandrin A, Capdevielle D, Boulenger J-P, et al. Transition from child to adult mental health services: a French retrospective survey. *The Journal of Mental Health Training, Education and Practice* 2016;11(5):286-93.
46. Signorini A, Singh S, Boričević V, et al. Architecture and functioning of child and adolescent mental health services: a 28-country survey in Europe. *Lancet Psychiatry* 2017;in press.
47. Aebi M, Kuhn C, Metzke C, et al. The use of the devlopment and well-being assessment (DAWBA) in clinical practice: a randomized trial. *Eur Child Adolesc Psychiatry* 2012;21:559-67.
48. Freeman G, Weaver T, Low J, et al. Promoting continuity of care for people with severe mental illness whose needs span primary, secondary and social care: a multi-method investigation of relevant mechanisms and contexts. London: NCCSDO, 2002.
49. Joyce AS, Wild TC, Adair CE, et al. Continuity of care in mental health services: toward clarifying the construct. *The Canadian Journal of Psychiatry* 2004;49(8):539-50.
50. Nelson EC, Eftimovska E, Lind C, et al. Patient reported outcome measures in practice. *Bmj* 2015;350:g7818.
51. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Silver Spring: U.S. Department of Health and Human Services Food and Drug Administration, 2009.
52. Flamarique I, Santosh P, Zuddas A, et al. Development and psychometric properties of the Suicidality: Treatment Occurring in Paediatrics (STOP) Suicidality Assessment Scale (STOP-SAS) in children and adolescents. *BMC pediatrics* 2016;16(1):213.
53. Relton C, Torgerson D, O'Cathain A, et al. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. *Bmj* 2010;340:c1066.
54. Stata Statistical Software: Release 14 [program]. College Station, TX: StataCorp LP, 2015.

55. Hayes RJ, Moulton LH. Cluster randomised trials. Interdisciplinary Statistics Series: Chapman & Hall/CRC, 2009.
56. Gowers SG, Harrington RC, Whitton A, et al. Brief scale for measuring the outcomes of emotional and behavioural disorders in children. Health of the Nation Outcome Scales for children and Adolescents (HoNOSCA). *Br J Psychiatry* 1999;174:413-6.
57. Garralda ME, Yates P, Higginson I. Child and adolescent mental health service use: HoNOSCA as an outcome measure. *The British Journal of Psychiatry* 2000;177(1):52-58.
58. Pirkis JE, Burgess PM, Kirk PK, et al. A review of the psychometric properties of the Health of the Nation Outcome Scales (HoNOS) family of measures. *Health Qual Life Outcomes* 2005;3:76.
59. Demartini B, Petrochilos P, Edwards MJ, et al. Multidisciplinary inpatient programme for functional neurological symptoms: a prospective study assessing efficacy and predictors of good outcome. *Journal of Neurology, Neurosurgery & Psychiatry* 2014;85(8):e3.
60. Gowers S, Levine W, Bailey-Rogers S, et al. Use of a routine, self-report outcome measure (HoNOSCA-SR) in two adolescent mental health services. Health of the Nation Outcome Scale for Children and Adolescents. *Br J Psychiatry* 2002;180:266-9.
61. Skevington SM, Sartorius N, Amir M. Developing methods for assessing quality of life in different cultural settings. The history of the WHOQOL instruments. *Soc Psychiatry Psychiatr Epidemiol* 2004;39(1):1-8.
62. Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res* 2004;13(2):299-310.
63. Chisholm D, Knapp MR, Knudsen HC, et al. Client Socio-Demographic and Service Receipt Inventory--European Version: development of an instrument for international research. EPSILON Study 5. European Psychiatric Services: Inputs Linked to Outcome Domains and Needs. *Br J Psychiatry Suppl* 2000(39):s28-33.
64. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36.
65. Achenbach T, Rescorla L. Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families, 2001.
66. Achenbach T, Rescorla L. Manual for the ASEBA Adult Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families, 2003.
67. van Staa A. Unraveling triadic communication in hospital consultations with adolescents with chronic conditions: the added value of mixed methods research. *Patient Educ Couns* 2011;82(3):455-64.
68. Vanheusden K, Mulder CL, van der Ende J, et al. Young adults face major barriers to seeking help from mental health services. *Patient Educ Couns* 2008;73(1):97-104.
69. Wolke D, Sapouna M. Big men feeling small: childhood bullying experience, muscle dysmorphia and other mental health problems in bodybuilders. *Psychol Sport Exerc* 2008;9(5):595-604.
70. Tippett N, Wolke D, Platt L. Ethnicity and bullying involvement in a national UK youth sample. *Journal of Adolescence* 2013;36(4):639-49.
71. Broadbent E, Petrie KJ, Main J, et al. The brief illness perception questionnaire. *J Psychosom Res* 2006;60(6):631-7.
72. Løchting I, Garratt A, Storheim K, et al. Evaluation of the Brief Illness Perception Questionnaire in Sub-Acute and Chronic Low Back Pain Patients: Data Quality, Reliability and Validity. *J Pain Relief* 2013;2(122).
73. van Staa A, Sattoe JN. Young Adults' Experiences and Satisfaction With the Transfer of Care. *J Adolesc Health* 2014.
74. Mucci A, Rucci P, Rocca P, et al. The Specific Level of Functioning Scale: Construct validity, internal consistency and factor structure in a large Italian sample of people with schizophrenia living in the community. *Schizophr Res* 2014;159(1):144-50.

75. Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: U.S. Department of Health, Education, and Welfare, 1976.
76. Goodman R, Ford T, Richards H, et al. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry* 2000;41(5):645-55.
77. Goodman A, Heiervang E, Collishaw S, et al. The 'DAWBA bands' as an ordered-categorical measure of child mental health: description and validation in British and Norwegian samples. *Soc Psychiatry Psychiatr Epidemiol* 2011;46(6):521-32.
78. Devlin N, Shah K, Feng Y, et al. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. OHE Research Paper 16/01. London: Office of Health Economics, 2016.
79. National Institute For Health and Care Excellence. Guide to the methods of technology appraisal 2013. London: NICE, 2013.
80. Shearer J, McCrone P, Romeo R. Economic Evaluation of Mental Health Interventions: A Guide to Costing Approaches. *PharmacoEconomics* 2016;34(7):651-64.
81. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj* 2009;338:b2393.
82. Gomes M, Ng ES, Grieve R, et al. Developing appropriate methods for cost-effectiveness analysis of cluster randomized trials. *Medical decision making : an international journal of the Society for Medical Decision Making* 2012;32(2):350-61.
83. Fenwick E, Marshall DA, Levy AR, et al. Using and interpreting cost-effectiveness acceptability curves: an example using data from a trial of management strategies for atrial fibrillation. *BMC Health Serv Res* 2006;6:52.
84. Manca A, Palmer S. Handling missing data in patient-level cost-effectiveness analysis alongside randomised clinical trials. *Appl Health Econ Health Policy* 2005;4(2):65-75.
85. Yan EG, Munir KM. Regulatory and ethical principles in research involving children and individuals with developmental disabilities. *Ethics & behavior* 2004;14(1):31-49.
86. Medical Research Council. MRC Ethics Guide: Medical research involving children. London: Medical Research Council, 2004.
87. Parliamentary Assembly. Promoting the participation by children in decisions affecting them. Recommendation 1864; Doc. 12080: Council of Europe, 2009.
88. Rock D, Preston N. HoNOS: is there any point in training clinicians? *J Psychiatr Ment Health Nurs* 2001;8(5):405-9.

FIGURES

Figure 1 MILESTONE study flow diagram

Figure 2 Flowchart of study intervention (Feedback of TRAM results) and follow-up assessments with young person

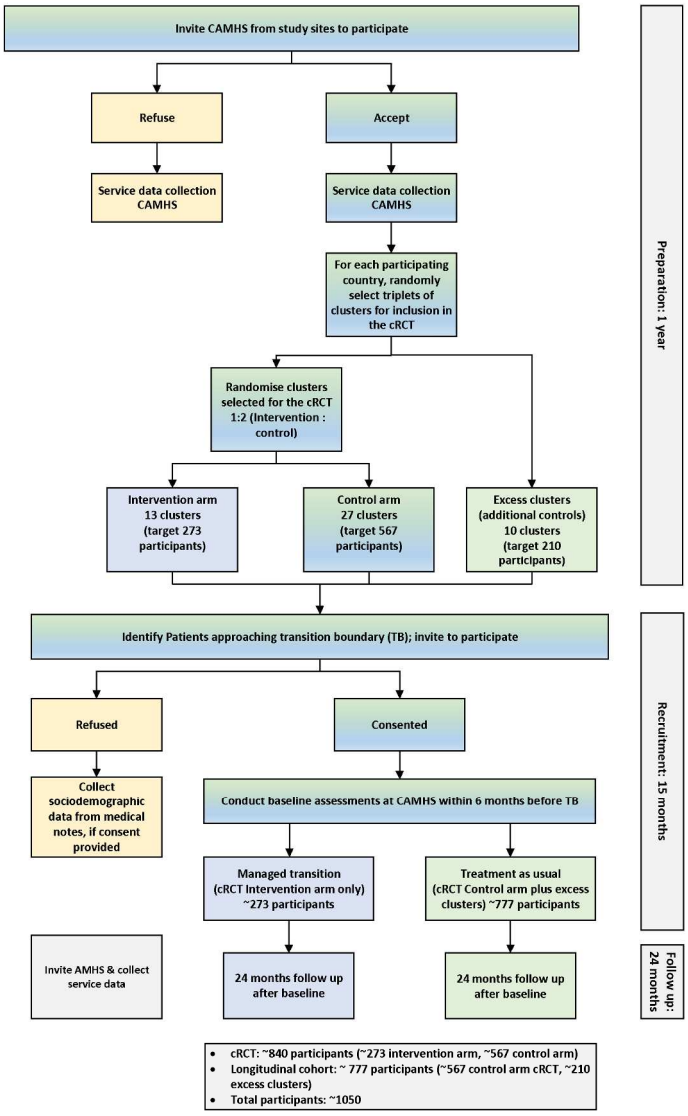

Figure 1 MILESTONE study flow diagram

210x297mm (300 x 300 DPI)

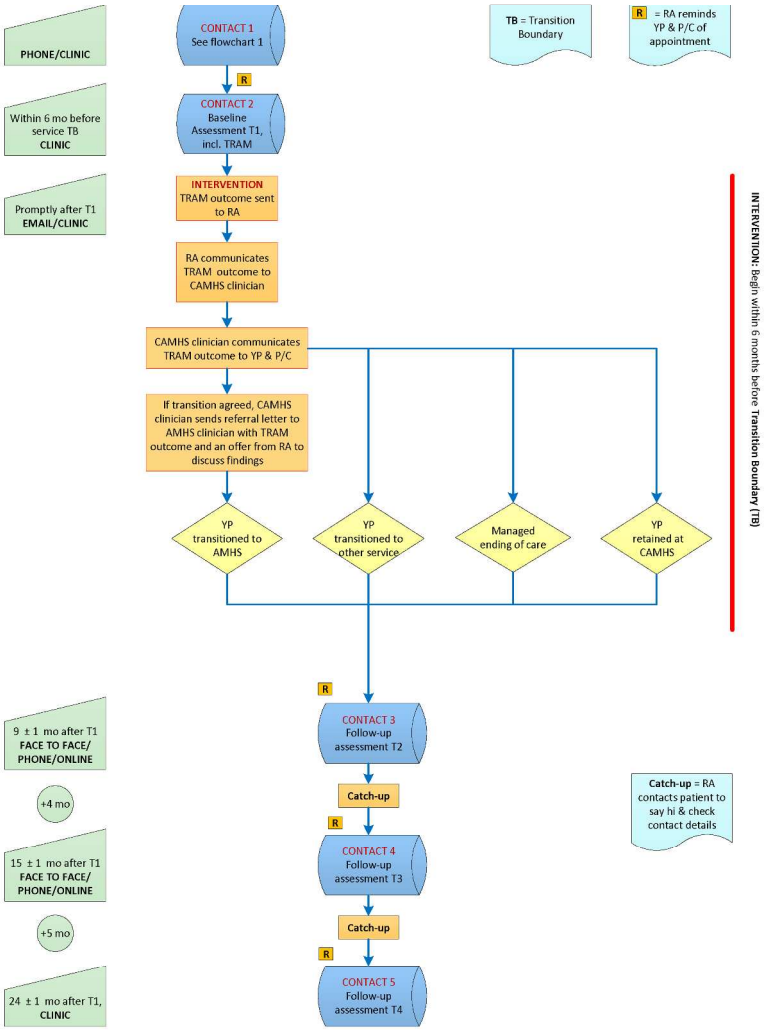

Figure 2 Flowchart of study intervention (Feedback of TRAM results) and follow-up assessments with young person

210x297mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			Protocol paper in track changes: PP Main protocol: MP v2.2 03.03.2017
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p. 1 (PP) _____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p. 4 (PP)_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	p. 1 (MP)_
Funding	4	Sources and types of financial, material, and other support	p. 41 (PP)_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p. 1-2 (PP)____
	5b	Name and contact information for the trial sponsor	p. 2 (MP)_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	p. 41 (PP) _____

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	p. 13-14 (PP)_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p. 5-12 (PP)_____
	6b	Explanation for choice of comparators	p. 13 (PP)_____
Objectives	7	Specific objectives or hypotheses	p. 12 (PP)_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p. 13 (PP)_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p. 14 (PP)_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p. 17-19 (PP)___
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p. 19-22_(PP)___
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_n/a_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_n/a_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_n/a_____

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p. 22-23, 25_(PP)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	p. 23_(PP) & Fig 1__
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p. 27-28 (PP)___
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	p. 17-19 (PP)___
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p. 16 (PP)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_n/a (cluster randomised)_____ __
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_n/a_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p. 16 (PP)_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_n/a_____ _
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.	p. 22-23, 24-27, 38-39_(PP)____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p. 28-29 (PP)_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p. 33-36 (PP)_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p. 29-30 (PP)_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p. 30 (PP)____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p. 30 (PP)
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	p. 13-14 (PP) p. 10, 58-59 (MP)_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_n/a_____ _
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p. 36 (PP)_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	p. 59 (MP)_____
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p. 4, 36_(PP)___
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p. 57 (MP)_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p. 18 (PP)_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_n/a_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p. 34-35 (PP)___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p. 42 (PP)____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p. 35 (PP)_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_n/a_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	p. 39-40 (PP)___
	31b	Authorship eligibility guidelines and any intended use of professional writers	p. 61 (MP)___
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	p. 35-36 (PP)___
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon request___

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_n/a_____ _

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Protocol for a cohort study of adolescent mental health service users with a nested cluster-randomised controlled trial to assess the clinical and cost effectiveness of managed transition in improving transitions from child to adult mental health services (The MILESTONE study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016055.R2
Article Type:	Protocol
Date Submitted by the Author:	18-Aug-2017

Complete List of Authors:	Singh, Swaran; University of Warwick, Warwick Medical School Tuomainen, Helena; University of Warwick, Warwick Medical School De Girolamo, Giovanni; Psychiatric Epidemiology and Evaluation Unit, Saint John of God Clinical Research Center, Brescia, Italy Maras, Athanasios; Yulius Academy, Rotterdam, Netherlands; Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands Santosh , Paramala; King's College London , Child and Adolescent Psychiatry ; HealthTracker Ltd McNicholas, Fiona; University College Dublin School of Medicine and Medical Science; Geary Institute, University College Dublin, Dublin, Republic of Ireland Schulze, Ulrike; Universitatsklinikum Ulm Klinik fur Kinder- und Jugendpsychiatrie Psychotherapie Purper-Ouakil, Diane; Centre Hospitalier Regional Universitaire de Montpellier Tremmery, Sabine; Katholieke Universiteit Leuven, Department of Neurosciences, Child & Adolescent Psychiatry; Universitaire Ziekenhuizen Leuven, Department of Child and Adolescent Psychiatry Franić, Tomislav; Department of Psychiatry, Clinical Hospital Center Split Madan, Jason; University of Warwick, Warwick Medical School Paul, Moli; Coventry and Warwickshire Partnership NHS Trust; University of Warwick, Warwick Medical School Verhulst, Frank; Erasmus MC, Department of Child and Adolescent Psychiatry and Psychology; Kobenhavns Universitet, Department of Clinical Medicine Dieleman, Gwen; Erasmus MC, Department of Child and Adolescent Psychiatry and Psychology Warwick, Jane; University of Warwick Warwick Medical School, Warwick Clinical Trials Unit Wolke, Dieter; University of Warwick, Department of Psychology and Warwick Medical School Street, Cathy; University of Warwick, Warwick Medical School Daffern, Claire; University of Warwick, Warwick Medical School Tah, Priya ; University of Warwick, Warwick Medical School Griffin, James; University of Warwick, Warwick Medical School, Clinical Trials Unit

	Canaway, Alastair; University of Warwick, Warwick Medical School Signorini, Giulia; Psychiatric Epidemiology and Evaluation Unit, Saint John of God Clinical Research Center, Brescia, Italy Gerritsen, Suzanne; Erasmus MC, Department of Child and Adolescent Psychiatry and Psychology Adams, Laura; University of Plymouth, School of Psychology O'Hara, Lesley; University College Dublin, Department of Child and Adolescent Psychiatry Aslan, Sonja; Universitat Ulm, Department of Child and Adolescent Psychiatry/Psychotherapy Russet, Frédérick; Centre Hospitalier Regional Universitaire de Montpellier Davidović, Nikolina; Department of Psychiatry, Clinical Hospital Center Split Tuffrey, Amanda; University of Warwick, Warwick Medical School Wilson, Anna; University of Warwick, Warwick Medical School Gatherer, Charlotte; University of Warwick, Warwick Medical School Walker, Leanne; University of Warwick, Warwick Medical School
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Health services research
Keywords:	Child & adolescent psychiatry < PSYCHIATRY, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, EPIDEMIOLOGY

Protocol for a cohort study of adolescent mental health service users with a nested cluster-randomised controlled trial to assess the clinical and cost effectiveness of managed transition in improving transitions from child to adult mental health services (The MILESTONE study)

CORRESPONDING AUTHOR

Swaran P Singh
Mental Health and Wellbeing
Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry CV4 7AL
UK
S.P.Singh@warwick.ac.uk
+44 (0) 2476 574 530

JOINT FIRST AUTHOR

Helena Tuomainen, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK

Swaran P Singh and Helena Tuomainen contributed equally to this paper.

CO-AUTHORS

Giovanni De Girolamo, Psychiatric Epidemiology and Evaluation Unit, Saint John of God Clinical Research Center, Brescia, Italy
Athanasios Maras, Yulius Academy, Rotterdam, Netherlands; Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands
Paramala Santosh, Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK; Centre for Interventional Paediatric Psychopharmacology and Rare Diseases (CIPPRD), National and Specialist Child and Adolescent Mental Health Services, Maudsley Hospital, London, UK; HealthTracker Ltd, Gillingham, UK
Fiona McNicholas, Department of Child and Adolescent Psychiatry, University College Dublin School of Medicine and Medical Science, Dublin, Republic of Ireland; Geary Institute, University College Dublin, Dublin, Republic of Ireland; Department of Child Psychiatry, Our Lady's Hospital for Sick Children, Dublin, Republic of Ireland; Lucena Clinic SJOG, Dublin, Republic of Ireland
Ulrike Schulze, Department of Child and Adolescent Psychiatry/Psychotherapy, University of Ulm, Germany
Diane Purper-Ouakil, Centre Hospitalier Universitaire de Montpellier, Montpellier, France
Sabine Tremmery, Department of Neurosciences, Child & Adolescent Psychiatry, University of Leuven, Belgium; Department of Child & Adolescent Psychiatry, University Hospitals Leuven, Leuven, Belgium
Tomislav Franić, Department of Psychiatry, Clinical Hospital Center Split, Split, Croatia
Jason Madan, Warwick Medical School, University of Warwick, Coventry, UK

Moli Paul, Coventry and Warwickshire Partnership NHS Trust, UK; Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Frank C Verhulst, Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands; Department of Clinical Medicine, University of Copenhagen, Denmark
Gwen C Dieleman, Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands
Jane Warwick, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
Dieter Wolke, Department of Psychology, University of Warwick, UK; Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Cathy Street, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Claire Daffern, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
Priya Tah, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
James Griffin, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
Alastair Canaway, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
Giulia Signorini, Psychiatric Epidemiology and Evaluation Unit, Saint John of God Clinical Research Center, Brescia, Italy
Suzanne Gerritsen, Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center, Rotterdam, Netherlands
Laura Adams, School of Psychology, Plymouth University, UK
Lesley O'Hara, Department of Child and Adolescent Psychiatry, UCD, Dublin, Republic of Ireland
Sonja Aslan, Department of Child and Adolescent Psychiatry/Psychotherapy, University of Ulm, Germany
Frédérick Russet, Centre Hospitalier Universitaire de Montpellier, Montpellier, France
Nikolina Davidović, Department of Psychiatry, Clinical Hospital Center Split, Split, Croatia
Amanda Tuffrey, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Anna Wilson, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Charlotte Gatherer, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
Leanne Walker, Mental Health and Wellbeing, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK

for the MILESTONE Consortium

WORDCOUNT

10906 (excludes references)

KEYWORDS

Mental health, child and adolescent mental health services, transition, health services research, cluster randomised controlled trial, longitudinal cohort study, youth mental health, Europe

ABSTRACT

Introduction: Disruption of care during transition from Child and Adolescent Mental Health (CAMHS) to Adult Mental Health Services (AMHS) may adversely affect the health and wellbeing of service users. The MILESTONE study evaluates the longitudinal course and outcomes of adolescents approaching the transition boundary (TB) of their CAMHS and determines the effectiveness of the model of managed transition in improving outcomes, compared to usual care.

Methods and analysis: A cohort study with a nested cluster randomised controlled trial. Recruited CAMHS randomised to provide either i) managed transition using the Transition Readiness and Appropriateness Measure (TRAM) score summary as a decision aid or ii) usual care for young people reaching the TB. Participants are young people within one year of reaching the TB of their CAMHS in eight European countries; one parent/carer and a CAMHS clinician for each recruited young person; and adult mental health clinician or other community based care provider, if young person transitions. Primary outcome is Health of the Nation Outcome Scale for Children and Adolescents (HoNOSCA) measuring health and social functioning at 15 months post-intervention. Secondary outcomes include mental health, quality of life, transition experience, and health care usage assessed at 9, 15 and 24 months post-intervention. With a mean cluster size of 21, a total of 840 participants randomised 1:2 intervention to control is required, providing 89% power to detect a difference in HoNOSCA score of 0.30 standard deviations. The addition of 210 recruits for the cohort study ensures sufficient power for studying predictors, resulting in 1050 participants and an approximate 1:3 randomisation.

Ethics and dissemination: The study protocol was approved by the UK National Research Ethics Service (15/WM/0052) and equivalent ethics boards in participating countries. Results will be reported at conferences, in peer-reviewed publications, and to all relevant stakeholder groups.

Trial registration numbers: ISRCTN83240263; NCT03013595

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first ever methodologically robust trial to test whether a decision support and assessment tool can improve the mental health and social outcomes and functioning of transition age young people receiving care at Child and Adolescent Mental Health Services.
- A large, prospectively identified and robustly evaluated cohort of young people across several European countries with diverse health care systems is taking part in the study.
- The cost-effectiveness of the intervention and research-related changes in health systems in terms of both expenditure and related health outcomes will be evaluated.
- There is a strong Patient and Public Involvement (PPI) at all stages of the study.
- Due to the nature of the intervention it is not possible for clinicians or assessors to be blind to the allocation of clusters or of the service users within these clusters.

INTRODUCTION

The MILESTONE (Managing the Link and Strengthening Transition from Child to Adult Mental Health Care) study focuses on the period when young people (YP) attending Child and Adolescent Mental Health Services (CAMHS) need to move on, or "transition" to, an adult mental health service (AMHS), if they still require ongoing care.

Adolescence is a high-risk period for psychological morbidity, and young adulthood is the period during which most of the serious mental disorders that disable or cause death in adult life have their onset.[1-4] The National Comorbidity Survey Replication in the USA found that 75% of people with a mental disorder have an age of onset younger than 24 years, 50% have an onset before 16.[1] However, only a small proportion of young people with mental health problems approaching adulthood, less than one in six, access services or receive appropriate care.[5 6]

There is international concern about young people who get 'lost' during their move from CAMHS to AMHS[7-15] and transition-related discontinuity of care is a major socioeconomic and societal challenge. In the UK, almost half of the service users reaching the transition boundary of their child and adolescent mental health service (CAMHS) do not go on to receive adult care.[7 16] The TRACK study found that less than 5% of patients undergoing CAMHS to AMHS transition experience continuity of care.[17] There is also a concern that despite recognition of ongoing mental health need, few young people are referred, with fewer than one third in one study.[18] Continuity of care is hampered by a multitude of reasons, including differences between adult and child models of care; differing referral criteria; lack of a planned, purposeful and needs-based assessment of those who reach the boundary; communication and information transfer problems between services caused partly by different beliefs, attitudes, mutual misperceptions and lack of understanding of different service structures; lack of shared protocols/manuals for transition; lack of shared client planning between child and adult systems; young people's level of maturity and understanding; and

adolescent and/or family resistance to transition.[19-21]. Furthermore, transition may differ widely across different regions and countries due to lack of or different procedures.

Problems at the CAMHS-AMHS interface are accentuated by the fact that young people are simultaneously negotiating developmental and situational transitions, such as changes in housing and relationships and moving on to adult roles.[8 17] A lack of information about possible options, planning that takes too long and where no one professional takes charge to ensure decisions are acted upon, compound the problem.[22] Those who slip through the care net are likely to present to adult services at a subsequent time, with more severe and enduring mental health problems.[23-25] Disruption of care during transition adversely affects the health, wellbeing and potential of this vulnerable group,[26-31] and negative transition experiences adversely impact the young person's future engagement with mental health services.[32]

Intervening at the level of transition represents one of the most important ways we can facilitate not only recovery but also mental health promotion and mental illness prevention in adulthood. Ensuring sustained treatment through the transitional period is very likely to be cost-effective, since the presence of mental illness during childhood leads to ten times higher costs during adulthood.[33-35] However, there is currently no evidence for any effective model of appropriate transitional mental health care or any interventions to reduce these individual and societal costs.[36]

Transitional care

Ideally, transition to adult mental health services should be a planned, orderly, purposeful and patient-centred process that ensures continuity of care, optimises health, minimises adverse events and ensures that the young person attains his/her maximum potential.[37-41] Good transitional care starts with preparing a service user to leave the child-centred health care setting and ends when that person is received in, and properly engaged with, the adult provider or an appropriate alternative, or is discharged from care in a planned and managed fashion.[42 43]

European research on transition from CAMHS to AMHS is sparse, with little information available on the quality of transition and transition experiences in different EU countries in relation to long term mental health outcomes. The organisation of CAMHS in the member states vary, including the age at which young people are transitioned to adult services, size and complexity, sources of funding, and service provision and care. There is some evidence though that transition is a problem across all EU states.[44-46]

Barriers to good transition have been mapped,[16 17] but the evidence of interventions for improving transitional care is scant. A recent systematic review of CAMHS to AMHS transition identified only three initiatives, all in the USA,[20] including a case management model, a transition support model and an outpatient transition programme. Although all three programmes showed improved clinical and social outcomes for those with facilitated transition, none of these was a randomised trial and each model was deeply rooted within its own particular and specific healthcare context. There is no consensus as to who can be discharged on reaching the CAMHS transitional boundary, who should receive transitional care, and how this care should be delivered. Furthermore, it is not clear what outcomes should be measured to assess clinical and cost effectiveness of the model, what the outcomes of those who fall through the care gap are, and what the individual, organisational and societal costs of poor, inadequate or inappropriate transition are. A recent NICE review on transition from child to adult care across all specialities found that there was no robust evidence on models of transitional care.[36]

In the absence of a planned, purposeful and needs-based assessment of those who reach the boundary, clinical judgment on transition can be influenced by misperceptions of other services, time and resource constraints, poor communication between CAMHS-AMHS, and poor adherence to existing policies.[19] Research has confirmed several information gathering biases in unstructured clinical judgements such as diagnostic biases, confirmation biases, ignoring conflicting information,

and assumptions based on patient and service background.[47] A recent study found that feeding back structured assessment results to clinicians is leading to improved clinical decision making.[47]

Ideally all young people who reach a transition boundary would be assessed in a structured and standardised way to determine ongoing need for care. Those who need such care would make a transition to adult services in a planned and managed manner ensuring continuity of care across all domains. Those without ongoing need would be appropriately discharged. Despite the intuitive simplicity and clinical importance of such a structured decision process, a transition model incorporating this approach with regard to mentally ill patients has not been evaluated or reported in research or health practice literature, although its need has been articulated.[11 14]

The MILESTONE project

The five year MILESTONE project (February 2014 to January 2019) aims to improve the understanding of, and strengthen, CAMHS-AMHS transitional care across different healthcare systems in the EU. In a series of work packages, it will 1) map current services and transitional policies across the EU; 2) develop and validate transition-specific outcomes measures; 3) conduct a longitudinal cohort study of transition process and outcomes across eight EU countries; 4) develop and test, in a cluster-randomised trial, the clinical and cost-effectiveness of an innovative transitional care model; 5) create clinical, organisational, policy and ethics guidelines for improving care and outcomes for transition age youth; and 6) develop and implement training packages for clinicians across the EU. This paper presents the protocol (v2.2) for the work packages dealing with the longitudinal cohort study, the cluster randomised controlled trial and the economic evaluation of the trial, which combined constitute the MILESTONE study.

MILESTONE model of managed transition

The model of transitional care we have developed consists of an evidence-based decision-making process and managed transition, incorporating key principles of continuity of care: adequate information transfer, appropriate joint working, therapeutic and relational continuity, and

engagement with adult services.[48 49] The model of managed transition can be seen as one of the cornerstones of a planned and purposeful transition process and can lead to more effective joint working between services. It addresses the need to involve young people and parent/carers in the planning process, tailor transition support to individual needs, identify barriers to smooth transition and act on these, plan transition in a timely fashion, produce a succinct medical summary of the service user, and improve information transfer and communication with adult providers.[36] The model includes:

1. The establishment and/or confirmation of shared understanding of criteria for good quality transitional care at the CAMHS-AMHS interface, and managed ending of care, taking into account clinicians' prior knowledge of good quality transition.
2. Systematic identification of all young people under CAMHS care who reach the transition boundary for their service.
3. Structured and standardised assessment of their mental health and social care needs using a bespoke Transition Readiness and Appropriateness Measure (TRAM), completed by the young person, their parent/carer if available and CAMHS clinician prior to, ideally six months before, the transition boundary.
4. Feedback of TRAM results from all parties in a short, clearly presented report to relevant clinicians in CAMHS, allowing clinicians to identify areas in which attention should be focused to ease a young person's path to transition.
5. Using the findings from the TRAM report to focus communication with service users and carers on issues surrounding end of care at CAMHS and potential transition to AMHS or other community based service.
6. Incorporation of critical information by clinician to young person's care or transition plan, and designing goals for critical items that are achievable.
7. Sending the TRAM findings, along with a referral letter, to the new adult service, if a referral to AMHS is made.

8. Structured and regular follow-up of all young people using Transition Outcome Measure (TROM) to assess whether those who needed care were appropriately engaged with adult services and those who had been discharged or referred to other services have no unmet needs following cessation of care.

Transition Readiness and Appropriateness Measure (TRAM) and the Transition Related Outcome Measure (TROM)

The Transition Readiness and Appropriateness Measure (TRAM), a decision support and assessment tool, uses the HealthTracker™ platform. The measure, together with the linked findings report, have been designed to help the clinician identify a) high-risk, high-need cases for whom transition to AMHS is advisable and appropriate; b) those who can be appropriately discharged in a planned manner from CAMHS to a General Practitioner (GP); or c) transitioned to another community based service (such as social services, voluntary sector or other non-statutory agencies). Obviously, the clinicians will need to take their local service provision into account when making the decisions. The Transition Related Outcome Measure (TROM) provides information on outcomes post-transition, and on the transition process and experience.

The TRAM and TROM were developed using existing literature, expert input and focus groups on developing and validating Patient Reported Outcome Measures (PROMS);[50 51] MILESTONE's group of young advisors also reviewed the scales and helped identify areas of duplication or unclear terms. These scales have been translated into Croatian, Dutch, Flemish, French, German, and Italian languages and provide a summary of all factors necessary to consider (including symptoms, functioning, risk and need for care) when making a transition decision and when assessing the outcomes of a transition. There are versions for young people pre-transition, young people post-transition, parents/carers and clinicians at CAMHS and AMHS which can be completed online, via the HealthTracker™ platform (https://www.healthtracker.co.uk/index.php/our-platform/), a web-based portal allowing measures to be completed remotely, which has been used in other EU FP7 projects [52].

TRAM and TROM contain 20 questions common to both scales for all participants; further eight questions are relevant only to the clinician versions and nine only to the young person and parent/carer. All participant versions of TRAM contain 15 additional questions that are not in TROM, yet to allow comparison of results over time, most of the domains present in TRAM are also present in TROM, with versions for AMHS and CAMHS clinicians and different follow-up time points (available from the corresponding author, upon request).

The construct validity, content validity, inter-rater validity, test-retest validity, and sensitivity to change of TRAM and TROM were assessed in a sub-study between June 2015 and April 2016.

The "TRAM score summary report" presents the scores from the young person, parent/carer and clinician for each item, with graphs visualising differences or similarities in scoring. The report contains items that are relevant to the clinician's transition decision (symptoms, risk factors and disruption experienced by the young person) and those that can facilitate a smooth transition. It displays all information in a user-friendly, relevant and accessible format, helping identify young people requiring further care and allowing key facts to be easily transferred to care plans and referrals. It should complement a much more comprehensive evaluation, with the ultimate decision about transition being the outcome of a process involving key stakeholders.

HealthTracker Ltd will optimize the TRAM on the HealthTracker™ platform based on decision making algorithms derived from the study. If appropriately funded, this will be made available to serve as the platform for optimization of transitions to adult mental health in the EU.

AIMS AND OBJECTIVES

The overall aim of the nested cRCT is to determine the effectiveness and cost-effectiveness of the model of managed transition in improving the health and social outcomes of young people, and their transition to adult roles, as compared to treatment as usual, in eight participating EU countries. The specific objectives are

1. To test the hypothesis that the implementation of the model of managed transition in CAMHS at the transition boundary improves the mental health and social outcomes of young people and their transition to adult roles when they move on from CAMHS, as compared to usual care.

2. To conduct an economic evaluation of the model of managed transition compared with usual care.

3. To explore the views and experiences of health professionals and young people concerning the intervention.

The prospective cohort study will delineate the transition journey of a large number of young people across eight EU countries. The aims are

4. To evaluate the mental health, quality of life, and functioning of young people who attend CAMHS and reach the CAMHS/AMHS transition boundary;

5. To evaluate the longitudinal course of mental health, social and adult functioning outcomes of young people who reach the CAMHS/AMHS transition boundary and transition into young adulthood;

6. To compare the outcomes in those young people who transition with those who do not transition to AMHS (i.e. remain in CAMHS, are discharged or referred to other care).

METHODS AND ANALYSIS

Study design and management

A large cohort of young people approaching the CAMHS-AMHS transition boundary in eight EU countries will be recruited and a nested cluster randomised controlled trial (cRCT) in a randomly selected subset of clusters (CAMHS services) will be implemented. The study design is a modification of the Cohort Multiple Randomised Controlled Trial,[53] by virtue of allocation to the intervention by cluster randomisation, with each distinct CAMHS comprising a cluster. The control arm clusters from

the cRCT together with additional excess clusters form the longitudinal cohort study, with a follow-up period of 24 months. The cRCT is a superiority trial; the aim is to show that managed transition is superior to usual care in improving patient reported outcomes. Usual care varies by CAMHS and may or may not include transitioning planning. The primary outcome endpoint is 15 months. The study flow diagram is presented in Figure 1. All arms of the study undergo the same data collection. The trial has economic and qualitative components, addressing objectives 2 and 3, respectively. Detailed Statistical Analysis Plans have been developed for both the cRCT and longitudinal cohort study. Final versions will be signed off prior to commencement of the analysis and made available on the study website.

Figure 1 MILESTONE study flow diagram

The study is sponsored by the University of Warwick and co-ordinated from the research office in the Mental Health and Wellbeing unit, Warwick Medical School, with Quality Assurance and Statistics from Warwick Clinical Trials Unit. The Study Coordinator is responsible for the day-to-day coordination and the Chief Investigator (CI) for clinical aspects. The study is managed by a trial management group (TMG), including work package leaders (i.e. country leads), and supported by MILESTONE research staff. The TMG speaks monthly by telephone conference chaired by the CI. The study conduct and progress is overseen by the independent MILESTONE Scientific, Clinical and Ethical Advisory Board (SCEAB) comprising five international experts and four Patient and Public Involvement representatives. The SCEAB members are invited to the annual general meetings in order to monitor the progress of work, to assess the scientific quality and to give feed-back to the Consortium members, but without a right to vote. The SCEAB will also review the main governance and any ethical issues which might require greater attention.

MILESTONE has strong Patient and Public Involvement (PPI) embedded throughout the project; young advisors, some with experience of transition in mental health services provided feedback on the protocol and study documents. Their ongoing role includes: attending and contributing to

project steering committee meetings, designing the intervention leaflet and other promotional materials, and advising on recruitment and the engagement of young people. The first five PPI representatives have been from the UK; in the third year service users from other participating countries will be involved.

Setting and site selection

The study is currently running in Belgium, Croatia, France, Germany, Italy, the Netherlands, Republic of Ireland, and the United Kingdom. Recruitment of participants is underway in 52 CAMHS clusters that fit the inclusion criteria below (October 2015 – December 2016, with last inclusions in January 2017). Face-to-face meetings with clinical and managerial leads were arranged at those sites that expressed an interest and the study explained in detail. Signed site agreements or equivalent were obtained from participating sites prior to the start of the study. The majority of sites received no funding from the EU grant (no 602442) for taking part in the study. However, two German recruiting sites received payments under subcontract to facilitate recruitment.

In most countries, other than the UK, there is no umbrella organisation to facilitate collaboration between AMHS and CAMHS. Furthermore, a single CAMHS may be linked with numerous AMHS (inpatient services, clinics, teams and individuals), making it difficult for AMHS clinicians to be engaged from the start, particularly given our limited resources. Also, we were not able to predict which AMHS would be involved, as this is dependent on transition decisions.

Cluster level eligibility criteria

For a CAMHS to be eligible, it had to be a service delivering medical and psycho-social interventions for children and adolescents with mental health problems and disorders, and/or neuropsychiatric/developmental disorders (e.g. emotional/neurotic disorders; eating disorders; hyperkinetic disorder/ADHD; autism spectrum disorders); community-based, or provide outpatient or inpatient care; publicly or privately funded; must have a formal upper *age limit* (the transition boundary) for providing care to young people and; be responsible for transfer of care to an adult

service for those who reach the transition boundary. Forensic services and highly specialised national services, which cater for rare/unusual disorders and/or serve a national population, such as specialist clinics for rare metabolic disorders or long-term residential care for severe autism were excluded. Eligible services could vary in size and complexity, ranging from single psychiatrists or psychologists (e.g. Germany) or circumscribed teams to services with multiple teams and localities offering multidisciplinary care (e.g. UK).

Baseline service level data collection

Baseline service data was collected from the CAMHS manager or leading CAMHS clinician at all recruited CAMHS in the year preceding recruitment of study participants. The questionnaire covered: 1) Size (number of staff), structure and function of CAMHS; 2) Transition boundary of the service (i.e. age at expected transition); 3) The number and type of adult mental health services (AMHS) that operate within the CAMHS catchment area; 4) Current transition policy and practice; 5) Size of the catchment population. This information was used to establish the organisational structure of CAMHS and identify potential cross-over and/or movement of staff between teams or units so that distinct units (clusters) could be identified. If one or more CAMHS teams share the same core clinicians, then these were classified as one cluster, becoming the unit of allocation.

The data revealed that the CAMHS-AMHS transition boundary for most countries was 18 years, i.e. the age of majority. In the UK, Belgium and France there was more variation, the boundary ranging from 15 to 18 years. We also discovered that some services in Belgium, France, the Netherlands and Germany adopt a more flexible approach to the boundary, and in these situations we agreed a nominal boundary (18 years), which reflects the age at which transitions most commonly occur and, in most instances, is also the official TB.

Upon leaving CAMHS care, young people may be referred on to AMHS or another community based service (e.g. social services, voluntary sector or other non-statutory agencies offering support and therapeutic interventions for mental health needs), or discharged back to their GP. AMHS and

community based services will be invited to participate in the study, and service level data will be collected once they are recruited.

Randomisation

As several countries only had three CAMHS clusters, this fixed the randomisation ratio at 1:2 and the randomisation was conducted in a two stage process: First, randomly selected triplets of clusters within each country were identified for inclusion in the cRCT. These three clusters were further randomised in a 1:2 ratio between intervention and control arms. The excess clusters (those not selected during the first stage for the cRCT) were used for the cohort study only to enhance numbers. Overall, this two-stage process equates approximately to a randomisation ratio of 1:3. All randomisation was conducted by the trial statistician using the statistical software Stata 14.[54]

The CAMHS were informed of their allocation after randomisation. The study personnel were also aware of the allocation as they are involved in delivering the intervention and assessing outcomes. The young people and their parents/carers, who are recruited after randomisation, are informed of their allocation after they have consented to the study, yet only if they ask about this specifically [55].

Participant eligibility and recruitment

Young people

Individual recruitment targets were set for each CAMHS (cluster), based on local capacity, but with the constraint that in the cRCT there should be on average 21 participants per cluster. Databases of all participating CAMHS are scrutinised by CAMHS personnel to identify all young people approaching the service's transition boundary and meeting the inclusion criteria over a 15 month recruitment period (between October 2015 and December 2016).

Young people are eligible, if a) their age is within one year of reaching the transition boundary of their CAMHS during the trial recruitment period and, in exceptional cases, not more than 3 months older than the transition boundary, if a decision about transition has not yet been made; b) they

have a mental disorder defined by DSM-IV-TR, DSM-5 or ICD 10/11, or they are under the regular care of CAMHS (attended at least one appointment, if not yet diagnosed); c) they have an IQ ≥ 70 as ascertained by previous standardised assessment or diagnosed by clinician, or no indication of intellectual impairment; and d) they provide valid written informed consent, or assent, if below the legal age of consent (in England this age is 16, in all other participating countries 18). They are ineligible if they a) are younger than a year before the transition boundary of their CAMHS; b) have a more severe intellectual impairment (IQ < 70) as ascertained by previous standardised assessment or diagnosed by clinician – if no data on intellectual functioning are available (because it has never been assessed) then care coordinators are asked to make a clinical judgement on intellectual impairment before baseline assessment takes place; c) are not able to (or expected not to be able to) complete the questionnaires due to severe physical disabilities or language problems, even with assistance from family members or a research assistant; d) are service users in a secure forensic institution; or e) don't provide valid written informed consent, or assent, if below the legal age of consent.

At each site, the clinicians of eligible young people advise the research team of the ability/capacity of the young person to give informed, voluntary consent or assent. Young people are introduced to the study (as appropriate, taking local ethical/legal conditions and best practice into consideration) either by a) a clinician or care coordinator, who provide a study leaflet and/or briefing sheet and seek consent for the individual to be contacted by a MILESTONE research assistant using a signed contact form; b) a letter signed by their care coordinator or clinician outlining the purpose of the study followed by a phone call by a CAMHS personnel if no response is received; or c) posters and/or leaflets displayed in the participating CAMHS sites, with contact details of the research team.

All young people who agree to be approached by a MILESTONE researcher are individually contacted and provided with further information about the study; interested individuals are asked to sign a study consent form. Young people who are below the legal age of consent are asked for their assent

and signed consent is obtained from a parent/carer (or, in some countries, parents/carers, according to national medical ethics requirements).

A compensatory inclusion process has been factored in; if one country is unable to meet its recruitment target, another country is allowed to over-recruit.

Parents/carers

The information provided to young people include separate information and consent forms for their parents/carers. After signing up to the study, the young person is asked to name his/her primary care giver whom s/he would like to be involved. For young people under the legal age of consent, the parent/carer has to be the legal guardian of the young person. The aim is to engage the same parent/carer throughout the whole study period. If the latter is not possible, then the aim is to involve another parent/carer. If the young person doesn't live with his/her biological parent/s, then his/her carer is involved. A carer may be the legal guardian or a partner or an older adult sibling, or another individual living with and/or providing regular support to the young person.

The parent/carer is eligible if the young person consents to parent/carer participation and he/she provides a valid written informed consent. A parent/carer is ineligible if he/she does not live with and/or provide regular support to the young person, and/or is not able to (or expected not to be able to) complete the questionnaires due to severe physical disabilities or language problems, even with assistance from family members or research assistant.

Young people who do not wish their parent/carer to be approached to participate in the study have their wishes respected, regardless of their own capacity to consent. If a parent/carer is unwilling to participate, their wishes are respected.

Clinicians/care providers

Clinicians/care providers are contacted and provided with separate information sheets and consent forms. They are eligible if they are responsible for the main care for the young person at CAMHS

(and AMHS or other relevant service provider, if referral is made) and provide a valid written informed consent.

Intervention

The CAMHS in the intervention arm receive information on good quality managed transition and feedback from the TRAM assessment in the form of a TRAM score summary report for each participating young person.

Information provision at CAMHS

A special meeting is held between MILESTONE personnel and participating CAMHS in the intervention arm prior to service user recruitment to establish clinicians' existing knowledge and current practice of transition, and to discuss optimal transition, using TRAM as a decision support tool, and managed ending of care. Each meeting follows a prescribed structure. Additionally, written information on good quality transitional care is provided to all clinicians in the intervention arm CAMHS teams. This consists of presentation handouts and a leaflet on good quality transition designed by our young project advisors.

Feedback of TRAM results

The aim is to conduct the TRAM assessment approximately six months prior to the transition boundary. The TRAM findings (TRAM score summary report) are fed back to clinicians soon after the young person, parent/carer and CAMHS clinician have completed the baseline assessments.

1) The TRAM results are communicated to the CAMHS clinician in a secure fashion via an email, attaching the TRAM score summary report (which contains no identifiable information), and an offer is made to explain the findings at a face-to-face meeting. If no response is received, the email is followed up once only with a telephone call.
2) The CAMHS clinician is encouraged to communicate the TRAM findings to the young person and parent/carer, and incorporate critical information to young person's care or transition plan, and design goals for critical items that are achievable.

3) The CAMHS clinician decides whether or not to refer the young person to adult services.

4) If a referral is made, the CAMHS clinician is asked, if appropriate and with relevant permissions, to send the TRAM score summary report along with the referral letter to the new adult service.

5) The AMHS clinician or other care provider is offered a chance to discuss the TRAM findings with an appropriate member of the MILESTONE research team.

The aim of the TRAM score summary report is to support clinicians in their decision making regarding transition, communication with stakeholders and planning of the transition process. A flowchart of the study intervention is depicted in Figure 2.

Figure 2 Flowchart of study intervention (Feedback of TRAM results) and follow-up assessments with young person

The control arm

Young people, parent/carers and clinicians in the control arm complete the same baseline assessments but the latter do not receive any additional training or feedback of TRAM scores, i.e. continue providing usual care, which may or may not include transition planning.

Outcome measures

Primary outcome measure

The primary outcome measure is the clinician-rated Health of the Nation Outcome Scale for Child and Adolescents (HoNOSCA),[56] which has 15 items scored on scale of 0-4, and covers the severity of the behaviour, impairments, symptoms and social functioning of children and young people with mental health problems. The clinical usefulness of the HoNOSCA has been validated and its sensitivity to change confirmed.[57 58]

Although the HoNOSCA is intended as a measure that is completed by a clinician who is also responsible for treatment of the client, the measure can also be completed by a mental health care professional not involved in the treatment using semi-structured interview.[59] In our study the measure is completed by a trained MILESTONE Research Assistant by interviewing the young person and taking into account all other available sources of information (parent/carer, relevant clinician and the medical records) to ensure accuracy of data.

To ensure consistency and comparability, HoNOSCA is used throughout (rather than switching to HoNOS at age 18 years). The primary outcome endpoint for the cRCT is 15 months.

Secondary outcome measures

The secondary outcome measures are as indicated in Table 1. Apart from the TROM, two others were developed specifically for the MILESTONE study.

Table 1 Outcome measures

Study Instrument	Description
Health of the Nation Outcome Scale for Children and Adolescents (HoNOSCA)[60]	Used to assess the need for care based on a wide range of problems (behaviour, impairment, symptoms and social functioning).
Transition Related Outcome Measure (TROM)[1]	Informs on quality of transition and changes in symptoms, risk factors and impairment due to transition. It has been developed based on the TRAM.
World Health Organization Quality of Life Brief Inventory (WHOQOL-BREF)[61 62]	Assesses quality of life, covering physical and psychological health, social relationships and current environment.
MILESTONE specific Client Service Receipt Inventory (CSRI)[63]	Focuses on the use of health and social services, and medication use.
EuroQol health questionnaire (EQ-5D-5L)[64]	Assesses health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).
ASEBA: Youth Self Report (YSR)/Adult Self Report (ASR)/Child Behavior Checklist (CBCL)/Adult Behavior Checklist (ABCL)[65 66]	Suite of measures assessing dimensions of emotional and behavioural problems.
Ethics of Transitioning[1]	Assesses ethical challenges regarding the delivery of transitional care.
Independent Behaviour During Consultation Scale (IBDCS)[67]	Measures independent behaviour.
Barriers to Care[68]	Assesses practical (e.g. costs, time) and psychological barriers (e.g. fear to stigmatization) to care.
Bullying – adapted from Retrospective Bullying and Friendship Interview Schedule[69 70]	Assesses the experiences with bullying in different settings (e.g. school, at home, college).
Life Events[1]	Assesses significant live events such as accidents, deaths in the family, separation of parents/carers, and parent/carer losing jobs.
Brief Illness Perception Questionnaire (B-IPQ)[71 72]	Assesses the cognitive and emotional representation of illness, including consequences. The term 'illness' has been replaced with the term 'condition'.
On Your Own Feet: Transition Experience Scale (OYOF-TES)[73]	Focuses on specific experiences with the transition process and has two versions: one for Young People who transition to AMHS (or other types of adult care) and one for Young People discharged from CAMHS.
Specific Levels of Functioning Scale (SLOF)[74]	Assesses adult functioning of the Young Person from the Parent/Carer's perspective.
Clinical Global Impression Severity scale (CGI-S)[75]	Assesses the severity of the patient's illness at the time of assessment, relative to the clinician's past experiences.

[1]Developed specifically for the MILESTONE study

The Ethics of Transitioning questionnaire was developed based on the themes raised by a systematic literature review and focus groups and addresses the following research question: "What are the ethical challenges of ensuring delivery of transitional care to those who need it most against the risk of pathologising transient and self-limiting distress and dysfunction, which may be normal during adolescence?". It contains seven items rated on a five-point Likert scale, with one version to be completed prior to, and another after, transitioning.

The Life Events questionnaire is a dichotomous 13-item scale that is appropriate for both young people and adults, and focuses on significant life events, such as accidents, deaths in the family, and separation of parents/carers.

Data collection

Data collection is the same in the intervention, control and cohort arms of the study.

Baseline data

Table 2 highlights the number of contacts with the participants, the time points of the various assessments, and the type of data to be collected from the young person, parent/carer and clinician.

Table 2 Study assessments for participants (transition scenario)

Contact	**1**	**2 (T1)**	**3 (T2)**	**4 (T3)**	**5 (T4)**
Contact Window (No. months ± No. months)		**Within 6m before TB*****	**9m (± 1m) after T1**	**15m (± 1m) after T1**	**24m (± 1m) after T1**
Inclusion/exclusion criteria	**YP P/C**				
Informed consent	**YP P/C**	**YP P/C C**	**(YP) (P/C) C**	**(YP) (P/C) (C)**	**(YP) (P/C) (C)**
Contact details	**YP P/C**	**YP P/C**	**YP P/C**	**YP P/C**	**YP P/C**
Sociodemographic & personal information		**YP P/C C**	**YP (C)**	**YP P/C (C)**	**YP P/C (C)**
Need for Care (HoNOSCA – SR) (HoNOSCA – Clinician report)		**YP RA (C;YP;P/C)**	**YP RA (C;YP;P/C)**	**YP RA (C;YP;P/C)**	**YP RA (C;YP;P/C)**
Transition readiness / Transition outcome (TRAM/TROM)		**YP P/C C**	**YP P/C C**	**YP P/C C**	**YP P/C C**
Referral and Transition Status (CAMHS clinician only)			**C**	**(C)**	**(C)**
Quality of Life (WHOQOL-BREF)		**YP**		**YP**	**YP**
Cost-effectiveness (EQ-5D-5L)		**YP**	**YP**	**YP**	**YP**
Service use (CSRI)		**YP**	**YP**	**YP**	**YP**
Emotional/behavioural problems (YP: YSR/ASR P/C: CBCL/ABCL)		**YP P/C**	**YP P/C**	**YP P/C**	**YP P/C**
Ethics of transitioning		**YP**		**YP**	
Independent behaviour** (IBDCS)		**YP**	**YP**	**YP**	**YP**
Barriers to Care (BtC)**			**YP**	**YP**	**YP**
Bullying		**YP**			**YP**
Life events		**YP**	**YP**	**YP**	**YP**
Illness perception (B-IPQ)		**YP**			**YP**
Transition experience & readiness (OYOF-TES)*			**YP P/C**	**(YP) (P/C)**	**(YP) (P/C)**
Functioning & Impairment (SLOF)		**P/C**		**P/C**	**P/C**
Illness severity (CGIS)		**C**	**(C)**	**(C)**	**(C)**
Psychopathology (YP: DAWBA 5-17/18+ SR) P/C: DAWBA 5-17/18+ PR) C: Clinical diagnosis		**YP P/C C**	**(C)**	**(C)**	**YP P/C (C)**

TB = Transition boundary of service; YP = young person; P/C = parent/carer

C = clinician. T1: CAMHS clinician; if YP is transitioned after T1, then at T2-T4 the clinician is based at AMHS. If there is a delay in transitioning, the clinician at T2-T4 will still be based at CAMHS. Consent and sociodemographic data is sought from the clinician only once. (C) = if YP is a mental health service user, then clinician is asked for information.

RA = Research Assistant

SR = Self-report

PR = Parent-report

* = completed only once at the first assessment after transition

** = if the YP is a service user the IBDCS is administered, if the YP is not a current service user, the BtC is administered.

*** = in exceptional cases, the assessment can take place up to 12 months before or 3 months after the TB (e.g. if transitions regularly happen earlier in a service or a decision about transition hasn't yet been made.

The baseline assessment (T1) is undertaken after consent/assent has been given but before the delivery of the intervention, within 6 months before the transition boundary of the service or, in exceptional cases, within 12 months before or 3 months after the boundary (e.g. if transitions regularly happen earlier in a service or a decision about transition hasn't yet been made). Young people and their parents/carers are assessed at the clinic, or at an alternative location suitable for the young person, with both semi-structured interview (sociodemographic and personal information, and HoNOSCA) and online assessment. The sociodemographic and personal information questionnaire for young people and parent/carers collects general information about the young person and family, and the care the young person receives. The questionnaire covers also medical history and additional variables previously shown to contribute to continuity of mental health problems (for example, history of mental health problems and alcohol or drug abuse by parents). The last online assessment of T1 is the structured sections of the Development and Well-being Assessment (DAWBA),[76 77] which obtains information on mental health. Information from the assessment with the young person and parent/carer will be combined with a computer algorithm that provides an estimate of the probability of a certain individual diagnosis. Information on clinical diagnosis is obtained from the clinician.

The length of the baseline assessment (YP) is approximately 1.5 – 2 hours. The participant can take a short break in between the online measures, and if required, complete them over multiple sessions. The research assistant is available to assist if there are any difficulties. The baseline assessment (T1) should be completed before the end of the recruitment period.

Follow-up data

Outcomes are measured 9 months (T2), 15 months (T3) and 24 months (T4) after T1. The aim is to complete measures at T2 and T3 via telephone and online assessment, and at T4 via face-to-face contact with young people and their parents/carers, within a month (±) of the calculated assessment

time point (Table 2). Assessments with CAMHS or AMHS clinicians (or other service provider), which is dependent on transition status, follow the same schedule.

Evaluation of the intervention and experiences of young people regarding services

The views and experiences of CAMHS clinicians in the intervention arm are captured using a semi-structured questionnaire. All clinicians are approached and those willing to engage are interviewed over the telephone or face-to-face.

A sub-sample of young people taking part in the study will be invited to take part in focus groups at T4 from three participating countries: Ireland, UK and Croatia. The purpose of the focus groups will be to explore their experiences of leaving CAMHS, transition to AMHS if applicable, and views of mental health services, the aim being to establish whether young people have better health, educational and social outcomes, better quality of life and satisfaction with services if they: a) have experienced a managed transition from child to adult services at the transitional boundary or b) have experienced usual care (i.e. their transition to adult services, or their discharge from services, is via the usual procedure of their CAMHS clinic). It is hoped that, as part of MILESTONE's patient and public involvement activity, some of the young advisors, or other young people trained in facilitation skills by some of the research sites, may co-facilitate these focus groups.

Three audio-recorded focus groups will be held in each country with 9-12 young people in each group. Recruitment will be from the study participants with purposive sampling to include some young people who a) did not transition to adult services, b) who transitioned to adult services via usual care and c) who experienced managed transition.

Sample size

Assuming an average cluster size of 15 participants, an allocation ratio of 2:1 (control : intervention), a coefficient of variation of cluster size of 0.4 (cluster sizes ranging from approximately 5 to 30), and an intracluster correlation coefficient of 0.01, with 600 participants (195 intervention arm [13 clusters], 405 control arm [27 clusters]), the cRCT has 89% power to detect a difference of 0.30

standard deviations in the primary outcome measure (HoNOSCA). To allow for 30% dropout, the required average cluster size is 21 participants. Thus, for the cRCT the target sample size is 840 participants in total (273 intervention - 13 clusters of size 21; 567 control - 27 clusters of size 21). The randomisation was stratified by country, with the number and size of clusters dictated by local capacity. Excess clusters (those not required for the cRCT) were allocated to the control arm and will be used in the analysis of the cohort study only to enhance numbers for sufficient power to study predictors for the longitudinal course and outcome of mental health during transition. There are 10 such excess clusters (average size 21 before drop outs). The recruitment target for the cohort study is therefore 777 participants (567 from the control arm of the cRCT plus 210), and the total recruitment target is 1050 (840 plus 210).

Retention of study participants

To ensure that contact is not lost with any members of the study population during the follow-up period and that data are as complete as possible, MILESTONE has paid considerable attention to its engagement and retention strategies, drawing extensively on the advice and experiences of its young advisors to create a special "Bonding Plan". Participants may be contacted using several methods of communication (post/phone/email); contact details of all participants, including GP and CAMHS clinician details, are recorded in a "keeping in touch" form; data is collected in several different ways (face-to-face, online, phone); and each contact, or contact attempt, made with participants is recorded in a bespoke contact log. There are multiple contact points between study assessments, where the participants can advise of any changes to their contact details. The Bonding plan activities vary by country taking local ethical and cultural requirements into consideration. Items include thank you cards, newsletters, gift vouchers and a chance to win a prize in a lottery. The value of gift vouchers provided after assessments range from £10-£20 or similar equivalent in Euros. In Italy and Croatia, the research ethics committees did not allow providing any gifts after the individual assessment time points. Reasonable travel expenses are reimbursed for young people and their parents/carers.

Losses to follow up

Due to the characteristics of the study population group (young people, highly mobile, in the process of moving on to higher education, training or work), we have allowed for a 30% drop out rate.

Withdrawal of young people from the study

All participants remain in the study and follow-up data is sought unless consent for participation in data collection is explicitly withdrawn.

Data analysis

Detailed Statistical Analysis Plans, which include specific methods of analysis for each outcome variable, have been developed individually for both studies, and final versions will be reviewed and approved by the Trial Management Group and made available on the study website (http://www.milestone-transitionstudy.eu/).

A sensitivity analyses using multiple imputation will be conducted to explore the potential impact of missing data.

cRCT

Basic descriptive methods will be used to present the data on study participants, trial conduct, clinical outcomes and safety (in total and for each study group separately). The primary outcome will be HoNOSCA score at T3 and we will test the hypothesis that there is no difference in this between the managed transition and standard care arms over the study period using a multilevel model with random effects to account for clustering and repeated measures, and adjustment for design factors (country and size of service). Where appropriate, a similar approach will be applied to the analysis of secondary outcomes. All analyses will be on an intention to treat basis.

Cohort study

Baseline, longitudinal course, and outcome data at T4 will be analysed. Trajectories of mental health, subjective need for care and quality of life will be determined using mixed growth models and related to whether transitions from CAMHS to AMHS took place.

Data will be analysed to predict and characterise those with higher primary and secondary outcome scores. Functional, clinical and quality of life outcomes will be assessed in those CAMHS users who transition with those who do not transition to AMHS.

Economic evaluation

Health economic data collection

To conduct the economic evaluation of the trial, information on health care usage, social care usage/social costs and intervention costs will be captured. Additionally, participant health-related quality of life, and HONOSCA score will be recorded.

Resource use data collection

Health and social care resource utilisation for both trial arms will be estimated using the MILESTONE specific Client Service Receipt Inventory (CSRI), which draws on a CSRI used previously to estimate mental health care costs in the UK,[63] but has been substantially revised for use in MILESTONE. It includes questions regarding not only health care usage, but also relating to social and judicial resource use, and these questions are tailored for each participating country to reflect local services. Young people complete the measure at all four time points. For the purpose of economic evaluation, a questionnaire on the burden and impact of TRAM will be completed by all clinicians within the cRCT. This will assess how much extra burden is placed upon staff involved within the transition process due to the intervention compared to usual care.

The intervention costs associated with managed transition include the cost of implementing, as well as the delivery of the intervention. Questionnaires have been distributed to researchers in each country to ascertain the resources required to set up the intervention, whilst Excel logbooks capture

the time spent by clinicians completing the TRAM. Likewise, the time spent by the University of Warwick preparing the TRAM report is logged within an Excel database and clinician questionnaires will be used to capture the impact of the intervention on resource use.

Outcomes for economic evaluation

The two primary outcomes for the economic evaluation are quality adjusted life years (QALYs) and HONOSCA score.[56 57] Health-related quality of life (HRQL) will be measured using the EQ-5D-5L[64] and index scores[78] will be applied to calculate QALYs to determine the impact of the intervention on HRQL. Changes in QALYs and HONOSCA score between the two trial arms will be examined in conjunction with the costs to examine the cost-effectiveness of the intervention on mental health.

Economic evaluation: analysis

General principles of the economic analysis

Intention to treat: As recommended by best practice,[79] an intention to treat (ITT) framework will be adopted. That is, for each individual within the trial, the analysis will be conducted according to which arm they were randomised.

Perspective: The base-case analysis will adopt a healthcare and personal social services (PSS) perspective in accordance with NICE recommendations.[79] However, given the widespread acknowledgement of the wider costs of mental health,[80] a societal perspective will be adopted as a secondary analysis. Societal costs will include: social care, productivity, and criminal justice system contacts.

Time horizon: The base-case analysis will be a trial based analysis and therefore consider just the years followed up within the trial. Given the complexity of the trial, the potential for long term decision modelling and extrapolation will be informed by a systematic review of the methods used within existing mental health literature. Long run extrapolation will therefore be considered in light of this.

Discounting: As recommended by NICE,[79] all costs and outcomes that occur after the first year of the trial will be discounted at 3.5%.

Missing data: Typically, within any economic evaluation of an RCT, there will be some missing data.[81] This may be for a number of reasons, and a certain degree of attrition is to be expected during follow up. Should missing data be prevalent, the health economics analysis will address missing data through the use of multiple imputation.[81]

Clustering: The hierarchical nature of the data needs to be addressed within multiple imputation procedures and within the analysis framework. To do this, random effects approaches will be used.[82]

Uncertainty: The uncertainty around the results will be assessed through sensitivity analyses and the generation of cost-effectiveness acceptability curves (CEACs).[83]

Calculating costs for economic evaluation

Data on staff time and other resources in the transition process will be obtained at each location, and costed using appropriate sources of unit cost data (e.g. for the UK, standard unit cost sources include the NHS reference costs and the Unit Costs of Health and Social Care report published annually by the Personal Social Services Research Unit at the University of Kent). This will result in location-specific estimates of the direct costs involved in implementing the managed transition process.

Outcomes for economic evaluation

The primary economic analysis will be a cost utility analysis. The EQ-5D-5L measure allows the calculation of QALYs. QALYs will be calculated for each child within the trial using the area under the curve method. The trapezium rule will be used to calculate the area under the curve and thus calculate QALYs. An underlying assumption of this methodology is that there is a linear line between each utility value at each follow up. When analysing incremental QALYs between trial arms, it is

important to adjust for baseline differences in utility.[84] In addition to controlling for baseline utility, it is important to account for the hierarchical nature the outcome data.[82] The base-case analysis of effectiveness will therefore use methods that incorporate a random-effects regression model controlling for baseline health status and accounting for clustering.[82] EQ-5D-5L tariffs for each participating country, where available, will be used to allow for country-specific economic analyses. The cost-effectiveness of the intervention over the duration of the trial will be examined, and decision uncertainty assessed using probabilistic sensitivity analysis and scenario analysis.

Data management

Online data collection

All measures apart from DAWBA are completed using HealthTracker™, which allows measures to be completed remotely using developmentally appropriate interfaces and subjects to skip modules if they do not score on screening questions for that module, thereby reducing the burden to participants. Each questionnaire has been optimised for the screen, based on feedback from service users and providers. HealthTracker™ automatically generates random participant (service user, parent, and clinician) ID numbers and passwords when the participant is entered onto the system. HealthTracker™ stores participant's month and year of birth. All other data is anonymised.

The DAWBA is completed using the website http://dawba.net and anonymised scores (identified and linked using the unique DAWBA ID) transferred to a bespoke form on the HealthTracker™ system. A secure database developed at Warwick Medical School stores information that is not collected by HealthTracker™. This includes participant name, unique study ID, HealthTracker™ and DAWBA IDs, contact details, information linking participants (for example, young person to CAMHS clinician) and service level information. This database is maintained locally at sites with access password controlled and strictly limited to MILESTONE personnel to ensure confidentiality. No personally identifiable information relating to participants leaves the local site. Only the unique

identifiers, linking information (using identifiers) and service level data is shared with Warwick Medical School.

Paper-copies of measures are only used as a last resort, or if preferred by the participant. All MILESTONE researchers have received training on the HealthTracker™ platform and other systems for data collection prior to the study beginning.

Data transfer

All transfers of study data are informed by and comply with the European Parliament and the Council of Europe's Directive 95/46/EC on protection of individuals with reference to the handling of personal data and on the free flow of such information between EU countries.

To ensure the security and integrity of data during such transfer an appropriate documented standard procedure has been established and is followed without exception. Any study data that is to be transferred between research sites is anonymised prior to transfer.

Data Storage

All essential documentation and trial records is stored by Warwick Medical School and participating local sites in conformance with the applicable regulatory requirements with access to stored information restricted to authorised personnel.

Data access and quality assurance

In all partner countries, local research ethics committee requirements and national and EU law underpin the collection, recording, sharing and secure storage of person identifiable data.

Personal information about potential and enrolled participants are collected, shared, and maintained in a manner, which protects their confidentiality before, during and after the trial. All researchers working on the MILESTONE Study are experienced in undertaking research in a way that maintains the privacy and confidentiality of study participants but which balances these demands

against the needs to ensure that participants are not at risk. Names or addresses of participants are not disclosed to anyone other than the staff involved in running the trial.

Data is only accessible by authorised personnel and made available to relevant bodies for audit purposes only.

At the end of the MILESTONE project, analysis datasets will be made available following University of Warwick's Research Data Management Policy which ensures that data produced through the University's research activities is registered, stored, made accessible for use and reuse as appropriate, managed over time and/or disposed of, according to legal, ethical, funder requirements and good practice.(http://www2.warwick.ac.uk/services/rss/researchgovernance_ethics/research_code_of_practice/datacollection_retention/research_data_mgt_policy/)

Archiving

Data from this study will be retained intact in an appropriate format and storage facility for a minimum of 10 years in the UK in line with the Medical Research Council's guidelines on Personal Information in Medical Research; other countries will follow their relevant guidelines. (http://www.mrc.ac.uk/documents/pdf/personal-information-in-medical-research/)

Monitoring

UK sites are monitored by Warwick Medical School. Monitoring includes compliance to the protocol, quality of data collection, storage of documentation and requires monitors to have access to relevant participant notes/charts and trial documentation. Each overseas party is responsible for monitoring their sites according to local procedures.

Adverse event management

A young person experiencing adverse events as a direct consequence of the intervention are unlikely, as the intervention is as aimed at the clinician. At each study assessment, the young person is asked whether any adverse events (bad or unfavourable medical occurrence) have occurred since

the last time point. This includes events from the first trial-related activity after the participant has signed the consent form until the end point of the trial as defined in the protocol. Any worsening of concomitant illness or new illness is recorded as adverse events at each visit. If the event is classified as a Serious Adverse (SAE) event, an SAE form is completed and the Principal Investigators (PIs) of each country report all SAEs immediately to the trial coordinating centre at Warwick Medical School. The trial CI determines whether SAEs require reporting to the trial sponsor or SCEAB.

ETHICS AND DISSEMINATION

Ethics and R&D governance

The study has been approved by the National Research Ethics Service in the UK (West Midlands: South Birmingham Research Ethics committee, Ref. no. 15/WM/0052) and by research ethics committees of all partaking countries. Regional and site-specific approvals have been obtained from NHS Research and Development offices in the UK and from other similar bodies in the other countries. The study is registered with the ISRCTN trial registry (ISRCTN83240263) (http://www.isrctn.com/ISRCTN83240263?q=MILESTONE&filters=&sort=&offset=3&totalResults=21&page=1&pageSize=10&searchType=basic-search) and ClinicalTrials.com (NCT03013595) https://clinicaltrials.gov/ct2/show/NCT03013595?term=NCT03013595&rank=1.

The ethical conduct of the study is monitored throughout by the MILESTONE Ethics work package.

Service users

We are involving a potentially vulnerable population in research: adolescent mental health service users who, in the main, are over the age of 16, but in areas where the transition boundary is 16 years (some parts of England) or 16.5 years (some parts of France) they are 15 years. In England, the legal age of consent is 16, in all other participating countries it is 18.

Despite best efforts, vulnerable people, either by virtue of being young and/or with mental health difficulties, are often omitted from research studies because of concerns regarding informed consent.[85 86] The researchers in this study acknowledge these concerns and risks but also

recognise the importance of including individuals with enduring mental health difficulties in the study to better inform practice. The Council of Europe strongly promotes the participation of children in decisions affecting them.[87] Young people will also have rights as service users, to expect appropriate and good quality services.

The participant information sheets and consent/assent forms make explicit the voluntary nature of young people's involvement. Even if the parent/carer gives consent but a young person refuses, that young person is not included in the study. The young person's consent is sought before follow-up assessments (verbal consent for telephone interviews), consent being implicit when they log on to give responses online. The forms also seek permission to delay data collection until a later point should a young person become unwell or due to some other pressing circumstances, as long as transition doesn't take place in the meantime, and to liaise with a young person's clinician and parent/carer should such a delay be deemed necessary. The forms explain the various safeguards in place, namely to liaise with a young person's clinician and/or family if required and the resulting impact on confidentiality.

In order to minimise any distress to young people taking part in face-to-face interviews, wherever possible these are organised in venues that are known to the young person and are scheduled at times when there are familiar staff or family members or carers on hand to offer support should a young person become upset during any data collection processes.

In the event that during an interview or other data collection session, a MILESTONE researcher identifies any situation where a young person is thought to be at risk of abuse or neglect, or that young person discloses information that raises concern about the young person's safety, then a detailed risk management plan is followed, which stipulates that the child protection policies and procedures applicable to that country are adhered to. This is likely to involve close liaison by the researcher and the MILESTONE lead for that study site, with the young person's clinician and/or the nominated child protection leads within the mental health service attended by the young person.

Also, young people consenting to the study are asked to nominate, and provide contact details for, a health/care professional (for example, GP or CAMHS clinician) who we may contact should any adverse event arise. This safeguard is made explicit in the study information leaflets, and at all data collection time points, so young people are aware of the impact on confidentiality during the process of data collection.

Training

All research assistants have participated in training sessions addressing Good Clinical Practice (GCP), transition practices, rating procedures, compliance, TRAM feedback, and communication with young people, families and clinicians. A special focus of the training has been the primary outcome measure, the clinician-rated HoNOSCA, completed by research assistants. The training has included ratings and discussions of clinical vignettes and how to conduct the HoNOSCA interview.[88] The study has been presented to all participating CAMHS teams and additional meetings have been held to implement the specific transition procedures in the intervention clusters.

Dissemination

The MILESTONE project has a work package that focuses on dissemination. Partnerships and networks with target bodies will be strategically developed to support both short- and long-term dissemination of the MILESTONE study and other project findings. External dissemination will target the scientific community, but also the general public, lay and patients' associations, health care authorities and care givers, scientific societies and professional boards, students, policy makers, and the pharmaceutical industry. Particular attention will be paid to the information needs of the various target audiences, and that they are addressed in the appropriate language and format.

The results of the MILESTONE study will be made available in the first instance to the clinicians of CAMHS and AMHS partaking in the study, and then to the scientific community at large via publications in scientific journals, presentations at meetings, the MILESTONE web site (http://milestone-transitionstudy.eu), press releases, and leaflets.

CONCLUSION

The continuity of adolescent psychopathology into adulthood means that transition to AMHS is necessary for many. However, there are real gaps in mental health care provision at this crucial stage, and those who experience transition frequently describe it as disruptive. The MILESTONE study is the first ever methodologically robust trial to test whether a decision support and assessment tool, the TRAM, can improve the mental health and social outcomes and functioning of transition age young people receiving CAMHS care. Young people in eight European countries are partaking in the trial; their longitudinal course of mental health, social and adult functioning outcomes are also evaluated as part of a longitudinal cohort study. The MILESTONE study has crucial input from young advisors, some with experience of transition in mental health services.

MILESTONE CONSORTIUM – CURRENT MEMBERS AND PARTNER INSTITUTIONS

Swaran Singh, Helena Tuomainen, Jason Madan, Moli Paul, Cathy Street, Dieter Wolke, Jane Warwick, Priya Tah, Alastair Canaway, James Griffin, Rebecca Appleton, Amanda Tuffrey, Anna Wilson, Charlotte Gatherer, Leanne Walker, Jude Taylor (University of Warwick, UK); Giovanni de Girolamo, Giulia Signorini, Alessandro Ferrari, Elisa Gheza, Cecilia Ferrari, Laura Rivolta, Flavia Levi, Maria Cataldo, Lidia Manenti, Giorgia Morini, Adriana Pastore, Cecilia Toselli, Pamela Varvara (Saint John of God Clinical Research Center, Italy); Paramala Santosh, Ilyas Sagar-Ouriaghli, Natalie Heaney , Jatinder Singh (Kings College London, UK); Diane Purper-Ouakil, Frédérick Russet, Virginie Maurice, Véronique Humbertclaude (Centre Hospitalier Universitaire de Montpellier, France); Athanasios Maras, Larissa van Bodegom, Mathilde Overbeek (Yulius Academy, Netherlands); Ulrike Schulze, Jörg M Fegert, Melanie Saam, Ulrike Breuninger, Renate Schepker, Michele Noterdaeme (University of Ulm, Germany); Sabine Tremmery, Gaëlle Hendrickx (Katholieke Universiteit Leuven, Belgium); Fiona McNicholas, Aleksandra Gronostaj (University College Dublin, Republic of Ireland); Tomislav Franić, Nikolina Davidović (University Hospital Split, Croatia); Kate Lievesley, Federico Fiori (HealthTracker Ltd, UK); Frank Verhulst, Gwen C Dieleman, Suzanne Gerritsen (Erasmus Medical Centre, Netherlands); Andrea Wohner (concentris research management GmbH, Germany).

ACKNOWLEDGEMENTS

We are very grateful for the CAMHS and AMHS services and research teams who are collaborating in this study in the eight European countries. We also extend thanks to all the participating service users and their parents/carers. We are also grateful for the members of the MILESTONE Scientific Clinical and Ethical Advisory Board (SCEAB) - Norman Sartorius, Pat McGorry, Maryann Davis, Mario Maj, and Adriana Mihai – and for Tanveer Sandhu, Philippa Coleman for reviewing the protocol. We would also like to thank members of the wider MILESTONE Consortium for their contribution. We extend a special thanks to Andrea Wohner, our project manager based at concentris research management gmbh, Fürstenfeldbruck, Germany, for excellent project management and delivery.

AUTHORS' CONTRIBUTIONS

SPS is the chief investigator who conceived the original study design and obtained funding, together with AM, GdG, PS, JM, FM, DPO, ST, US, TF, CS, MP, DW, FV, and GD. HT is the study coordinator who prepared the first draft and subsequent versions of the protocol and this manuscript, and is joint first author with SPS. JW and AC contributed to the manuscript. JW is the senior trial statistician who led the calculation of the sample size; JG will undertake the statistical analysis under her direction. JM designed the health economic component and AC will undertake the health economics analysis under his direction. CD is the quality assurance manager. PT, SG, GS, LA, FR, SA, LOH, and ND are research assistants and helped set up the study in their countries and gain local ethical approvals. The UK young advisors, AT, AW, CG, and LW, reviewed the proposed study scales (including the likely time required for completion, to assess for possible burden on study participants), participated in the design of the intervention leaflet and reviewed all study information material before submission to ethics. All authors critically reviewed the protocol and the manuscript, and gave approval for the publication.

FUNDING

The MILESTONE project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602442. This paper reflects only the authors' views and the European Union is not liable for any use that may be made of the information contained therein. The funding body has had no role in the study design, in the writing of the protocol or in the decision to submit the paper for publication.

COMPETING INTERESTS

Paramala Santosh is the director and shareholder of HealthTracker Ltd. Frank Verhulst publishes the Dutch translations of ASEBA from which he receives remuneration.

REFERENCES

1. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62(6):617-27.
2. McGorry P. The specialist youth mental health model: strengthening the weakest link in the public mental health system. *Med J Aust* 2007;187(7):s53-s56.
3. McGorry P. Transition to adulthood: the critical period for pre-emptive, disease-modifying care for schizophrenia and related disorders. *Schizophr Bull* 2011;37(3):524-30.
4. Pottick KJ, Bilder S, Vander Stoep A, et al. US patterns of mental health service utilization for transition-age youth and young adults. *J Behav Health Serv Res* 2008;35(4):373-89.
5. Kataoka SH, Zhang L, Wells KB. Unmet need for mental health care among U.S. children: variation by ethnicity and insurance status. *Am J Psychiatry* 2002;159(9):1548-55.
6. Offord DR, Boyle MH, Fleming JE, et al. Ontario Child Health Study. Summary of selected results. *Can J Psychiatry* 1989;34(6):483-91.
7. Singh SP, Paul M, Ford T, et al. Transitions of care from child and adolescent mental health services to adult mental health services (TRACK study): a study of protocols in Greater London. *BMC Health Serv Res* 2008;8(135):1-7.
8. Singh SP, Paul M, Ford T, et al. Process, outcome and experience of transition from child to adult mental healthcare: multiperspective study. *Br J Psychiatry* 2010;197(4):305-12.
9. Davis M, Geller JL, Hunt B. Within-state availability of transition-to-adulthood services for youths with serious mental health conditions. *Psychiatr Serv* 2006;57(11):1594-99.
10. Davis M, Vander Stoep A. The transition to adulthood for youth who have serious emotional disturbance: Developmental transition and young adult outcomes. *J Ment Health Adm* 1997;24(4):400-27.
11. Royal College of Nursing. Adolescent transition care. London: RCN Publications, 2004.
12. Royal College of Paediatrics and Child Health. Bridging the gaps: healthcare for adolescents. Secondary Bridging the gaps: healthcare for adolescents 2003. www.rcpsych.ac.uk.
13. Royal College of Physicians of Edinburgh Transition Steering Group. Think transition: developing the essential link between paediatric and adult care. Edinburgh: Royal College of Physicians of Edinburgh, 2008.

14. Royal College of Psychiatrists. Building and sustaining specialist child and adolescent mental health services: council report CR137. London: Royal College of Psychiatrists, 2006.
15. Davis M, Sondheimer DL. State child mental health efforts to support youth in transition to adulthood. *J Behav Health Serv Res* 2005;32(1):27-42.
16. Paul M, Ford T, Kramer T, et al. Transfers and transitions between child and adult mental health services. *Br J Psychiatry Suppl* 2013;54:s36-40.
17. Hovish K, Weaver T, Islam Z, et al. Transition experiences of mental health service users, parents, and professionals in the United Kingdom: a qualitative study. *Psychiatr Rehabil J* 2012;35(3):251-7.
18. McNicholas F, Adamson M, McNamara N, et al. Who is in the transition gap? Transition from CAMHS to AMHS in the Republic of Ireland. *Ir J Psychol Med* 2015;32(01):61-69.
19. McLaren S, Belling R, Paul M, et al. 'Talking a different language': an exploration of the influence of organizational cultures and working practices on transition from child to adult mental health services. *BMC Health Serv Res* 2013;13(1):254.
20. Paul M, Street C, Wheeler N, et al. Transition to adult services for young people with mental health needs: A systematic review. *Clin Child Psychol Psychiatry* 2014.
21. Singh S, P., Paul M, Islam Z, et al. Transition from CAMHS to Adult Mental Health Services (TRACK): A Study of Service Organisation, Policies, Process and User and Carer Perspectives. Report for the National Institute for Health Research Service Delivery and Organisation programme (SDO Project 08/1613/117), 2010.
22. Wilson A, Tuffrey A, McKenzie C, et al. After the flood: young people's perspectives on transition. *Lancet Psychiatry* 2015;2(5):376-78.
23. Davis M. Addressing the needs of youth in transition to adulthood. *Adm Policy Ment Health* 2003;30(6):495-509.
24. Department of Health. Continuity of care for people with severe mental illness? London: Department of Health, 2003.
25. Vostanis S, Richards V. Transition services for 16-19 year olds. Leicester: Leicester University, 2002.
26. Department for Children Schools and Families, Department of Health. A transition guide for all services: key information for professionals about the transition process for disabled young people. Secondary A transition guide for all services: key information for professionals about the transition process for disabled young people 2007. http://www.everychildmatters.gov.uk/_files/TransitionGuide.pdf.
27. Department for Children Schools and Families, Department of Health. Transition: moving on well. A good practice guide for health professionals and their partners on transition planning for young people with complex health needs or a disability. London: Department of Health, 2008.
28. Forbes A, While A, Ullman R, et al. A multi-method review to identify components of practice which may promote continuity in the transition from child to adult care for young people with chronic illness or disability. Report for the National Coordinating Centre for NHS Service Delivery and Organisation R & D (NCCSDO): The Florence Nightingale School of Nursing and Midwifery, King's College, London, UK, 2002.
29. Kennedy A, Sloman F, Douglass JA, et al. Young people with chronic illness: the approach to transition. *Intern Med J* 2007;37(8):555 - 60.
30. Kennedy P, Pugh R, Millar E. Towards managing the whole system of care and improving continuity of care. *Psychiatr Bull* 2005;29(7):252-54.
31. Whaley AL. Racism in the provision of mental health services; a social cognitive analysis. *Am J Orthopsychiatry* 1998;68:47-57.
32. Singh SP. Transition of care from child to adult mental health services: the great divide. *Current opinion in psychiatry* 2009;22(4):386-90.

33. Suhrcke M, Pillas D, Selai C. Economic aspects of mental health in children and adolescents. . Social Cohesion for Mental Wellbeing among adolescents: WHO, 2008:43-64.
34. Petrou S, Johnson S, Wolke D, et al. Economic costs and preference-based health-related quality of life outcomes associated with childhood psychiatric disorders. *Br J Psychiatry* 2010;197(5):395-404.
35. Copeland WE, Wolke D, Shanahan L, et al. Adult Functional Outcomes of Common Childhood Psychiatric Problems: A Prospective, Longitudinal Study. *JAMA psychiatry* 2015;72(9):892-9.
36. National Institute For Health and Care Excellence. Transition from children's to adults' services for young people using health or social care services. NICE guideline: Full version. London: NICE, 2016.
37. Blum R, Garell D, Hodgman C, et al. Transition from child-centered to adult health-care systems for adolescents with chronic conditions: a position paper for the Society of Adolescent Medicine. *Journal of Adolescent Health* 1993;14:570–76.
38. McDonagh JE. Growing up ready for emerging adulthood: an evidence base for professionals involved in transitional care for young people with chronic illness and/or disabilities. Cambridge: Eastern Region Public Health Observatory, 2006.
39. McDonagh JE, Kelly DA. Transiting care of the pediatric recipient to adult care givers. *Pediatric Clinic of North America* 2003;50:1561-83.
40. McDonagh JE, Viner R. Lost in transition? Between paediatric and adult services. *British Medical Journal* 2006;332:435-36.
41. Singh SP, Anderson B, Liabo K, et al. Supporting young people in their transition to adults' services: summary of NICE guidance. *Bmj* 2016;353:i2225.
42. Coleman EA, Berenson RA. Lost in transition: challenges and opportunities for improving the quality of transition of care. *Annals of Internal Medicine* 2004;141(7):533-36.
43. Singh SP, Tuomainen H. Transition from child to adult mental health services: needs, barriers, experiences and new models of care. *World Psychiatry* 2015;14(3):358-61.
44. Brittlebank A, Hermans M, Bhugra D, et al. Training in psychiatry throughout Europe. *Eur Arch Psychiatry Clin Neurosci* 2016;266(2):155-64.
45. Schandrin A, Capdevielle D, Boulenger J-P, et al. Transition from child to adult mental health services: a French retrospective survey. *The Journal of Mental Health Training, Education and Practice* 2016;11(5):286-93.
46. Signorini A, Singh S, Boričević V, et al. Architecture and functioning of child and adolescent mental health services: a 28-country survey in Europe. *Lancet Psychiatry* 2017;in press.
47. Aebi M, Kuhn C, Metzke C, et al. The use of the devlopment and well-being assessment (DAWBA) in clinical practice: a randomized trial. *Eur Child Adolesc Psychiatry* 2012;21:559-67.
48. Freeman G, Weaver T, Low J, et al. Promoting continuity of care for people with severe mental illness whose needs span primary, secondary and social care: a multi-method investigation of relevant mechanisms and contexts. London: NCCSDO, 2002.
49. Joyce AS, Wild TC, Adair CE, et al. Continuity of care in mental health services: toward clarifying the construct. *The Canadian Journal of Psychiatry* 2004;49(8):539-50.
50. Nelson EC, Eftimovska E, Lind C, et al. Patient reported outcome measures in practice. *Bmj* 2015;350:g7818.
51. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Silver Spring: U.S. Department of Health and Human Services Food and Drug Administration, 2009.
52. Flamarique I, Santosh P, Zuddas A, et al. Development and psychometric properties of the Suicidality: Treatment Occurring in Paediatrics (STOP) Suicidality Assessment Scale (STOP-SAS) in children and adolescents. *BMC pediatrics* 2016;16(1):213.
53. Relton C, Torgerson D, O'Cathain A, et al. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. *Bmj* 2010;340:c1066.
54. Stata Statistical Software: Release 14 [program]. College Station, TX: StataCorp LP, 2015.

55. Hayes RJ, Moulton LH. Cluster randomised trials. Interdisciplinary Statistics Series: Chapman & Hall/CRC, 2009.
56. Gowers SG, Harrington RC, Whitton A, et al. Brief scale for measuring the outcomes of emotional and behavioural disorders in children. Health of the Nation Outcome Scales for children and Adolescents (HoNOSCA). *Br J Psychiatry* 1999;174:413-6.
57. Garralda ME, Yates P, Higginson I. Child and adolescent mental health service use: HoNOSCA as an outcome measure. *The British Journal of Psychiatry* 2000;177(1):52-58.
58. Pirkis JE, Burgess PM, Kirk PK, et al. A review of the psychometric properties of the Health of the Nation Outcome Scales (HoNOS) family of measures. *Health Qual Life Outcomes* 2005;3:76.
59. Demartini B, Petrochilos P, Edwards MJ, et al. Multidisciplinary inpatient programme for functional neurological symptoms: a prospective study assessing efficacy and predictors of good outcome. *Journal of Neurology, Neurosurgery & Psychiatry* 2014;85(8):e3.
60. Gowers S, Levine W, Bailey-Rogers S, et al. Use of a routine, self-report outcome measure (HoNOSCA-SR) in two adolescent mental health services. Health of the Nation Outcome Scale for Children and Adolescents. *Br J Psychiatry* 2002;180:266-9.
61. Skevington SM, Sartorius N, Amir M. Developing methods for assessing quality of life in different cultural settings. The history of the WHOQOL instruments. *Soc Psychiatry Psychiatr Epidemiol* 2004;39(1):1-8.
62. Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res* 2004;13(2):299-310.
63. Chisholm D, Knapp MR, Knudsen HC, et al. Client Socio-Demographic and Service Receipt Inventory--European Version: development of an instrument for international research. EPSILON Study 5. European Psychiatric Services: Inputs Linked to Outcome Domains and Needs. *Br J Psychiatry Suppl* 2000(39):s28-33.
64. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36.
65. Achenbach T, Rescorla L. Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families, 2001.
66. Achenbach T, Rescorla L. Manual for the ASEBA Adult Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families, 2003.
67. van Staa A. Unraveling triadic communication in hospital consultations with adolescents with chronic conditions: the added value of mixed methods research. *Patient Educ Couns* 2011;82(3):455-64.
68. Vanheusden K, Mulder CL, van der Ende J, et al. Young adults face major barriers to seeking help from mental health services. *Patient Educ Couns* 2008;73(1):97-104.
69. Wolke D, Sapouna M. Big men feeling small: childhood bullying experience, muscle dysmorphia and other mental health problems in bodybuilders. *Psychol Sport Exerc* 2008;9(5):595-604.
70. Tippett N, Wolke D, Platt L. Ethnicity and bullying involvement in a national UK youth sample. *Journal of Adolescence* 2013;36(4):639-49.
71. Broadbent E, Petrie KJ, Main J, et al. The brief illness perception questionnaire. *J Psychosom Res* 2006;60(6):631-7.
72. Løchting I, Garratt A, Storheim K, et al. Evaluation of the Brief Illness Perception Questionnaire in Sub-Acute and Chronic Low Back Pain Patients: Data Quality, Reliability and Validity. *J Pain Relief* 2013;2(122).
73. van Staa A, Sattoe JN. Young Adults' Experiences and Satisfaction With the Transfer of Care. *J Adolesc Health* 2014.
74. Mucci A, Rucci P, Rocca P, et al. The Specific Level of Functioning Scale: Construct validity, internal consistency and factor structure in a large Italian sample of people with schizophrenia living in the community. *Schizophr Res* 2014;159(1):144-50.

75. Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: U.S. Department of Health, Education, and Welfare, 1976.
76. Goodman R, Ford T, Richards H, et al. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry* 2000;41(5):645-55.
77. Goodman A, Heiervang E, Collishaw S, et al. The 'DAWBA bands' as an ordered-categorical measure of child mental health: description and validation in British and Norwegian samples. *Soc Psychiatry Psychiatr Epidemiol* 2011;46(6):521-32.
78. Devlin N, Shah K, Feng Y, et al. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. OHE Research Paper 16/01. London: Office of Health Economics, 2016.
79. National Institute For Health and Care Excellence. Guide to the methods of technology appraisal 2013. London: NICE, 2013.
80. Shearer J, McCrone P, Romeo R. Economic Evaluation of Mental Health Interventions: A Guide to Costing Approaches. *PharmacoEconomics* 2016;34(7):651-64.
81. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj* 2009;338:b2393.
82. Gomes M, Ng ES, Grieve R, et al. Developing appropriate methods for cost-effectiveness analysis of cluster randomized trials. *Medical decision making : an international journal of the Society for Medical Decision Making* 2012;32(2):350-61.
83. Fenwick E, Marshall DA, Levy AR, et al. Using and interpreting cost-effectiveness acceptability curves: an example using data from a trial of management strategies for atrial fibrillation. *BMC Health Serv Res* 2006;6:52.
84. Manca A, Palmer S. Handling missing data in patient-level cost-effectiveness analysis alongside randomised clinical trials. *Appl Health Econ Health Policy* 2005;4(2):65-75.
85. Yan EG, Munir KM. Regulatory and ethical principles in research involving children and individuals with developmental disabilities. *Ethics & behavior* 2004;14(1):31-49.
86. Medical Research Council. MRC Ethics Guide: Medical research involving children. London: Medical Research Council, 2004.
87. Parliamentary Assembly. Promoting the participation by children in decisions affecting them. Recommendation 1864; Doc. 12080: Council of Europe, 2009.
88. Rock D, Preston N. HoNOS: is there any point in training clinicians? *J Psychiatr Ment Health Nurs* 2001;8(5):405-9.

FIGURES

Figure 1 MILESTONE study flow diagram

Figure 2 Flowchart of study intervention (Feedback of TRAM results) and follow-up assessments with young person

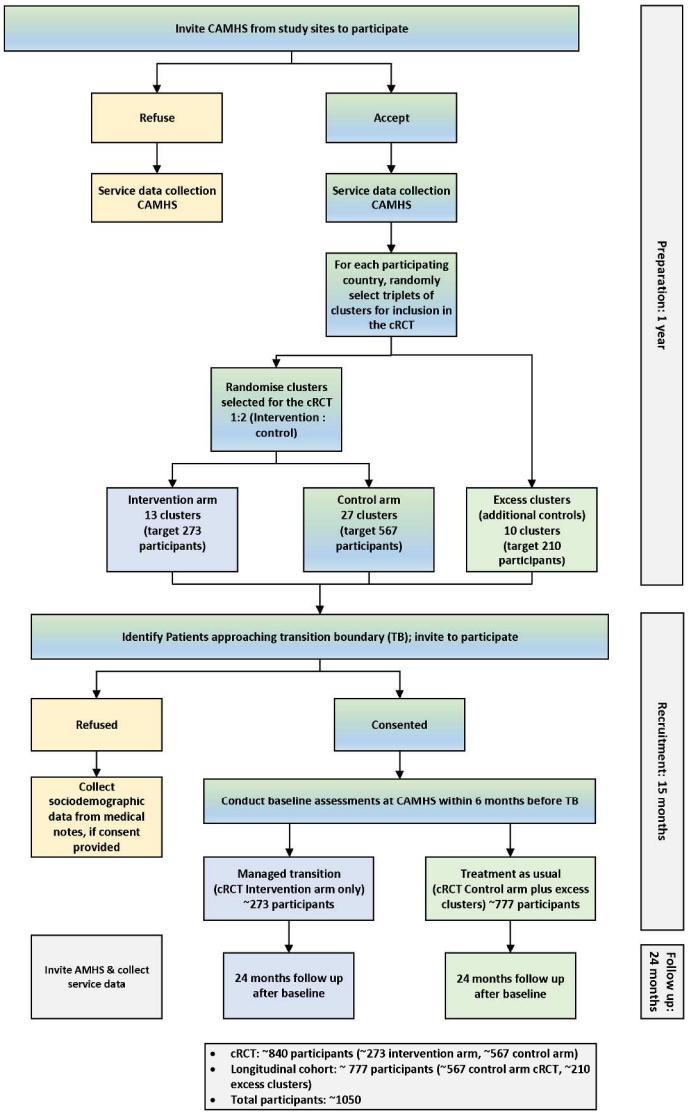

Figure 1 MILESTONE study flow diagram

210x297mm (300 x 300 DPI)

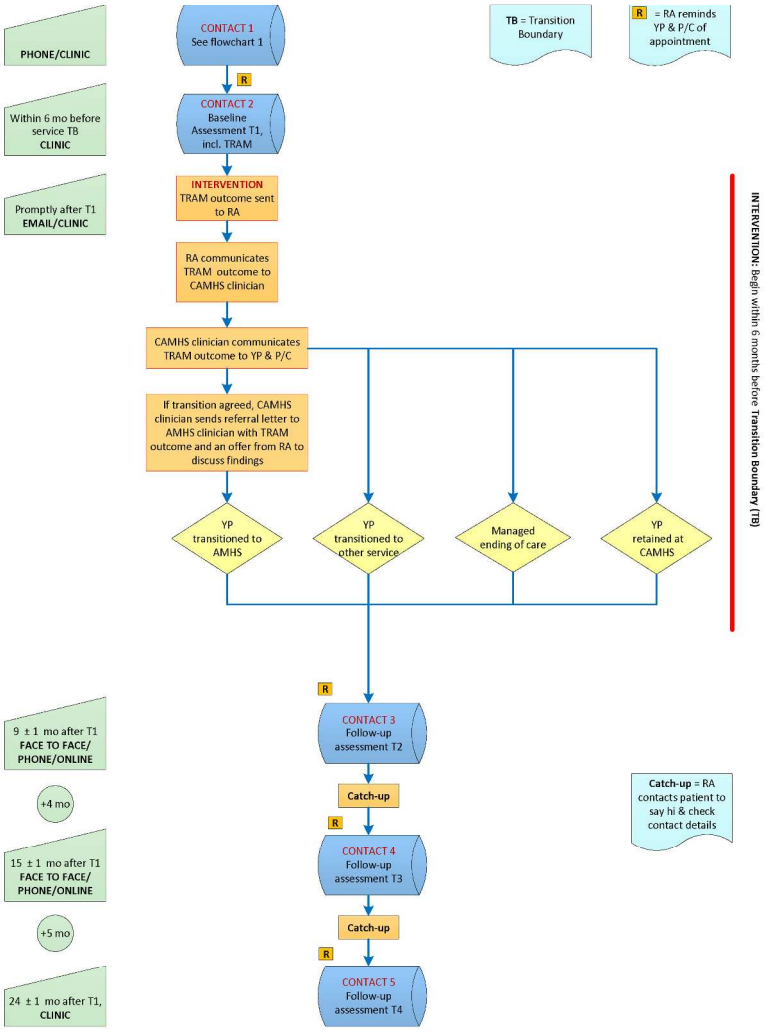

Figure 2 Flowchart of study intervention (Feedback of TRAM results) and follow-up assessments with young person

210x297mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			Protocol paper in track changes: PP Main protocol: MP v2.2 03.03.2017
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p. 1 (PP) _____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p. 4 (PP)_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	p. 1 (MP)_
Funding	4	Sources and types of financial, material, and other support	p. 41 (PP)_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p. 1-2 (PP)____
	5b	Name and contact information for the trial sponsor	p. 2 (MP)_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	p. 41 (PP) _____

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	p. 13-14 (PP)_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p. 5-12 (PP)_____
	6b	Explanation for choice of comparators	p. 13 (PP)_____
Objectives	7	Specific objectives or hypotheses	p. 12 (PP)_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p. 13 (PP)_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p. 14 (PP)_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p. 17-19 (PP)___
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p. 19-22_(PP)___
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_n/a_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_n/a_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_n/a_____

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p. 22-23, 25_(PP)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	p. 23_(PP) & Fig 1__
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p. 27-28 (PP)___
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	p. 17-19 (PP)___
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p. 16 (PP)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_n/a (cluster randomised)_____ __
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_n/a_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p. 16 (PP)_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_n/a_____ _
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.	p. 22-23, 24-27, 38-39_(PP)____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p. 28-29 (PP)_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p. 33-36 (PP)_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p. 29-30 (PP)_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p. 30 (PP)____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p. 30 (PP)
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	p. 13-14 (PP) p. 10, 58-59 (MP)_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_n/a_____ _
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p. 36 (PP)_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	p. 59 (MP)_____
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p. 4, 36_(PP)___
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p. 57 (MP)_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p. 18 (PP)_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_n/a_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p. 34-35 (PP)___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p. 42 (PP)____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p. 35 (PP)_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_n/a_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	p. 39-40 (PP)___
	31b	Authorship eligibility guidelines and any intended use of professional writers	p. 61 (MP)___
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	p. 35-36 (PP)___
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon request___

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_n/a_____ _

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.