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Study protocol on advance care planning in multiple sclerosis (ConCure-SM): Intervention construction and multicenter feasibility trial

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ONLINE SUPPLEMENTAL APPENDIX 1 – SPIRIT CHECKLIST; DSMC CHARTER

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 8
	2b	All items from the World Health Organization Trial Registration Data Set	Yes (available in trial register)
Protocol version	3	Date and version identifier	7
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	1
	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	21
	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)	20-21, Appendix 3
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of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6

	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	7, Box
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)	3, 8
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	3, 10, 20-21
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)	10-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9, 11-12
	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	12-14
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)	10-12, Figure 2

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	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
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	N/A
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
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	N/A
	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	11-14
	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	12

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	Appendix 3
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	16-17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	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)	17
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	20, Appendix 3, DSMC Charter (pages 8-15 below)
	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	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3, 18

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)	Appendix 3
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	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	Appendix 3
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
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	18
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	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18, 22
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	11

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. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

ConCure-SM Phase 2 Study
DSMC CHARTER[1]

A. CONTENT	***B.***
1. **Introduction**	
Name (and sponsor's ID) of trial plus SRCTN and/or EUDRACT number	Advance Care Planning in Multiple Sclerosis: Pilot study (ConCure-SM Phase 2 Study) PROTOCOL N. FISM 2020/R-MULTI/024 ISRCTN48527663
Objectives of trial, including interventions being investigated	ConCure-SM is a project aimed to set up and evaluate the efficacy of an Advance Care Planning (ACP) intervention in people with primary or secondary progressive MS (pwPMS) in Italy. In Phase 1, the ACP booklet was produced involving the key stakeholders: pwPMS, pwPMS' significant others (SOs), and HPs. In Phase 2, the safety and efficacy of the ACP intervention (pwPMS-physician ACP conversation using the ConCure-SM booklet) will be pilot tested in different MS care settings in Italy using a six-month mixed-methods prospective study. This pilot study will inform the decision to proceed with / design a 'full' trial. The Pilot Trial will involve at least 40 pwPMS from six centers (MS centers, rehabilitation centers) across the three geographic areas of Italy. The primary outcome is completion of an advance care plan document. Secondary efficacy outcomes are the quality of communication about future medical treatment and EOL care, congruence in treatment preferences between pwPMS and their carers, mood symptoms, and caregiver burden. A qualitative study using Normalization Process Theory (personal semi-structured interviews with purposely selected pwPMS and SOs; focus group meetings with HPs) will help understand the quantitative findings, and the challenges in implementation of the intervention in clinical practice (process evaluation).
Outline of scope of charter	The purpose of this document is to describe the roles and responsibilities of the independent Data and Safety Monitoring Committee (DSMC) for the ConCure-SM Pilot Trial, including the frequency, format and times of meetings, methods of providing information to the DSMC, methods of disseminating information by the DSMC, relationships with other committees, and statistical issues.

2. **Roles and responsibilities**	
Aims of the committee	The DSMC has been established to monitor the ConCure-SM Pilot Trial and ensure it is conducted ethically and efficiently, to safeguard the rights and interests of trial participants, to assess the safety and efficacy of the intervention during the trial, to monitor the overall conduct of the trial, and to protect its validity. In detail: (1) To oversee the progress of the trial, and ensure it is conducted, recorded, and reported in accordance with the study protocol, good clinical research practice, and applicable regulatory requirements. (2) To monitor the accrual of safety data and data on efficacy endpoints. (3) To review relevant

	information from other sources (e.g. other related trials) to recommend whether to continue, modify, or prematurely terminate the trial**.**
Terms of reference	The DSMC will review trial progress and data accrual, and provide advice on the conduct of the study to the ConCure-SM Steering Committee (SC). The DSMC will inform the SC committee if, in their view, the intervention should be terminated for safety reasons (at any time during the study).
Specific roles of DSMC	To undertake interim review of the trial's progress by: ▪ Assessing data quality, including completeness; ▪ Monitoring recruitment figures and losses to follow-up; ▪ Monitoring compliance with the protocol by participants and investigators; ▪ Monitoring evidence for treatment harm; ▪ Suggesting additional data analyses; ▪ Advising on protocol modifications suggested by investigators or sponsors; ▪ Monitoring planned sample size assumptions; ▪ Monitoring compliance with previous DSMC recommendations; ▪ Considering the ethical implications of any recommendations made by the DSMC; ▪ Assessing the impact and relevance of external evidence.

3. Before or early in the trial	
Whether the DSMC will have input into the protocol	All DSMC members should receive the ConCure-SM Pilot Trial protocol in its most recent version before the first DSMC meeting. DSMC members will be named (unless they specifically ask not to be) in the published protocol. All DSMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
IDSMC meeting before the start of the trial	The DSMC is scheduled to have its first meeting not later than 2 months after accrual has commenced, to discuss the protocol, the analysis plan, and decision-making rules; schedule future meetings; complete in the Competing Interests Disclosure Form; and to have the opportunity to clarify any issues arising with the study principal investigators (PIs).
Whether members of the IDSMC will have a contract	All DSMC members should formally register their assent by confirming (1) that they agree to be on the DSMC and (2) that they agree with the contents of this Charter.

4. Composition	
Membership and size of the DSMC	The members of the DSMC (Advisory Board in ConCure-SM Phase 1) for this trial are: (1) Prof David Oliver (Chair) (2) Prof Kevin Brazil (3) Prof Bobbie Farsides (4) Dr. Luciano Orsi (5) Dr Carlo Peruselli Members should be independent of the trial (i.e. should not be involved in the trial in any other way or be involved in any other activity that could impact the trial). Members should not serve on DSMCs of similar, ongoing trials as this could compromise the independence of the trial and possibly the confidentiality of the results. Any actual or potential competing interests should be declared in the competing interest form to be completed by each DSMC member and returned to the trial coordinating unit.
The Chair, how they are chosen and the Chair's role.	The Chairman, Prof David Oliver, was chosen by the PI because of his considerable experience in palliative care research.
The responsibilities of the IDSMC methodologist	The DSMC membership includes a methodologist with expertise in process evaluation (Prof Kevin Brazil) to provide independent advice.
The responsibilities of the trial coordinator	See next paragraph.
The responsibilities of the PI and other members of the Trial Management Group (TMG)	Dr. Alessandra Solari and Dr. Ludovica De Panfilis (study PIs) will oversee the production of reports to the DSMC and will participate in DSMC meetings, explain to the DSMC salient aspects of the reports, and participate in DSMC discussions (open sessions).Other trial members will not usually be expected to attend, but can attend open sessions when necessary (see Organisation of DSMC Meetings).

5. Relationships	
Advisory role of the DSMC	The DSMC does not make decisions about the trial, but it does make recommendations to the SC (the executive body for the ConCure-SM Pilot Trial).
Payments to DSMC members	Members should be reimbursed for any reasonable travel, accommodation, or other costs incurred. No payment is expected for DSMC members or their collaborators.
Competing interests disclosure	Competing interests should be disclosed in the Competing Interests Disclosure Form. These are not restricted to financial

	matters; involvement in other trials or intellectual investment could also be relevant. Most competing interests are acceptable if disclosed. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility.

6. Organisation of IDSMC meetings	
Expected frequency of DSMC meetings	The first meeting will take place not later than 2 months after accrual has commenced; additional meetings will take place about every 4 months thereafter up to trial termination; the precise frequency will depend on requirements and trial events.
Whether meetings will be face-to-face or by teleconference	Meetings will be by teleconference.
How DSMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	Meetings should be attended by all DSMC members. Besides the study PIs, other trial members will not usually be expected to attend but can attend when necessary. **Closed sessions**. Since this is an open trial and no interim analysis is planned, it is not expected to have closed sessions to be attended by DSMC members only. **Reports to IDSMC.** The study PIs are responsible for drawing up reports to the DSMC, illustrating salient aspects of reports the DSMC, and participating in DSMC discussions. The DSMC will receive each report at least two weeks before meetings. Reports will generally include the following information: • Summary of accrual, overall and by centre; • Summary of status of enrolled participants, overall and by centre. For participants who are off study, the reason should be indicated (i.e., completed study, died, refused further participation, lost-to-follow-up, or other); • Summary of SAEs. **Reports from DSMC.** The DSMC will report in writing to the SC, usually within three weeks of a meeting. The DSMC Chair will provide the SC with a written summary containing (a) date of the review, (b) a statement that all relevant interim safety data have been reviewed, (c) recommendations concerning the study execution or modifications to the study protocol, and (d) the anticipated date of the next review. If the DSMC recommends (to the SC) that the study be terminated, suspended or amended, this recommendation will be discussed by the SC. The SC will report their decision regarding the DSMC's recommendation to each centre PI for submission to local Ethics Committees, to the DSMC, and to funding body.

7. Trial documentation and procedures to ensure confidentiality and proper communication	
Intended content of material to be available in open sessions	Accumulated information relating to recruitment and data quality will be presented. Safety data will be presented and total numbers of events for the primary outcome measure and other outcome measures may be presented, at the discretion of the DSMC.
Intended content of material to be available in closed sessions	N/A
Will the DSMC be blinded to the treatment allocation	N/A
Who will see the accumulating data and interim analysis	No interim analyses planned.
Who will be responsible for identifying and circulating external evidence (from other trials/ systematic reviews)	Identification and circulation of external evidence is not the responsibility of the DSMC members. The study PIs will be responsible for identifying and circulating external evidence.
To whom will the DSMC communicate decisions/ recommendations	The DSMC will communicate its recommendations in writing to the SC. Recommendations should be sent in time to be discussed at SC meetings. If the trial is to continue largely unchanged then it is often useful for the report from the DSMC to include a summary paragraph suitable for trial promotion purposes (see DEMOCLE's Report Template).
Whether reports to the DSMC be available before the meeting or only at/during the meeting	The DSMC will receive reports from the study PIs at least 2 weeks before meetings.

8. Decision making	
What decisions/recommendations will be open to the DSMC	DSMC decisions/recommendations include: ▪ No action needed, trial continues as planned; ▪ Early stopping due to harm of study intervention; or relevant external evidence; ▪ Protocol changes.
The role of formal statistical methods,	Safety analysis will be descriptive, considering the following SAEs: death (any cause); hospitalizations in Psychiatry

specifically which methods will be used and whether they will be used as guidelines or rules	Unit/Department; suicide attempt. AEs will be collected and reported to the study PI as well as the DMSC. AEs will include: a) any contact of the patient with the referring physician due to the occurrence of emotional problems during the study; b) an increase of ≥ 20% in the HADS Anxiety or/and Depression score (assessed after the ACP conversation and at six months).
How decisions or recommendations will be reached within the DSMC	Every effort will be made to reach unanimous decisions. The role of the Chair will be to summarise discussions and encourage consensus. If the DSMC cannot achieve consensus, votes may be taken. The DSMC should consider the implications (e.g. ethical, practical, financial) for the trial before making any recommendations.
When the DSMC is quorate for decision-making	All members should attend meeting. If, at short notice, a DSMC member cannot attend, the DSMC may still meet if at least three members, including the Chair, are present. If the DSMC is considering recommending major changes after such a meeting, the Chair should talk with the absent members as soon as possible after the meeting to check for agreement. If there are strong objections, a second meeting should be arranged and all DSMC members must attend.
Can DSMC members who cannot attend the meeting input	DSMC members unable to attend the meeting may pass comments to the DSMC Chair for consideration during the discussions.
What happens to members who do not attend meetings	If a member does not attend a meeting, the member should make every effort to attend the next meeting. If a member does not attend the next meeting, he/she should be asked if he/she wishes to remain part of the DSMC. If a member does not attend the third meeting, he/she will be discharged or replaced, at the discretion of the Chair.

9. Reporting	
To whom will the DSMC report their recommendations/decisions, and in what form	The DSMC will report in writing to the SC, usually within three weeks of a meeting being held.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	Meeting minutes need not be detailed. A summary of the main points discussed and actions that have been agreed is sufficient. At the start of each meeting it should be agreed who takes the minutes (considering that some are excluded from closed sessions). All members of the DSMC should see and comment on the minutes. The DSMC Chair will be responsible for signing (validating) the minutes.
What will be done if there is disagreement between the DSMC and the body to which it reports	The SC has ultimate responsibility for the trial. However, the SC should report to the DSMC how they act on DSMC recommendations. If the DSMC has serious problems or concerns with a SC decision, a joint DSMC/SC meeting will be held to clarify the situation and attempt to reach a consensus. Information disclosed at such a meeting would depend on the action proposed and DSMC concerns. The joint meeting will be chaired by an external expert acceptable to both Committees and not directly involved in the pilot trial.

10. After the trial	
Publication of results	The study PIs are responsible for publishing trial results in a timely fashion on behalf of all investigators. The SC should oversee this process.
The information about the DSMC that will be included in published trial reports	DSMC members will be named (unless they specifically ask not to be) in the main published reports.
Whether the DSMC will have the opportunity to approve publications, especially with respect to reporting of any DSMC recommendation regarding termination of a trial	DSMC members must be given at least 2 weeks to read and comment on draft publications that report outcome measures and/or details of DSMC recommendations. Draft publications can be circulated to other groups reviewing the draft manuscript (e.g. SC, investigators) at the same time.
Any constraints on DSMC members divulging information about their deliberations after the trial has been published	The DSMC will not discuss confidential issues relating to the trial until the main trial results have been published, unless prior permission obtained from the SC.

(1) References

1. The DAMOCLES Study Group. **A proposed charter for clinical trial 2005 data monitoring committees: helping them do their job well.** Lancet 2005; 365: 711-22
2. Clemens F, Elbourne D, Darbyshire J, Pocock S and the DAMOCLES group. **Data monitoring in randomised controlled trials: surveys of recent practice and policies.** Clinical Trials 2005; 2: 22-23.

(2) Subordinate to acceptance by ConCure-SM Phase 2 SC