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

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ABSTRACT

Introduction. Multiple sclerosis (MS) is the most common cause of progressive neurological disability in young adults. The use of Advance care planning (ACP) for people with progressive MS (pwPMS) remains limited. The ConCure-SM project aims to assess the effectiveness of a structured ACP intervention for pwPMS. The intervention consists of a training program on ACP for healthcare professionals (HPs) caring for pwPMS, and a booklet to be used during the ACP conversation. Herein we describe the first two project phases.

Methods. In phase 1 we translated and adapted, to the Italian legislation and MS context, the ACP booklet of the National ACP programme for New Zealand. Acceptability, comprehensibility and usefulness of the booklet were assessed via 13 personal cognitive interviews with pwPMS and significant others (SOs), and one HP focus group. Based on these findings, we will revise the booklet. In phase 2 we will conduct a single-arm pilot/feasibility trial with nested qualitative study. Participants will be 40 pwPMS, their SOs, HPs from six MS and rehabilitation centers in Italy. In the six months following the ACP conversation, we will assess completion of an advance care plan document (primary outcome), as well as safety of the intervention. Secondary outcomes will be a range of measures to capture the full process of ACP; pwPMS-carer congruence in treatment preferences; quality of pwPMS-HP communication; and caregiver burden. A qualitative process evaluation will help understand the factors likely to influence future implementation and scalability of the intervention.

Ethics and dissemination. The project is co-leaded by a neurologist and a bioethicist. Phase 1 has received ethical approvals from each participating center, while phase 2 will be submitted to the centers by April 2021. Findings from both phases will be disseminated widely through peer-reviewed publications, conferences and workshops.

Trial registration number ISRCTN48527663.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength of the study is the use of a mixed-methods approach to construct and pilot test the efficacy of an intervention (booklet and healthcare professional training program) for advance care planning (ACP) in multiple sclerosis (MS)
- The intervention is co-produced with users (chiefly people with progressive MS) and with the authors of the original booklet
- Study results will be key to inform the feasibility of a full-scale trial, and its design
- A limitation is that the pilot trial is a non-randomized study (all participants will receive the ACP intervention)
- Long-term outcomes (chiefly the concordance between preferred and received end of life care and treatments) are not included

KEYWORDS: Shared Decision Making; Advance Care Planning; End-of-Life Care; Multiple Sclerosis; Complex Intervention; Normalization Process Theory.

INTRODUCTION

With a lifetime risk of 1 in 400, multiple sclerosis (MS) is the most common cause of progressive neurological disability in young adults. Approximately 2.3 million people worldwide have MS, with Canada, USA and some European countries, including Italy, having the highest prevalence rates [1]. Around 15% of people with MS have a primary progressive course at diagnosis, and a further 35% develop secondary progressive disease after 15 years [2]. A mean reduction in life expectancy by 7–14 years has been reported in people with MS, with improved figures over the last two decades [3-5].

Few treatment options are currently available to delay or prevent further clinical worsening of people with primary or secondary progressive MS (pwPMS). They may live for many years experiencing a wide range of symptoms, impairments (including cognitive impairment which affects 40-70% of sufferers [6]) and comorbidities [5,7-10].

Advance care planning (ACP) is a process that "enables individuals who have decisional capacity to identify their values, to reflect upon the meanings and consequences of serious illness scenarios, to define goals and preferences for future medical treatment and care, and to discuss these with family and healthcare professionals (HPs)" [11].

Consistently with the shared decision-making (SDM) model [12-14], ACP involves both the patient and his/her HPs. Together, they make informed decisions about the patient's (future) care. Also, the family can be involved in the process, if the patient wishes. ACP differs from general medical decision-making in that it is based on an anticipated deterioration in the health of a patient. It includes a focus on the person's wishes and preferences for the time when they lose decisional capacity. In fact, it aims to align evidence-based practice and person-centered care [15] using a bioethical focus to identify the patient's values, preferences and desires. The planning process helps the patient to identify his/her personal values and goals, understand his/her health status, and the treatment and health care options available. Finally, ACP encourages discussion around end-of-life (EOL) care (a subject that is generally not considered part of health care planning, and one that can be avoided by both patients and HPs). It is up to the patient to determine the occurrence and content of any ACP discussion: if the patient does not wish to engage in conversations about his/her future care, this preference should be respected. The ACP process may result in the patient choosing to write an advance care plan document and to appoint a trustee (or else).

On December 22, 2017, the Italian Parliament approved the first law on EOL: "Provisions for informed consent and advance directives" (L. 219/2017;

http://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=62663). This law regulates advance directives (AD; Article 4) and ACP (Article 5), and a number of rights citizens have regarding healthcare issues, including the right to: be fully informed about one's health status and to give consent (or dissent) to treatment; withhold consent to lifesaving treatments; be assisted until death. Moreover, the law states that the physician has a duty to respect the patient's wishes. In a recent Italian survey, 88% (1752/2000) of citizens considered the Law 219/2017 as quite or very important, and 76% had a positive attitude towards making/registering AD or ACP [16]. Importantly, this Law triggers HPs and health care authorities in promoting educational programs on the topic, as well as programs to implement ACP in daily clinical practice.

To optimize the alignment between patient preferences and values and the care they receive, HPs should integrate best ACP practices in the care of pwPMS. A recent guideline on palliative care in MS found no evidence of the effects of ACP in pwPMS [17]. However, there is some evidence from non-neurological progressive and life-threatening illnesses that ACP decreases the use of life-sustaining treatment, increases hospice/palliative care, reduces hospitalizations and increases alignment with patients' end of life (EOL) wishes [18]. Furthermore, there is evidence that MS patients and caregivers often would like to discuss the issues of death and dying and HPs should acknowledge and encourage these discussions [19, 20]. However, often HPs leave EOL discussions until the later stages of progression in MS [21], and caregivers may be left having to take difficult decisions [22]. A scoping review identified two main barriers for ACP discussions taking place: the long and uncertain MS trajectory, with periods of stability punctuated by crisis; and lack of ACP communication skills and confidence of HPs [23].

ConCure-SM is a project aimed to set up and evaluate the efficacy of an ACP intervention for pwPMS in Italy. The SDM model described above is the theoretical framework of the project [12-14]. The Medical Research Council (MRC) framework for developing and evaluating complex interventions is the methodological framework of the project. The MRC framework has a phased approach, from a pre-clinical research phase to a final phase in which the intervention is introduced into the health service, leading to a theory-driven intervention: a "bottom up" development which guarantees to enter a phase III trial with an appropriate theory and pilot work [24]. Furthermore, both quantitative and qualitative methods are integrated within the framework, in order to better appraise the effects of the (complex) intervention both as a whole and on its components.

Our study hypotheses are that the intervention will produce: higher completion of an advance care plan document; increased congruence in treatment preferences between pwPMS and their carers; increased quality communication about EOL care.

METHODS AND ANALYSIS

The study protocol (FISM 2020/R-Multi/024; Version 1.0; March 15th, 2021) was designed following the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines (online supplemental appendix 1) [25] and The SPIRIT-PRO Extension [26]. The pilot/feasibility study follows the CONSORT guidance for trials on social and psychological interventions (CONSORT-SPI 2018) [27]. It was registered on the ISRCTN registry (isrctn.org Identifier: ISRCTN48527663) the 30th March, 2021. Qualitative data will be reported following the Consolidated criteria for Reporting Qualitative Research (COREQ) checklist [28].
Figure 1 outlines the two project phases and inscribed actions. The red dot identifies the current advancement status.

[Insert Figure 1 about here]

Phase 1

The first project phase involves production of the ACP booklet (Figure 1).

Provisional booklet

Early in 2020, an inter-disciplinary panel translated into Italian and adapted to the MS context and to the Italian legislation, the ACP booklet of the Health Quality & Safety Commission's New Zealand National ACP Programme (https://www.myacp.org.nz). The panel was made of five neurologists, one palliative care physician, one palliative care nurse, one psychologist, one bioethicist, one expert patient, one representative of the Italian MS Society, and the author of the original booklet. The resulting booklet in its provisional version (online supplemental appendix 2) consists of an introduction, a 'guidance' (the odd pages in most instances) and the advance care plan document (the even pages) to be completed electronically or manually by the pwPMS together with his/her referring physician. A significant other (SO), such as a family member, can participate in the process if requested by the pwPMS. The introduction explains the concepts of ACP and AD according to the Italian Law 219/2017, and describes why ACP is important in MS. Ten sections follow: 'My Advance Care Plan'; 'What matters to me'; 'What worries me'; 'Why I'm

making an Advance Care Plan'; 'How I make decisions'; 'If I were no longer able to make decisions: my trustee'; 'Thinking about my EOL'; 'My treatment and care choices'; 'Signatures'; 'Acronyms'. If the advance care plan document is completed, the pwPMS (and, when applicable, the pwPMS trustee) sign on page 29; the document is then scanned and stored, together with the completed booklet, in the (electronic) medical record.

Users' assessment and revision

Between September and November 2020, the acceptability (contents, format, envisaged administration procedure), comprehensibility and usefulness of the provisional booklet were assessed by conducting 13 personal cognitive interviews with pwPMS, pwPMS' SOs, and a focus group meeting (FGM) with HPs. Due to the COVID-19 pandemic, all the interviews and the FGM were held using digital platforms. Results of the qualitative (thematic) analysis and the revision of the booklet are underway.

Phase 2

The second project phase will be dedicated to the conduction of the multi-center, pilot and feasibility single-arm trial with a nested qualitative study. This phase has three inscribed actions: intervention set up; pilot trial; and qualitative study (Figure 1).

Intervention set up

Training program - The goal of this intervention is to prime HPs to discuss goals of care and ACP. To achieve this, HPs will attend a training program (called Train-ConCure-SM) that will be Continuing Medical Education accredited, residential, and last one-and-half days (12 hours). The program aims to: improve the HP knowledge, competencies and skills in ACP based on up-to-date scientific evidence; support and guide HPs in the ACP embedment in clinical practice; improve the communication between HPs and patient promoting an effective patient-practitioner partnership in decision-making.

The training will be interactive in style. Its residential nature and the use of role-playing exercises aim at supporting group discussion and the exchange of experiences between participants.

It will consist of the following: one 2.5-hour theoretical session on the clinical, ethical and statutory principles of SDM and ACP; two 4-hour empirical sessions (one on each day) on conducting ACP conversations in various clinical scenarios using the ConCure-SM booklet through

guided role play exercises; two 45-minute self-evaluation sessions (at the beginning and at the end of the training program).

Trainees will be physicians and other HPs from the six enrolling centers. The Italian Law 219/2017 prescribes that ACP involves the patient, his/her referring physician, and (when applicable) the trustee. We decided to train HPs other than physicians in order to promote ACP knowledge within the caring team. Each center will provide 1-3 physicians, plus one HP from the following: MS nurse, therapist, psychologist, or social worker. Thus, there will be 12-24 participants overall (2-4 from each center). Trainers will be a panel (TP) of neurologists, psychologists, a palliative care physician, a palliative care nurse, and a bioethicist. All have consolidated experience in leading training courses and workshops on patient-clinician communication and SDM, and four on ACP and EOL conversations. These four researchers will support physicians at the centers for issues concerning the conduction of the ACP conversation during the pilot trial.

Web platform - As part of the intervention set up action, a web-based trial platform will be created containing the pseudo-anonymized trial case record form (eCRF) and the outcome measures. The platform will be ID/password protected, with dedicated accesses based on the stakeholder (pwPMS, SO, HPs, center principal investigator [PI], interviewer, data manager) and operation (completion, consultation).

Linguistic validation of measures - Two outcome measures not available in Italian will be translated and cross-culturally adapted, following accepted guidelines [29, 30]: the 4-item ACP Engagement questionnaire (4-item ACP-E) [31], and the Quality of Communication Questionnaire (QOC) [32]. The main steps in this process are the following:

1) Forward translation. Two qualified translators, both living in Italy, will produce two independent translations. A panel consisting of the translators, two MS HPs and two lay persons will review the forward translations and a consensus version will be produced.

2) Backward translation. The consensus translation generated in step 1 will be independently translated back into the source language by a third qualified translator, living in the target country. The backward translation will be produced without access to the original version and without consulting the other translators.

3) Translation refinement. In a meeting between those participating in step 1 and the backward translator, the backward translation will be compared with the original, and further refinements to the Italian version will be made. Differences will be resolved by discussion.

4) Each translated questionnaire will be proof read, and then administered to/debriefed with 5 to 10 patients.

Pilot and feasibility trial

The six centers involved in the pilot trial are located in northern (four centers), central and southern Italy (one center each). Two of the centers are rehabilitation hospitals (one of which a research hospital), three are MS centers (two university hospitals, one research hospital) and one is a rehabilitation and MS center from a research hospital. Recruitment will be competitive, with no pre-specified minimum number of enrolled subjects per center. The maximum number of enrolled subjects per center is 12.

There will be a baseline assessment (T0), an ACP conversation taking place within one month from the baseline assessment, and a follow-up assessment within one week of the ACP conversation (T1) and six months (T2) thereafter. The baseline and follow-up assessments will be performed via the web-based ConCure-SM platform. The physician will record on the platform subsequent ACP conversations that should occur during follow-up. Participants (pwPMS, SOs) will be free to withdraw from the study at any time, without giving reasons and with no risk of prejudicing future care. Study personnel will make every effort to obtain, and record, information about the drop out reasons.

The objectives of the pilot and feasibility trial are reported in the Box. Trial procedures are summarized in Figure 2.

[Insert Box about here]

Eligibility and screening - PwPMS (in- or outpatients) will be included if they are: ≥18 years of age; diagnosed with primary or secondary PMS [33] one or more years before inclusion; able to communicate in Italian; and gave written consent. In addition, one or more of the following conditions that would make ACP relevant must be present: expressed desire for ACP; questions about own future; thoughts about hastening death or medically assisted suicide; high risk for death within two years using the 'Surprise Question' [34]; high risk for development of severe cognitive compromise/dementia within two years; high risk for development of impairments preventing communication within two years; significant suffering (e.g. uncontrolled physical symptoms, psychosocial or existential issues). PwPMS will be excluded if they have one or more of the following: severe cognitive compromise (MMSE < 19) or impairments preventing communication; psychosis or other serious psychiatric conditions; advance care plan document completed.

PwPMS are recruited prospectively by the ACP-trained physicians involved in their care, when the potentially eligible pwPMS attends the center for an outpatient visit or hospitalization. PwPMS who show interest in participating receive full verbal and written information about the study purpose and procedures.

[Insert Figure 2 about here]

Baseline assessment (T0) - The ACP-trained physician makes an appointment with pwPMS who provided initial verbal consent to participate in the study, and checks all eligibility criteria. A written, signed informed consent is obtained, according to the Declaration of Helsinki and to the Good Clinical Practice (GCP) Guidelines of the EU. The informed consent is kept on file by the study personnel, and is available for inspection by regulatory authorities or authorized persons.
Then, the physician gives the pwPMS the credentials to the trial platform, so that the pwPMS completes the baseline set of questionnaires/instruments (completion time around 40 minutes). If the pwPMS has difficulties in using the trial platform, a telephone interview is scheduled within a week with an independent, trained interviewer who will administer the questionnaires/instruments.
The ACP conversation is scheduled at the center, within a month. It is the starting point of a process that is followed-up during the study. However, for feasibility reasons and to adapt to participant needs, subsequent conversations are recorded, but not scheduled a priori. The pwPMS is invited to involve his/her SO (family member, relative, or friend, who is next of kin or is key decision maker as designated by the pwPMS and with whom the pwPMS shares his/her life). If the pwPMS agrees on involving his/her SO, the SO is contacted by a study researcher to confirm eligibility, explain the study and obtain verbal consent. Consenting SOs receive credentials to access the trial platform and complete the baseline set of questionnaires (completion time about 15 minutes). If the SO has difficulty in using the trial platform, a telephone interview is scheduled within a week with an independent, trained interviewer who will administer the questionnaires.
Finally, the physician completes the eCRF via the trial platform.
Each center will collect information on the number of pwPMS and SOs approached, screened, and eligible prior to enrollment, with reasons for non-enrolment.

The ACP conversation - The conversation involves the pwPMS, the ACP-trained physician involved in his/her care and, when applicable, the SO. In addition, if the pwPMS agrees, the non-physician ACP-trained HP at the center will participate. The first conversation takes place in a dedicated room at the center, and is audio-recorded. At MS centers and rehabilitation centers, physician

time and space are at premium, particularly for outpatient care. For this reason, one-hour slot is reserved for the conversation. In the case a SO participates it is envisaged that there will be a session closed to the SO, followed by an open session.

About one week before the scheduled ACP conversation, reminder emails (or telephone calls) are sent to pwPMS/SOs. At the end of the ACP conversation, the physician invites the pwPMS (when applicable the SO) to complete the T1 follow-up assessment within one week. The physician completes the QOC-Doc immediately after the ACP conversation ends.

Follow-up assessments (T1, T2) - The pwPMS completes the questionnaires by one week (T1, assessment time of about 20 minutes) and six months (T2, assessment time of about 30 minutes) after the first ACP conversation using the trial platform. The SO completes the questionnaires/instruments (T1, assessment time of about 20 minutes) using the trial platform. In the event the pwPMS/SO have difficulties in using the trial platform, a telephone interview is scheduled with an independent, trained interviewer who will administer the questionnaires/instruments.

About one week before the T2 assessment, reminder emails (or telephone calls) are sent to pwPMS. The physician completes the questionnaire (T1, QOC-Doc) and the eCRF using the trial platform. He/she records on the platform the date, duration, participants, and mode (face to face, teleconference or on the telephone) of subsequent ACP conversations that occur during follow-up.

Outcome Measures - A range of measures will be collected to capture the full process of ACP and whether the ConCure-SM intervention has any effect on completion of an advance care plan document (primary outcome measure), congruence in treatment preferences between pwPMS and their carers, quality of patient-clinician communication, and caregiver burden (Table 1). In addition, since a study-related increase in emotional burden can't be excluded, serious adverse events (SAE: admission to psychiatric ward, suicide attempt, death) will be monitored by the independent Data and Safety Monitoring Committee (DSMC).

We will use the published Italian version of the following inventories: Control Preference Scale (CPS) [37]; Hospital Anxiety and Depression Scale (HADS) [38]; Observing Patient Involvement in Decision Making (OPTION) [39]; 29-item Multiple Sclerosis Quality of Life (MSQOL)-29 [40]; Zarit Burden Interview (ZBI) [41]. The 4-item ACP-E and the QOC inventories will be translated/culturally adapted from source language (see above).

[Insert Table 1 about here]

ACP engagement - The ACP process will be assessed using the 4-item ACP-E questionnaire [31]. Originally developed and validated to measure the complex behavior of ACP, the questionnaire is available in four versions (55-item, 34-item, 9-item, 4-item). In this study, we will use the 4-item version which focuses on the readiness behavior change construct within the quality of life ACP domain. Responses are on a 5-point Likert scale (1 "I have never thought about it"; 2 "I have thought about it, but I am not ready to do it"; 3 "I am thinking about doing it in the next 6 months"; 4 "I am definitely planning to do it in the next 30 days"; 5 "I have already done it") [31].

Role preferences - The CPS is the most used instrument to assess patient preferences for involvement in decisions about their health [42, 43]. It consists of five ''cards'' on a board, each illustrating a different role in decision-making by means of a cartoon and short descriptive statement. In its original version, administration requires a trained examiner, who asks the patient to choose the preferred card, which is then covered up. The procedure continues (four choices) until one card is left. If the second preference is incongruent with the first (non- adjacent pairing, such as card A with card C), the test is explained again, and immediately re-administered. In the event of a further incongruence, the test is not re-administered, and a preference is not assigned. Six scores are possible based on the subject's two most preferred roles: active–active, active–collaborative, collaborative–active, collaborative–passive, passive–collaborative, and passive–passive. These scores are grouped as: active (active–active or active–collaborative), collaborative (collaborative–active or collaborative–passive), or passive (passive–collaborative or passive–passive) [42]. We will use the electronic, Italian self-administered CPS (eCPS) [44].

Quality of the conversation – We will assess the quality of the first ACP conversation considering three perspectives: an independent observer, the pwPMS, and the physician. Each conversation will be unobtrusively audio-taped and transcribed verbatim; subsequently a specially trained third observer will evaluate the behavior of the physician in terms of patient involvement in decision-making using the OPTION (http://www.glynelwyn.com/observer-option-instrument.html) [45]. The OPTION consists of 12 items, each rated on a five-point Likert scale ranging from 0 (behavior not observed) to 4 (behavior observed to high standard). A total score (range 0–48) is obtained by adding the scores of each item. After the ACP conversation, pwPMS will complete the QOC [32]; SOs will complete the SO version (QOC-SO), and physicians the physician version (last two items) of the QOC. Developed from qualitative studies with patients, families, and clinicians, the QOC consists of 19 items measuring general communication (nine items) and communication about

EOL care (eight items), each rated on a scale from 0 ('very worst I can imagine'/'not at all') to 10 ('very best I can imagine'/'extremely'), or identified as something the clinician did not do. The 0/10 ratings are recoded to 1/11, with 0 imputed for 'did not do' (http://depts.washington.edu/eolcare/products/instruments/).

Other outcome measures – PwPMS quality of life will be assessed using the electronic version of the MSQOL-29, which is the shortened form of the MSQOL-54 [40]. MSQOL-29 includes 25 items forming 7 subscales and 4 single items, and one filter question for 3 'sexual function' items. Mood symptoms will be assessed with the HADS, a self-assessed questionnaire consisting of 14 multiple-choice (0–3 Likert scale) items probing symptoms of anxiety (7 items) and depression (7 items). HADS anxiety (HADS-A) and depression (HADS-D) scores range from 0 (no symptoms) to 21 (most severe symptoms) [46]. A cutoff score of 8 or above was recommended for MS patients, since it was found to be an accurate indicator of major depression (90% sensitivity, 87% specificity) and generalized anxiety disorder (88.5% sensitivity; 81% specificity) in this population [47]. Finally, SO burden will be assessed using the ZBI [48], a 22-item self-report measure of subjective burden among caregivers addressing functional and behavioral impairments as well as the home care circumstances. A total 0 (low burden) to 88 (high burden) score is obtained by summing item responses, each scored on a 5-point Likert scale ranging from 0 (never) to 4 (nearly always present).

Meetings - There will be two study meetings (teleconferences): the investigators' meeting will be held before enrolment starts. Participants will be the Steering Committe, the center principal investigators (PIs), and the HPs who participated in the training program. The aim of this meeting is to provide clear information on the study procedures, and to train HPs on the use of the trial platform. A second meeting will be run about two months after enrollment starts, in order to monitor possible difficulties, top up centers' motivation and provide a safe place for peer discussion on the implementation of the intervention. Both meetings will last about two hours. Additional meetings will be organized whenever needed. In addition, the study PIs and the TP will be available for inquiries about the implementation of the intervention at the participating centers.

Nested qualitative study

We will perform one-on-one semi-structured interviews with pwPMS and SOs, chosen using a maximum variation strategy, and FGMs of HPs involved in intervention delivery. For pwPMS and SOs interviews were considered most appropriate to limit interview burden and hopefully make it easier for participants to express their feelings, and recount their experiences of the intervention. For the patient referring physicians and the other HPs we chose FGMs as they promote interaction and exchange of ideas. A minimum of 10 interviews (five with pwPMS and five with SOs) and two FGMs will be held, the final number depending on the achievement of 'data saturation' [49]. Interviews and FGMs will be run via video teleconference, which will ease participation of pwPMS with severe disability and SOs with caregiving commitments, as well as HPs. If the pwPMS and/or SOs have no access to internet using personal computer or other devices, such participants will be interviewed on the telephone.

The interviews aim to provide important feedback on participant perception of the quality of the intervention provided, and will serve as a process measure. Insights from this qualitative analysis will serve to inform fine-grain intervention refinement. They will take place within two months of trial completion, and last no more than an hour. To reduce social desirability response bias, the interviewers will be researchers not involved in the ConCure-SM intervention delivery. Before starting, interviewees will be informed of study aims and requirements, and provide written consent. The interviewer will then explain that the aim of the interview is to obtain participant feedback on experience of the pilot study and stress that positive and negative experiences of, and feelings about, the intervention are welcome. Participants will be assured that the interviews are confidential, and that the audio recordings and subsequent transcripts will be fully anonymized. The interviewer will then pose each question in turn, neutrally (so as to not suggest any particular reply) and in an open-ended fashion (to allow many possible replies). As each question is discussed, follow-up questions will clarify and explore participant responses. Participants will be also encouraged to elaborate on any pertinent themes or views that emerge. The interviewer will note any potentially informative non-verbal gestures. At the end of the interview, the interviewer will verbally summarize the key points and ask the participant if the summary is full and correct.

The *FGMs* aim to collect insights and living experiences about the intervention and to identify possible barriers to its implementation; they will provide important feedback on the intervention and on factors that can enable its implementation and adoption. For this reason, HPs other than the physicians involved in the ACP conversation will be involved. Each FGM (teleconference) will last about 2 hours; participants will be 6-10 physicians who delivered the intervention and HPs

from the participating centers. All participants will provide written informed consent prior to the FGM, that will be conducted by two psychologists specifically trained in qualitative research. One will be the facilitator, whose job is to engage all participants, promote exchange, moderate conflicts, ensure that all pre-specified topics will be adequately covered, and allow exploration of any pertinent issues that arise. He/she will first explain the purpose of the meeting and ask participants to introduce themselves. He/she will then introduce each topic in turn, in an open-ended fashion. At any point the facilitator can probe for further information and ask follow-up questions to stimulate further discussion. After all pre-specified topics are fully discussed, the facilitator will summarize the main points, and ask for further feedback and whether all concerns have been fully aired. The co-moderator will take notes and oversee the audio recording. Subsequently, they will produce a report from the audio recordings/transcript and field notes, which will be submitted to participants for review (respondent validation).

Data analysis

Study power

As this is a pilot and feasibility study, a formal sample size calculation is not required. We aim to recruit at least 40 pwPMS from six centers to assess feasibility across a diverse range of participants including those with different care needs and living conditions. There are no data available on the occurrence of ACP in pwPMS: by hypothesizing a proportion in the pwPMS population of 10%, a sample size of 35 subjects achieves a power of 90%, assuming a type I error of 5%, to detect a proportion of ACP documentation of 30%. By hypothesizing a proportion in the pwPMS population of 8%, a sample size of 35 subjects achieves a power of 95%, assuming a type I error of 5%, to detect a proportion of ACP documentation of 30%. By adding 15% of drop outs or incomplete data, 40 pwPMS should be recruited.

Statistics

Descriptive statistics will be calculated for general and clinical variables. Specifically, continuous variables will be summarized by their mean and SD, or median and interquartile range; categorical variables will be summarized as numbers and percentages. Categorical variables will be compared using the chi-squared test. The normality assumption of continuous variables will be tested with the Shapiro-Wilk test. Depending on data distribution, between-group comparisons will be carried out using either the two-sided unpaired t-test or the Wilcoxon two sided two sample test; within-

group comparisons will be carried out using either the paired t-test or the Wilcoxon signed-rank test; correlations will be computed using Pearson's or Spearman's coefficients.

Our primary end-point is the proportion of pwPMS completing an ACP during the six-month period. Change in the secondary outcome measures will be also calculated. In addition, we will calculate the following feasibility outcomes: recruitment rate (enrollment per month; reasons for non-eligibility, non-enrollment); retention rate (proportion completing the intervention and study follow-up); missing data (proportion fully completed, for each scale, at each time point). Data will be analyzed according to the intention-to-treat principle. Multiple imputation of missing values will employ Rubin's approach. A p-value less than 0.05 will be considered statistically significant. No correction for multiple comparisons will be applied. All analyses will be performed using STATA 16 (College Station, Texas 77845 USA). Assumptions in determining the sample size of the main trial will be checked.

Qualitative data

Interviews and FGMs will be audio-recorded and transcribed verbatim. Data analysis will be conducted by three researchers with experience in qualitative research. Researchers will analyze interviews and FGM data using thematic analysis, with interpretation guided by the four Normalization Process Theory (NPT) components (see process evaluation below). Data will be triangulated across sources. The analytical stages can be summarized as follows [50]: 1) Each researcher will read the transcriptions and write comments and initial thoughts in a memo. 2) Each researcher will extract portions of the text individually and then share their work to reach an initial agreement. During this stage, they will conduct the thematic analysis inductively providing their insights. 3) Researchers will independently review themes and allocate portions of the text to the newly reconfigured themes. 4) Together, they will re-define themes and re-name them to achieve internal consistency. 5) One researcher will extract from the interviews and draft the final report, which will be checked and amended by the other two.

Process evaluation

We will follow the MRC guidance on process evaluation [51], which describes three components using a mixed-methods approach: implementation or delivery; mechanisms of impact; contextual factors. We will use NPT to determine if, and in what ways, the ConCure-SM intervention can be successfully 'normalized' (embedded) into clinical practice [52, 53]. At the feasibility and piloting stage, basic quantitative measures of implementation may be combined with in-depth qualitative

data to provide detailed understandings of intervention functioning on a small scale [51]. Quantitative measures will include structured observations of audio recorded ACP conversations. These will be used to examine aspects of fidelity (such as consistency with SDM principles), and dose (the duration of conversations). Qualitative methods will be used to investigate mechanisms of impact and contextual factors, using NPT. NPT identifies four essential determinants of 'normalizing' complex interventions into common practice: *coherence* (the extent to which an intervention is understood as being meaningful, achievable and valuable); *cognitive participation* (the engagement of HPs necessary to deliver the intervention); *collective action* (the work that brings the intervention into use); and *reflexive monitoring* (the on-going process of adjusting the intervention to keep it in place) [53]. These components are considered to be dynamic and interact within the wider context of the intervention, such as existing organizational structures and procedures [53]. Further, we will use qualitative data to identify required modifications and to develop practical strategies for enabling and sustaining intervention delivery in clinical settings.

Patient and public involvement statement

An expert MS patient and a representative of the Italian MS Society are part of SC of the project and co-authors of the present paper. These same persons were part of the inter-disciplinary panel that produced the ACP booklet, which was revised based on the results of a qualitative study with users (pwPMS, SOs and HPs).

Prior to designing and conducting a full trial, the intervention will be pilot tested in a multicenter study involving MS and rehabilitation centers across Italy, and using a mixed-method approach. We will disseminate key study findings to pwPMS via the Italian MS Society.

Ethics and dissemination

The project is co-leaded by a neurologist and a bioethicist. Phase 1 has received ethical approvals from each participating center, while phase 2 will be submitted to the centers by April 2021. Findings from both phases will be disseminated widely through peer-reviewed publications, conferences and workshops. Authorship eligibility will be based on The International Committee of Medical Journal Editors. The final trial (pseudo-anonymized) dataset will be accessed by the study principal investigators and the data management/analysis team. Details about panels and centers, ethics and administrative considerations, and study management and monitoring are available in the online supplemental appendix 3.

DISCUSSION

One of the 10 clinical questions of the EAN guideline on palliative care of pwPMS specifically addressed ACP [17]. For this clinical question, formulated with direct patient and caregiver involvement [54], no evidence was found and two good practice statements were produced: “It is suggested that early discussion of the future with ACP is offered to patients with severe MS”; “It is suggested that regular communication about the future progression of MS is undertaken with patients and families/caregivers” [17]. To fill this knowledge gap, we conceived the present study, which adheres to the SDM model [12-14], and to the MRC framework for developing and evaluating complex interventions [24]. Within this methodological context, the study follows the CONSORT guidance for trials on social and psychological interventions (CONSORT-SPI 2018) [27], as many of the guidance items (excluding items that are specific to the randomization nature of the study) are relevant for reporting other types of pilot and feasibility studies [55]. This includes the development of the study protocol following the SPIRIT guidance [26], protocol’s publication, and the trial public registration (ISRCTN registry). The consolidated criteria for reporting qualitative research will guide the presentation of findings in the study reports and publications [28, 57].

To increase generalizability of the study, participants (pwPMS, SOs, and HPs) will be enrolled from university hospitals, research hospitals and clinical centers from the different areas of Italy. Personal, semi-structured interviews and FGMs will be run via video teleconference, which will ease participation of pwPMS with severe disability and SOs with caregiving commitments, as well as HPs. If pwPMS and/or SOs have no internet access, using personal computer or other devices, these participants will be interviewed on the telephone. Other measures adopted to minimize bias include: all study personnel will be trained to conform to GCP regulation; electronic version of the study questionnaires/inventories will be used to ensure the data entered is of high quality; an IDSMC will monitor and supervise the progress of the trial, and the safety data.

The ConCure-SM intervention (booklet and HP training program) can be adapted for use in other neurological and non-neurological conditions for which consolidated ACP interventions are not available. The electronic format will ease the incorporation of the advance care plan document (and its updates) in the electronic medical record, that is currently available in some Italian regions and hopefully will be soon available all over Italy.

Study limitations

Three study limitations are noted. We used a single arm design for the pilot trial. This decision was taken as ACP is currently at premium in MS [17, 23], and designing a randomized (cluster) trial with standard care or any 'low intensity' intervention as a comparator was considered ethically and practically unviable. Another limitation is that our training program was for HPs only. A multiple-component intervention that targets clinicians and patients simultaneously has been suggested in other disciplines [57]. In the current situation regarding ACP, we preferred to have a clear focus on enhancing HP competencies [17, 23]. Finally, our pilot trial lacks long-term outcomes, chiefly the concordance between preferred and received EOL care and treatments. However, the MS trajectory further challenges the collection of this outcome in the typical timeframe of a clinical trial. In line with the principles of ACP, we agreed not to narrow the inclusion criteria only to pwPMS in the late stage of the disease, deserving this relevant outcome to future studies.

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ConCure-SM Steering Committee: LDP, SV, MB, MC, MGG, PK, AL, SM, FP, EP, CS, AGi, AS. *Data Safety and Monitoring Committee*: Kevin Brazil, School of Nursing and Midwifery, Queen's University of Belfast, Belfast, Northern Ireland, UK; Bobbie Farsides, Brighton & Sussex Medical School, Falmer, Brighton, United Kingdom; Luciano Orsi, The Italian Society of Palliative Care (SICP), Milan, Italy; Carlo Peruselli, SICP, Milan, Italy; and David Oliver, The Tizard Centre, University of Kent, Canterbury, UK (Chair). *Data Management and Analysis Committee*: AGi, Mariangela Farinotti, Unit of Neuroepidemiology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy. *Qualitative Analysis Panel*: LDP, SV, MC, Luca Ghirotto, Qualitative Research Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; Katia Mattarozzi, Department of Experimental, Diagnostic and Specialistic Medicine, School of Medicine, Alma Mater Studiorum University of Bologna, Italy; Marta Perin, Unit of Bioethics, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy. *HP Training Panel*: LDP, SV, MC, KM, EP, Michela Rimondini, Section of Clinical Psychology, Department of Neuroscience, Biomedicine and Movement Sciences, University of

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AUTHOR CONTRIBUTIONS

LDP, SV, and AS conceived and developed the study protocol. All authors contributed to the refinement of the study protocol. LDP, SV, and AS drafted the manuscript. All authors approved the final manuscript.

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COMPETING INTERESTS STATEMENT

AL reports grants from Novartis, during the conduct of the study; personal fees from Biogen, Merck Serono, Mylan, Novartis, Roche, Sanofi/Genzyme, Teva and FISM. FP received personal compensation for serving on advisory board and/or speaking activities by Almirall, Bayer, Biogen, Bristol Meyers & Squibb, Merck, Novartis Roche, Sanofi and TEVA; he further received research grants by Biogen Italy, Biogen Global, Merck, University of Catania, FISM and Reload Onlus Patients Association. AS reports grants from FISM and European Academy of Neurology, during the conduct of the study; personal fees from Almirall and Merck Serono. This does not alter our adherence to BMJ Open policies on sharing data. All the other authors report no competing interests.

DATA STATEMENT SECTION

Data will be available at: https://zenodo.org/communities/besta/.

FIGURE LEGENDS

Figure 1. Flow chart of the ConCure-SM project. The red dot identifies the advancement status at the time of manuscript submission. FGM, focus group meeting; HP, health professional; MS, multiple sclerosis; NPT, normalization process theory; PwPMS, people with progressive MS; SO, significant other.

Figure 2. Summary of trial procedures. ACP, Advance Care Planning; ACP-E, ACP Engagement; eCPS, Control Preference Scale, electronic; EDSS, Expanded Disability Status Scale; HADS, Hospital Anxiety and Depression Scale; MSQOL-29, 29-item Multiple Sclerosis Quality of Life; OPTION, Observing Patient Involvement in Shared Decision Making; QOC, Quality of Communication; SO, significant other; ZBI, Zarit Burden Interview.

REFERENCES

1. Browne P, Chandraratna D, Angood C, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology* 2014; 83(11): 1022-4.
2. Filippi M, Bar-Or A, Piehl F, et al. Multiple Sclerosis. *Nat Rev Dis Primers* 2018; 4: 43.
3. Kingwell E, van der Kop M, Zhao Y, et al. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. *J Neurol Neurosurg Psychiatry* 2012; 83: 61–6.
4. Scalfari A, Knappertz V, Cutter G, et al. Mortality in patients with multiple sclerosis. *Neurology* 2013; 81: 184–92.
5. Lunde HMB, Assmus J, Myhr K-M, Bø L, Grytten N. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. *J Neurol Neurosurg Psychiatry* 2017; 88: 621–5.
6. Chiaravalloti ND, De Luca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol* 2008; 7: 1139–51.
7. Higginson IJ, Hart S, Silber E, Burman R, Edmonds P. Symptom prevalence and severity in people severely affected by multiple sclerosis. *J Palliat Care* 2006; 22: 158–65.
8. Hirst C, Swingler R, Compston DA, et al. Survival and causes of death in multiple sclerosis: a prospective population-based study. *J Neurol Neurosurg Psychiatry* 2008; 79: 1016-21.
9. Sumelahti ML, Hakama M, Elovaara I, et al. Causes of death among patients with multiple sclerosis. *Mult Scler* 2010; 16: 1437-42.
10. Giordano A, Ferrari G, Radice D, et al. on behalf of the POSMOS study. Health-related quality of life and depressive symptoms in significant others of people with multiple sclerosis: A community study. *Eur J Neurol* 2012; 19: 847-54.
11. Rietjens JAC, Sudore RL, Connolly M, et al. Definition and recommendations for advance care planning: an international consensus supported by the European Association for Palliative Care. *Lancet Oncol* 2017; 18(9): e543-e551.
12. Archer J, Stevenson L, Coulter A, Breen AM. Connecting patient experience, leadership, and the importance of involvement, information, and empathy in the care process. *Healthc Manage Forum* 2018; 31(6): 252-5.
13. Coulter A, Collins A. Making shared decision-making a reality. London, United Kingdom: King's Fund. 2011. Available at: https://www.kingsfund.org.uk/publications/making-shared-decision-making-reality. Accessed March 14, 2020.

14. Elwyn G, Frosch D, Thomson R, et al. Shared decision making: a model for clinical practice. *J Gen Intern Med* 2012; 27: 1361-7.
15. Forte DN, Kawai F, Cohen C. A bioethical framework to guide the decision-making process in the care of seriously ill patients, *BMC Medical Ethics* 2018; 19: 78.
16. De Panfilis L, Giorgi Rossi P, Mazzini E, et al. Knowledge, opinion and attitude about the Italian law on Advance Directives: a population-based survey. *J Pain Symptom Manage* 2020: S0885-3924(20)30561-3.
17. Solari A, Giordano A, Sastre-Garriga J, et al. EAN guideline on palliative care of people with severe, progressive multiple sclerosis. *Eur J Neurol* 2020; 27(8): 1510-29.
18. Brinkman-Stoppelenburg A, Rietjens JAC, van der Heide A. The effects of advance care planning on end-of-life care: A systematic review. *Palliat Med* 2014; 28(8): 1000–25.
19. Golla H, Galushko M, Strupp J, et al. Patients feeling severely affected by multiple sclerosis: addressing death and dying. *Journal of Death & Dying* 2016; 74(2): 275–91.
20. Golla H, Mammeas S, Galushko M, Pfaff H, Voltz R. Unmet needs of caregivers of severely affected multiple sclerosis patients: A qualitative study. *Palliat Support Care* 2015; 13(6): 1685–93.
21. Walter HAW, Seeber AA, Willems DL, de Visser M. The role of palliative care in chronic progressive neurological diseases-a survey amongst neurologists in the Netherlands. *Front Neurol* 2019; 14; 9: 1157.
22. McCurry MK. An exploratory study of decision making by informal caregivers of individuals with multiple sclerosis. *J Neurosci Nurs* 2013; 45(1): 52–60.
23. Cottrell L, Economos G, Evans C, et al. A realist review of advance care planning for people with multiple sclerosis and their families. *PLoS ONE* 2020; 15(10): e0240815.
24. Craig P, Dieppe P, Macintyre S, et al. Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008; 337: a1655.
25. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ* 2013; 346: e7586.
26. Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. *JAMA* 2018; 319(5): 483–94.
27. Grant S, Mayo-Wilson E, Montgomery P. CONSORT-SPI 2018 Explanation and Elaboration: guidance for reporting social and psychological intervention trials. *Trials* 2018; 19: 406.

28. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32 item checklist for interviews and focus groups. *Int J Qual Health Care* 2007; 19(6): 349–57.
29. Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. *J Clin Epidemiol* 1993; 46: 1417–32.
30. Wild D, Eremenco S, Mear I, et al. Multinational trials-recommendations on the translations required, approaches to using the same language in different countries, and the approaches to support pooling the data: the ISPOR Patient-Reported Outcomes Translation and Linguistic Validation Good Research Practices Task Force report. *Value Health* 2009; 12(4): 430-40.
31. Sudore RL, Heyland DK, Barnes DE, et al. Measuring advance care planning: Optimizing the Advance Care Planning Engagement Survey. *J Pain Symptom Manage* 2017; 53(4): 669-81.
32. Engelberg R, Downey L, Curtis JR. Psychometric characteristics of a quality of communication questionnaire assessing communication about end-of-life care. *J Palliat Med* 2006; 9(5): 1086-98.
33. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology* 1996; 46: 907–11.
34. Downar J, Goldman R, Pinto R, Englesakis M, Adhikari NKJ. The “surprise question” for predicting death in seriously ill patients: a systematic review and meta-analysis. *CMAJ* 2017; 189 (13): E484–93.
35. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444-52.
36. Mahoney FI, Barthel D. Functional evaluation: The Barthel Index. *Maryland State Med Journal* 1965; 14: 56-61.
37. Giordano A, Mattarozzi K, Pucci E, et al. Participation in medical decision-making: Attitudes of Italians with multiple sclerosis. *J Neurol Sci* 2008; 275: 86–91.
38. Costantini M, Musso P, Viterbori F, et al. Detecting psychological distress in cancer patients: validity of the Italian version of the Hospital Anxiety and Depression Scale. *Support Care Cancer* 1999; 7: 121–7.
39. Goss C, Fontanesi S, Mazzi MA, Del Piccolo L, Rimondini M. The assessment of patient involvement across consultation. The Italian version of the OPTION scale. *Epidemiol Psichiatr Soc* 2007; 16: 339–49.
40. Rosato R, Testa S, Bertolotto A, et al. eMSQOL-29: Prospective validation of the abbreviated, electronic version of MSQOL-54. *Mult Scler* 2019; 25(6): 856-66.

41. Chattat R, Cortesi V, Izzicupo F, et al. The Italian version of the Zarit Burden Interview: a validation study. *Int Psychogeriatr* 2010; 16: 1-9.
42. Degner LF, Sloan JA, Venkatesh P. The control preference scale. *Can J Nurs Res* 1997; 29: 21–43.
43. Kryworuchko J, Stacey D, Bennett C, Graham ID. Appraisal of primary outcome measures used in trials of patient decision support. *Patient Educ Couns* 2008;73: 497–503.
44. Solari A, Giordano A, Kasper J,et al; AutoMS project. Role preferences of people with multiple sclerosis: Image-revised, computerized self-administered version of the Control Preference Scale. *PLoS One* 2013; 8(6): e66127.
45. Elwyn G, Hutchings H, Edwards A, et al. The OPTION scale: measuring the extent that clinicians involve patients in decision-making tasks. *Health Expect* 2005; 8: 34–42.
46. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; 67: 361–70.
47. Honarmand K, Feinstein A. Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. *Mult Scler* 2009; 15: 1518–24.
48. Hérbert R, Bravo G, Préville M. Reliability, validity, and reference values of the Zarit Burden Interview for assessing informal caregivers of community-dwelling older persons with dementia. *Canadian Journal on Aging* 2000; 19: 494-507.
49. Denzin NK, Lincoln YS. Handbook of qualitative research. London, UK: Sage Publications; 2000.
50. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006; 3:77–101.
51. Moore G, Audrey S, Barker M, et al. Process evaluation of complex interventions: Medical Research Council guidance. London: MRC Population Health Science Research Network; 2014. 7.
52. Murray E, Treweek S, Pope C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. *BMC Med* 2010; 8(1): 63.
53. May CR, Cummings A, Girling M, et al. Using Normalization Process Theory in feasibility studies and process evaluations of complex healthcare interventions: a systematic review. *Implement Sci* 2018;13(1):80.
54. Kopke S, Giordano A, Veronese S, et al. Patient and caregiver involvement in formulation of guideline questions: findings from the EAN guideline on palliative care of people with severe multiple sclerosis. *Eur J Neurol* 2019; 26(1): 41–50.
55. Lancaster GA, Thabane L. Guidelines for reporting non-randomised pilot and feasibility studies. *Pilot and Feasibility Studies* 2019; 5: 114.

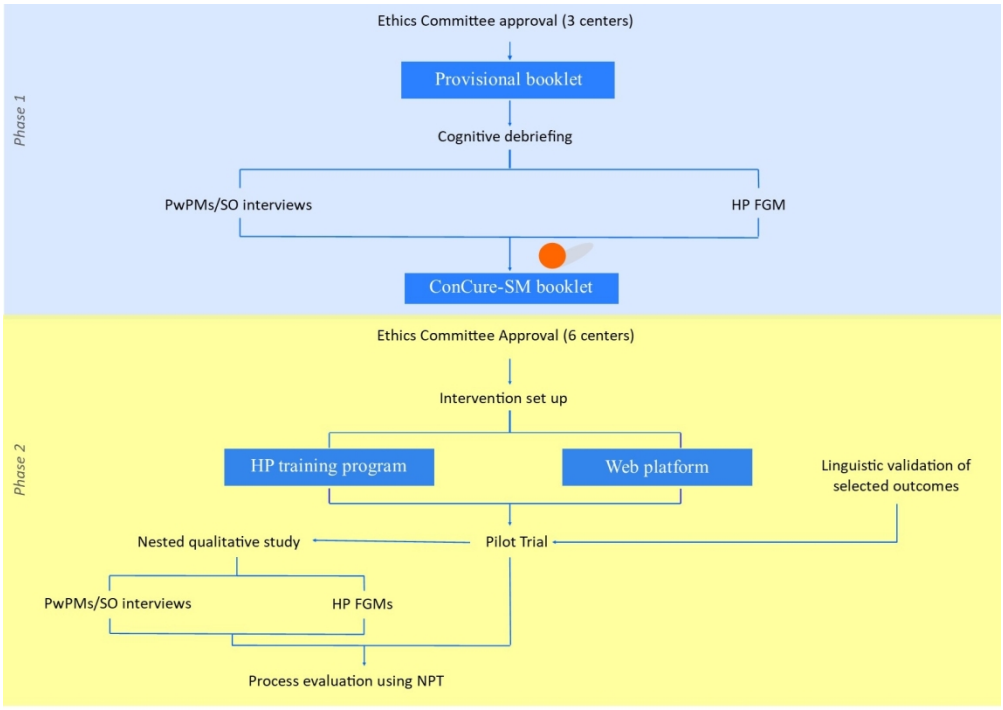
56. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. *Acad Med* 2014; 89(9): 1245–51.
57. Schichtel M, Wee B, Perera R. Clinician-targeted interventions to improve advance care planning in heart failure: a systematic review and meta-analysis. *Heart* 2019; 105: 1316–24.

Box. Objectives of the pilot trial.

1. To determine how many people with progressive multiple sclerosis (pwPMS) accept the invitation to participate in the study
2. To determine how many participants receive the intervention
3. To estimate recruitment and refusal rates, and 6-month follow-up rates
4. To estimate advance care planning (ACP) completion during the 6-month follow-up (primary study outcome)
5. To estimate occurrence of serious adverse events and adverse events during the 6-month follow-up
6. To assess, qualitatively, the acceptability of the recruitment processes, assessments, intervention delivery and secondary outcome measures with key stakeholders
7. To measure changes in the secondary outcome measures
8. To explore the barriers and facilitators to implementing ACP in pwPMS, and the influence of the clinical setting
9. To inform the sample size estimation for a subsequent phase III trial, should this be feasible

Table 1. Secondary outcome measures of the trial (in alphabetical order). ACP-E, Advance Care Planning Engagement; eCPS, Control Preference Scale, electronic; HADS, Hospital Anxiety and Depression Scale; MSQOL-29, 29-item Multiple Sclerosis Quality of Life; OPTION, Observing Patient Involvement in Shared Decision Making; QOC, Quality of Communication; SO, significant other; ZBI, Zarit Burden Interview.

Scale name	*Assessor*	*Construct*	*Author*	*Italian version*	*Timing*
4-item ACP-E	Patient	ACP engagement	Sudore 2017	–	T0/T1/T2
eCPS	Patient	Role preferences	Degner 1997	Solari 2013	T0
HADS	Patient	Mood symptoms	Zigmond 1983	Costantini 1999	T0/T1/T2
MSQOL-29	Patient	Health-related QOL	Rosato 2019	Rosato 2019	T0/T2
OPTION	Third observer	SDM (physician's skills)	Elwyn2005	Goss2007	–
QOC	Patient	Communication quality (physician's skills)	Engelberg 2006	–	T1
QOC-Doc	Physician	Communication quality (physician's skills)	–	–	T1
QOC-SO	SO	Communication quality (physician's skills)	–	–	T1
ZBI	SO	Caregiver burden	Hérbert 2000	Chattat 2010	T0/T1/T2



297x209mm (150 x 150 DPI)

Eligible pwPMS:
- ► Age ≥ 18 years
- ► At least one out of seven conditions that would make ACP relevant
- ► Able to communicate in Italian
- ► Adequate cognitive and communicative ability to participate
- ► No serious psychiatric conditions
- ► No previous advance care plan document completed

Participant screening:
- ► Confirm eligibility
- ► Obtain name/contact of SO (if applicable) and permission to contact

Baseline assessment (T0):

PwMS
- ► HADS
- ► eCPS
- ► 4-item ACP Engagement
- ► MSQOL-29

SO
- ► General data
- ► ZBI

Physician
- ► PwPMS general and clinical data (EDSS [35], Barthel Index [36])
- ► Physician's general data

First ACP conversation:
- ► OPTION scale (physician's competences)

Follow-up assessment (T1):

PwMS
- ► HADS
- ► QOC
- ► 4-item ACP

SO
- ► ZBI
- ► QOC-SO

Physician
- ► QOC-Doc

Follow-up assessment (T2):

PwMS
- ► HADS
- ► 4-item ACP Engagement
- ► MSQOL-29

SO
- ► ZBI

Physician
- ► PwPMS clinical/ACP update

BMJ Open

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

Ludovica De Panfilis, Simone Veronese, Michela Bruzzone, Marta Cascioli, Alberto Gajofatto, Maria Grazia Grasso, Paola Kruger, Alessandra Lugaresi, Leigh Manson, Sara Montepietra, Francesco Patti, Eugenio Pucci, Claudio Solaro, Andrea Giordano, Alessandra Solari

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ONLINE SUPPLEMENTAL APPENDIX 1 – SPIRIT CHECKLIST; DSMC CHARTER

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.

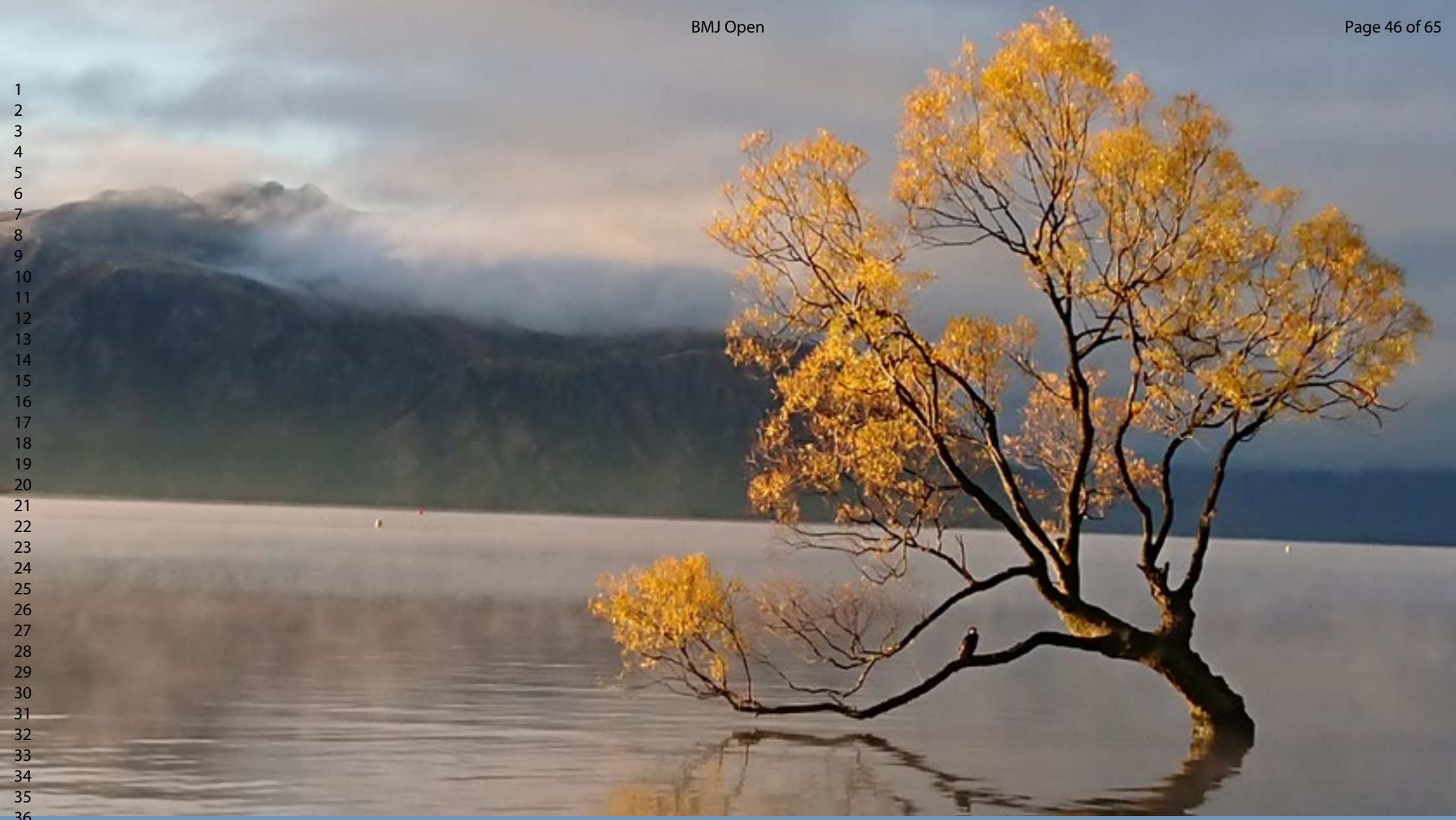
9. Reporting	
To whom will the DSMC report their recommendations/decisions, and in what form	The DSMC will report in writing to the SC, usually within three weeks of a meeting being held.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	Meeting minutes need not be 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



La mia pianificazione condivisa delle cure

Le mie scelte di cura rispetto alla mia salute e al fine vita

È importante quello che tu pensi, ciò in cui credi, quello che vorresti accadesse, o non accadesse, nel corso della tua vita. Se ne parli con i tuoi cari, con le persone importanti per te, con gli operatori sanitari, con chi pensi che ti sarà vicino quando il tuo stato di salute sarà compromesso, sarà più facile per tutti aiutarti nelle decisioni che riguardano la tua vita.

Se però vuoi assicurarti che le tue preferenze vengano rispettate ed abbiano un valore vincolante, devi metterle per iscritto o videoregistrarle. Questo permetterà ai medici di consultarle e di comportarsi in modo da soddisfare i tuoi desideri.

La legge italiana 219/2017 prevede la possibilità di fare delle scelte per situazioni future tramite due differenti modalità. La prima è rivolta a chi sta bene e non ha una malattia progressiva, ma desidera esprimersi rispetto a scelte di cura future, nell'ipotesi in cui perdesse la capacità di decidere o di esprimersi, e si chiama Disposizioni Anticipate di Trattamento (DAT). Le DAT possono essere redatte da qualunque cittadino adulto, adeguatamente informato e capace di decidere. Nelle DAT il cittadino può indicare le sue preferenze e volontà rispetto ai trattamenti sanitari che desidera, o non desidera ricevere, e stabilire se è disposto ad accettare condizioni come l'intubazione, la nutrizione "artificiale", la respirazione meccanica e così via. Le DAT devono essere depositate presso il comune di residenza o presso un notaio. Entrambi si occuperanno di trasmettere il documento ad un registro nazionale consultabile dai medici che entrano in contatto con il cittadino.

La seconda modalità si chiama Pianificazione Condivisa delle Cure (PCC), riguarda chi ha una malattia progressiva, che nel tuo caso è la sclerosi multipla (SM), e viene redatta insieme al proprio medico di fiducia (per esempio il neurologo, il palliativista o il medico di medicina generale). La PCC è un documento che permette al paziente di pianificare le scelte di cura in modo graduale rispetto all'andamento della sua malattia. Essa viene registrata nella cartella clinica o, nelle regioni in cui è attivo, nel fascicolo sanitario elettronico, in modo da poter essere condivisa tra tutti i sanitari che si prendono cura della persona malata. Una copia del documento di PCC rimane al paziente, che potrà conservarla nella sua documentazione sanitaria.

In entrambi i casi la nostra Legge prevede che si possa nominare un fiduciario, ovvero una persona di fiducia che rappresenterà e farà le veci del paziente nelle relazioni con il personale di cura e con le strutture sanitarie, nel caso in cui la persona malata perdesse la capacità di decidere (a causa del peggioramento della malattia, per la comparsa di un evento acuto, o un incidente) e i medici dovessero prendere una decisione importante sulle terapie da iniziare (o non iniziare, o sospendere). In questa evenienza, il fiduciario potrà partecipare alla decisione discutendone con i medici, portando il punto di vista del paziente e le sue preferenze. Si può anche scegliere più di un fiduciario, anche perché non è possibile sapere se la persona identificata in questo compito sarà necessariamente disponibile al momento del bisogno, ma dovrà essere chiaro un ordine di preferenza, per evitare che insorgano contrasti tra i fiduciari rispetto alle scelte. È auspicabile che una copia della PCC sia consegnata anche al fiduciario.

Sia le DAT che la PCC possono essere riviste, ripensate e ridiscusse nel corso del tempo. Questo perché le preferenze e la visione della vita possono cambiare, così come la scelta della persona che si vuole indicare come fiduciario.

Per questo è importante aggiornare regolarmente la PCC, per ripensare alle scelte e ridiscuterle con il medico curante e gli altri professionisti sanitari.

Questo opuscolo è destinato alla persona con SM che desidera redigere la propria PCC. A fianco del **documento di PCC** è presente una **guida** che ha lo scopo di facilitare la compilazione, che deve sempre avvenire attraverso una discussione e condivisione con il proprio medico di fiducia. La guida ti aiuterà a pensare e ad esprimerti su:

- Cosa è importante per te adesso
- Come desideri prendere le decisioni
- Che tipo di assistenza e di cure vorresti per il futuro
- Come vorresti essere assistito alla fine della tua vita

Non devi necessariamente riempire tutti gli spazi di compilazione del **documento di PCC**, ma solo le parti che ti interessano. Ciò che deve essere compilato in ogni parte è la sezione "Firme".

Questo spazio è a tua disposizione per descrivere le tue idee, i tuoi valori, la tua visione della vita e del tuo futuro.

In questo spazio puoi scrivere le tue domande sulle scelte per il futuro, le cure o altre scelte per le quali necessiti di risposte da parte dei medici o di chi si prende cura di te:

La SM è una malattia cronica, caratterizzata da una riduzione variabile dell'aspettativa di vita (tra 7 e 14 anni) rispetto alla popolazione generale, e da un decorso altrettanto variabile. Nella forma progressiva di malattia, i sintomi e le limitazioni funzionali coinvolgono, in modo e con gravità variabile, diversi aspetti, come l'autonomia nei movimenti, la vista, il controllo degli sfinteri, la capacità di alimentarsi, di comunicare, e le funzioni mentali. Questi disturbi possono stabilizzarsi anche per lunghi periodi, permettendo un adattamento personale ed una qualità della vita accettabili, se non soddisfacenti. Ulteriori peggioramenti, come la comparsa di complicanze o di altri problemi di salute e le mutate condizioni familiari che possono verificarsi rendono più difficoltoso questo adattamento continuo. Può accadere di dover condividere la scelta di ricorrere, talvolta in emergenza, a trattamenti di supporto vitale per evitare la morte. Questi trattamenti sono, ad esempio, la tracheostomia (che consente la respirazione facendo passare l'aria direttamente in trachea attraverso un foro chirurgico praticato alla base del collo), oppure la gastrostomia percutanea o PEG (che consente l'alimentazione attraverso un foro chirurgico praticato nell'addome). I trattamenti di supporto vitale possono assicurare anni di vita, tuttavia possono causare ulteriori sofferenze. È utile interrogarsi per tempo sul significato personale di una qualità di vita accettabile.

Lo scopo della PCC è di condividere col proprio medico di fiducia e riportare per iscritto le decisioni rispetto alle scelte terapeutiche ed assistenziali che potranno essere necessarie nel corso della malattia.

Essa costituisce uno strumento vincolante rispetto a queste specifiche decisioni ed aiuterà i tuoi curanti e i tuoi cari a prendere le decisioni qualora tu non potessi più esprimerle.

Questa PCC è tua, ma potrai modificarla in accordo con il tuo medico di fiducia ogni volta che vorrai, avendo cura di condividere il nuovo piano anche con il tuo fiduciario che potrà avere la possibilità di confermare il suo ruolo o meno, a seconda delle indicazioni e preferenze che indicherai.

Contenuti:

1. La mia pianificazione condivisa delle cure

Questa è la mia Pianificazione Condivisa delle Cure e contiene le mie scelte.

Per favore, seguitela qualora non fossi più in grado di esprimere quello che desidero:

Nome _____ **Cognome** _____

Nato/a il: _____ **a:** _____

Indirizzo: _____

_____

Telefono: _____

E-mail _____

2. Cosa è importante per me

Alcune domande che possono aiutarti a definire cosa sia importante per te:

- Cosa ti rende felice?
- Cosa ti reca piacere e gioia?
- Che cosa ti piace fare?
- Quali sono i tuoi hobby e i tuoi interessi?
- Ci sono delle abitudini alle quali sei affezionato?
- Che cosa dà senso alla tua giornata?
- Con chi ti piace trascorrere il tempo?
- Hai principi spirituali, religiosi, o riti che sono importanti per la tua vita?

Ecco alcune altre cose che potrebbero essere importanti o significative per te:

- Parlare e stare vicino alle persone
- Renderti conto di chi sei e dove ti trovi
- Sentire l'amore e l'affetto degli altri
- Vivere esperienze significative
- Avere vicino il cane o l'animale di compagnia
- Partecipare al culto della mia religione
- Sentirti attivo culturalmente
- Contribuire al bene della società
- Sentire che qualcuno ti abbraccia e ti tiene per mano
- Mantenere il più possibile l'autonomia
- Avere momenti di intimità o sessualità

Questo è ciò che voglio che i miei curanti ed i miei cari sappiano di me, e di cosa è importante per me:

Questi sono i valori culturali, spirituali, religiosi e i riti importanti per me:

Per onorare questi valori desidero che i miei curanti e i miei cari:

3. Cosa mi preoccupa

Ci sono cose che ti preoccupano quando pensi al tuo futuro?

Per esempio, ti preoccupi quando pensi:

- Che la tua salute potrà compromettere le tue scelte
- Che la tua salute potrà causare problemi ai tuoi cari
- Dove sarai assistito in futuro
- Di provare dolore o sofferenza
- Di non essere più in grado di comunicare
- Di perdere la capacità di ragionare
- Di essere di peso per gli altri
- Di venire ricoverato in struttura
- Di morire da solo
- Di come le persone che ami possano andare avanti senza di te
- Di rimanere bloccato in un letto
- Che le tue scelte non siano rispettate
- Che i tuoi valori non siano considerati
- Di avere problemi economici

Questo è ciò che voglio che i miei curanti e i miei cari sappiano rispetto a ciò che mi preoccupa:

Segna le caselle corrispondenti

☐ **Soffrire. La sofferenza per me significa:**

☐ **Non poter comunicare, ad esempio:**

☐ **Non poter far cose, ad esempio:**

☐ **Mi preoccupo per i miei cari perché:**

☐ **Altre cose che mi preoccupano:**

4. Perché voglio fare una Pianificazione Condivisa delle Cure

Alcune cose a cui pensare:

- Come è stato l'andamento della tua SM e della tua salute in generale nell'ultimo anno?
- Il tuo stato di salute ti limita fortemente in attività che sono importanti per te?
- Sei aiutato e sostenuto da familiari e più in generale da persone care?
- Sei di aiuto e sostegno a familiari e persone care?

Per comprendere meglio che impatto potrà avere il tuo stato di salute sul tuo futuro, parlane con i professionisti sanitari che si prendono cura di te.

Per esempio, potresti chiedere loro: Se la mia SM dovesse peggiorare...

- Che livello di indipendenza potrò avere?
- Cosa è bene/giusto pianificare ora?
- Cosa accadrà al mio corpo e alla mia mente?
- Che impatto potrebbe avere il mio stato di salute sulle persone che si prendono cura di me?

Ecco perché voglio fare una PCC:

Se penso al mio futuro mi viene in mente:

Se penso al mio futuro mi sento:

Se il tempo davanti a me fosse breve allora vorrei:

5. Come prendo le decisioni

Pensa alle decisioni che potresti dover prendere nel corso della malattia.

Pensa a come sei abituato a prendere le decisioni.

Hai bisogno di tempo? Ti piace essere molto informato sulle possibilità di scelta, o preferisci che siano altri a decidere per te?

Hai mai pensato che nella vita possano verificarsi eventi improvvisi, come incidenti o eventi acuti, in cui debbano essere prese rapidamente delle decisioni importanti?

Chi vorresti che decidesse per te, se tu non fossi in grado di farlo?

Ricorda che, qualora non fossi più in grado di esprimerti, altri dovranno decidere per te. Prenditi dunque del tempo per pensare e per parlare di questo con le persone che ti sono vicine.

Se decidi di nominare una persona come tuo fiduciario, perché pensi che possa rappresentare adeguatamente il tuo punto di vista nelle decisioni che riguardano la tua salute, potrebbe essere il momento giusto per farlo. Potrai revocare questa scelta in ogni momento. Il tuo fiduciario deciderà per te solo in caso tu non possa esprimere la tua preferenza.

Rispondendo a ciascuna delle affermazioni riportate di seguito potrai chiarire meglio le tue preferenze relative alle scelte di cura che ti riguardano.

Segna la casella che più corrisponde alla tua preferenza

Voglio avere...

Solo le informazioni strettamente necessarie	☐ ☐ ☐ ☐ ☐	Tutti i dettagli sulla mia malattia e le terapie

Voglio che i miei curanti...

Facciano quello che pensano sia meglio per me	☐ ☐ ☐ ☐ ☐	Mi consentano di dire la mia in ogni circostanza

Se la mia SM raggiungesse una fase avanzata vorrei...

Sapere quanto mi resta da vivere	☐ ☐ ☐ ☐ ☐	Non sapere quanto mi resta da vivere

Voglio che i miei cari…

Decidano rispettando esattamente la mia volontà, anche se questo li facesse stare male	☐ ☐ ☐ ☐ ☐	Prendano la decisione che li faccia sentire in pace, anche se dovesse essere contraria alla mia volontà

Voglio che i miei cari…

Non sappiano nulla sul mio stato di salute	☐ ☐ ☐ ☐ ☐	Ricevano ogni informazione sul mio stato di salute

6. Se non fossi più in grado di decidere: il mio fiduciario

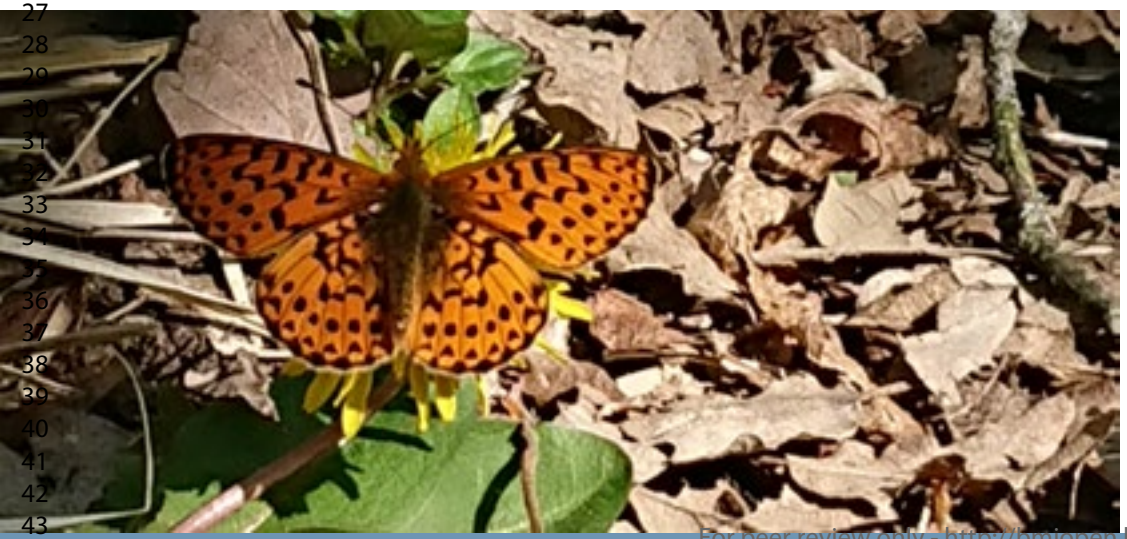
Se hai deciso di nominare un fiduciario, devi coinvolgerlo nelle tue scelte future.

Parla con lui, o con lei, del tuo piano di cure e consegna al fiduciario una copia del documento di PCC, dopo che l'avrai compilato.

Se non hai ancora deciso di nominare un fiduciario, prova a pensare se non sia il caso di farlo ora.

Se devi scegliere una persona, o più persone, che dovranno decidere per la tua salute nel momento in cui tu non fossi più in grado di farlo, scegli qualcuno che:

- Ti conosca bene
- Si preoccupi di cosa è importante per te
- Sia disponibile a parlare di questi aspetti con te
- Ti ascolti e sia rispettoso
- Sia disposto a difendere le tue volontà affinché vengano esaudite.



Se perdessi la capacità di decidere, vorrei che:

Segna la casella che corrisponde alla tua preferenza

☐ **Le decisioni riguardanti le mie cure future venissero concordate con il mio fiduciario di seguito indicato:**

Nome e Cognome

Indirizzo

Telefono e-mail

Se il mio fiduciario fosse impossibilitato a svolgere il suo ruolo, indico come seconda, terza persona di fiducia:

Nome e Cognome

Telefono e-mail

Nome e Cognome

Telefono e-mail

Oppure:

☐ **Non ho scelto un fiduciario.**

Vorrei inoltre che la persona di seguito indicata sia comunque informata dai sanitari che prenderanno decisioni sulle mie cure future in base alle indicazioni contenute in questo documento ed in funzione del mio migliore interesse.

Nome e Cognome

Indirizzo

Telefono e-mail

7. Pensando alla fine della mia vita

Morire è parte del vivere, ma ci preoccupa e spaventa. È desiderabile che la fine della vita avvenga nel rispetto della propria dignità e autonomia, in un luogo adeguato e possibilmente di nostra scelta, in presenza delle persone a noi care, se lo vogliamo, e limitando ogni tipo di sofferenza. Non esiste un percorso uguale per tutti alla fine della vita, esso infatti può essere influenzato dall'età, dalle malattie di cui soffriamo e da altre circostanze. In questa fase, potrebbe essere necessario ricevere farmaci e trattamenti con l'obiettivo di controllare sintomi che possono presentarsi quali dolore, mancanza di fiato, nausea, ansia, agitazione. Nei rari casi nei quali la sofferenza non fosse gestibile con terapie ordinarie potrebbe essere indicata una sedazione palliativa profonda, ovvero un trattamento che annulla gradualmente la coscienza, con lo scopo di ridurre la sofferenza sino al sopraggiungere della morte (la sedazione palliativa profonda infatti non anticipa né procrastina il momento della morte).

Pensando a cosa significhi per te mantenere una buona qualità della vita, in questa fase cosa credi che sarebbe importante?

- Restare vigile e mantenere il controllo il più a lungo possibile
- Non sentire alcuna sofferenza anche a costo di essere sonnolento o addormentato
- Avere accanto chi amo
- Stare da solo

Dovendo pensare alla fine della tua vita:

- Quale sarebbe la tua morte ideale?
- Pensando alla morte ed al morire, cosa ti preoccupa di più?
- Chi vorresti avere accanto?
- Che tipo di assistenza spirituale o religiosa vorresti?
- In prossimità della morte, cosa vorresti e cosa non vorresti?

Per me una buona qualità della vita in prossimità della morte significa:

Vorrei anche aggiungere:

Quando starò morendo desidero essere curato e accudito nel rispetto della mia persona e della mia dignità. Inoltre desidero:

Segna la casella che corrisponde a ciò che desideri

☐ **Che vengano rimossi tubi ed altri presidi che possano ostacolare il contatto con le persone che mi sono care**

☐ **Che vengano interrotti trattamenti non più utili**

☐ **Avere un sostegno spirituale o religioso**

7. Pensando alla fine della mia vita

Dove vorresti trascorrere le tue ultime settimane o giorni?

- Cosa ritieni necessario affinché questo possa avvenire?

Chi dovrà essere informato del fatto che stai per morire?

- Dove conservi i contatti (nome, telefono) di queste persone?
- C'è qualcuno che potrà contattarle?

Nel caso non fosse possibile soddisfare la tua scelta sul luogo dove morire, hai altre preferenze da esprimere?

Quali altre cose sarebbero importanti per te? (Per esempio, mantenere la tua privacy, ascoltare una musica particolare, poter vedere alcune persone significative, ecc.)

Il luogo nel quale morire è importante per me:

Segna la casella che corrisponde alla tua preferenza

☐ **Sì** ☐ **No**

Quando starò morendo vorrei essere assistito:

☐ **A casa, che per me significa:**

☐ **In ospedale**
☐ **In una struttura (comunità, casa di riposo)**
☐ **In hospice**
☐ **Non è rilevante il luogo dove sarò assistito**

Altri aspetti che vorrei venissero considerati:

8. Le mie scelte di cura

Questa parte del documento va compilata con l'aiuto del tuo medico di fiducia.

I trattamenti di supporto vitale possono mantenerti in vita nelle stesse condizioni in cui ti trovi ora. Altre volte essi possono consentire condizioni di vita per te inedite e difficili da immaginare, o risultare fastidiosi o dolorosi. Tra questi trattamenti vi sono l'idratazione/nutrizione 'artificiale' (per sondino naso-gastrico, PEG, per via parenterale/endovenosa), la rianimazione cardiopolmonare (RCP), la ventilazione meccanica con o senza tracheostomia, la dialisi. I trattamenti di supporto vitale in sé non sono né buoni né cattivi, dipende da come e quando vengono utilizzati. È importante, inoltre, ricordare che questi trattamenti non devono essere considerati irreversibili e che si può tornare indietro anche in queste scelte.

Puoi decidere se ricevere, o meno, questi trattamenti. I tuoi curanti ti proporranno solo trattamenti utili per la tua condizione, come per esempio la RCP, che potrebbe riattivare la funzione del cuore o dei polmoni. In tal caso sei chiamato a decidere se vuoi che venga fatta o meno.

Pensa a cosa è importante per te. Per esempio, la qualità della tua vita (non soffrire) o la durata della tua vita (poter vivere il più a lungo possibile). La tua PCC serve in particolare nelle condizioni di emergenza, ove tu non sia in grado di prendere delle decisioni per facilitare i curanti a mettere in atto o meno, trattamenti nel tuo miglior interesse. Trattamenti appropriati sul piano strettamente tecnico, potrebbero infatti essere inappropriati alla luce delle tue preferenze.

Ci sono circostanze nelle quali non vorresti essere mantenuto in vita e preferiresti non iniziare o sospendere terapie di supporto?

Se mi trovassi in condizioni di estrema gravità, in pericolo di vita ed incapace di decidere per me, ciò che segue descrive al meglio le mie preferenze di cura. Sono consapevole di non poter pretendere trattamenti che i medici giudichino inappropriati per le mie condizioni. Estrema gravità per me significa:

Scrivi nel riquadro in fondo alla pagina il numero corrispondente alla tua scelta di cura e, dove applicabile, indica con un segno i trattamenti specifici (punto 2).

1 Vorrei ricevere **tutti i trattamenti disponibili** ritenuti necessari e appropriati dai medici che mi cureranno, per mantenermi in vita il più a lungo possibile.

2 Vorrei ricevere **solo quei trattamenti** mirati non solo a prolungare, ma anche a preservare una qualità di vita ancora accettabile per me.

Nello specifico, accetto di ricevere i seguenti trattamenti:

- ☐ idratazione/nutrizione per sondino naso-gastrico
- ☐ PEG
- ☐ idratazione/nutrizione parenterale/endovenosa
- ☐ rianimazione cardiopolmonare
- ☐ ventilazione meccanica senza tracheostomia
- ☐ ventilazione meccanica con tracheostomia
- ☐ dialisi

3 Vorrei ricevere solo le cure mirate al **controllo dei sintomi e al mio comfort**, nel rispetto della mia dignità. Non voglio alcun trattamento finalizzato solo a prolungare la mia vita.

4 Non sono in grado di decidere adesso. **Delego i medici** che mi cureranno a prendere le decisioni migliori per me, tenendo in considerazione il parere delle persone che ho indicato nella sezione 6.

Ho scelto l'opzione numero: ☐

Ho già redatto le mie **Disposizioni Anticipate di Trattamento**, depositate presso il comune

di ☐ in Data ☐

e reperibili presso il Registro Nazionale DAT.

Questo documento:

☐ Aggiorna le mie DAT ☐ Conferma le mie DAT

9. Firme

La firma di questo documento è necessaria affinché esso sia ritenuto valido e sia applicato. Se non puoi firmare, è sufficiente una videoregistrazione in cui i sanitari leggeranno le sezioni 6, 7 e 8 del documento e registreranno le tue scelte.

Se hai nominato un fiduciario, è necessaria anche la sua firma.

Anche il tuo medico di fiducia, ed eventuali altri professionisti sanitari che ti hanno in cura dovrebbero firmarlo, perché questo garantisce che la PCC è avvenuta in modo informato e condiviso.

Firmando questo documento io confermo:

1. **Di avere compreso la finalità dello stesso e che esso rispecchia le mie volontà**
2. **Di averlo compilato in piena libertà e dopo essere stato adeguatamente informato**
3. **Di acconsentire alla conservazione delle informazioni nei registri, nelle cartelle cliniche e nei fascicoli elettronici previsti, secondo la normativa sulla privacy (Regolamento UE 2016/679) e relativa normativa italiana di adeguamento (D.Lgs. n. 196 del 30 Giugno 2003, così come modificato dal D.Lgs. n. 101 del 10 Agosto 2018).**

Nome e Cognome _____

Indirizzo _____

Telefono _____ **e-mail** _____

Data _____ **Firma** _____

☐ **Ho scelto come fiduciario:**

Nome e Cognome _____

Indirizzo _____

Telefono _____ **e-mail** _____

Data _____ **Firma** _____

☐ **Non ho scelto un fiduciario**

Ho condiviso con il mio medico di fiducia questo documento:

Dr

Telefono e-mail

Data Firma

E, dove applicabile, con il professionista sanitario:

Dr

Telefono e-mail

Data Firma

10. Abbreviazioni

DAT: Disposizioni anticipate di trattamento

PCC: Pianificazione condivisa delle cure

PEG: Gastrostomia percutanea endoscopica

RCP: Rianimazione cardiopolmonare

SM: Sclerosi multipla

Autori: Michela Bruzzone[1], Marta Cascioli[2], Ludovica De Panfilis[3], Andrea Giordano[4], Maria Grazia Grasso[5], Alessandra Lugaresi[6], Luisa Motti[7], Emanuela Pelle[8], Eugenio Pucci[9], Alessandra Solari[4], Claudio Solaro[10], Simone Veronese[8]

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BMJ Open

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

Ludovica De Panfilis, Simone Veronese, Michela Bruzzone, Marta Cascioli, Alberto Gajofatto, Maria Grazia Grasso, Paola Kruger, Alessandra Lugaresi, Leigh Manson, Sara Montepietra, Francesco Patti, Eugenio Pucci, Claudio Solaro, Andrea Giordano, Alessandra Solari

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ONLINE SUPPLEMENTAL APPENDIX 3 – EXCERPTS FROM THE STUDY PROTOCOL VERSION 1.0

1 PANELS AND CENTERS

1.1 Trial Steering Committee (TSC)

The TSC is the executive body for the study. Members are from the Gruppo di Studio di Bioetica e Cure Palliative of the Società Italiana di Neurologia (L De Panfilis, MG Grasso, A Giordano, A Lugaresi, E Pucci, A Solari, S Veronese), from the National ACP programme for New Zealand (L Manson), and from patient associations (M Bruzzone, P Kruger).

1.2 Data Safety and Monitoring Committee (DSMC)

The independent DSMC has been established to: (1) oversee the progress of the pilot study and the safety data, and ensure that it is conducted, recorded, and reported in accordance with the protocol, GCP, and the applicable regulatory requirement(s); (2) monitor and supervise the progress of the pilot study, and the safety data. Members are: K Brazil, B Farsides, L Orsi, C Peruselli, and D Oliver (Chair). The DSMC is scheduled to meet (teleconference) before enrollment starts, at the end of the enrollment, and at the end of the follow-up, and depending on the needs of the trial. One week prior to each teleconference, the trial PI will send each DSMC member a report with trial data

(overall and by site) such as recruitment rates, reasons for exclusion, reason for drop out, plus other information if needed. The DSMC should report in writing to the TSC, usually within 3 weeks after the teleconference.

1.3 Data Management and Analysis Committee (DMAC)

The DMAC is responsible for data entry, quality assurance, and the statistical analyses. Members are M Farinotti (data manager) and A Giordano. DMAC will be in charge of the data protection to respond to the European and Italian law on privacy and data storage and conservation.

1.4 Qualitative Analysis Panel (QAP)

The QAP devised the design, procedures and analysis plan of the qualitative study. QAP members will conduct the personal interviews and the FGMs, and the analysis. Members are: M Cascioli, L De Panfilis, L Ghirotto, K Mattarozzi, and S Veronese.

8.5 HP Training Panel (HTP)

The HTP devised the HP training program. HTP members will have responsibility of conducting the residential program, and revise it based on training findings. Members are: M Cascioli, L De Panfilis, K Mattarozzi, E Pucci, M Rimondini, A Solari, and S Veronese.

1.6 Linguistic validation Panel (LP)

The LP was appointed to translate and adapt the outcome measures not available in Italian. Members are M Farinotti, A Giordano, A Solari, S Veronese and three independent translators (section 5.3.8).

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2 ETHICS AND ADMINISTRATIVE CONSIDERATIONS

2.1 Ethical Considerations

This clinical study was designed and shall be implemented and reported in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for GCP, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki.

2.2 Ethics Committee Approval

The protocol, Subject Information Sheet, Informed Consent Form must be reviewed and approved by an appropriately constituted Ethics Committee (EC), as required in chapter 3 of the ICH E6 Guideline. Written EC approval must be obtained by the Sponsor prior to shipment of study agent or subject enrolment.

2.3 Subject Information and Informed Consent

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), EC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents. No study procedure can be performed before the written informed consent has been provided.

2.4 Confidentiality

The investigator must ensure participant anonymity. On database and other documents, participants must not be identified by name but by patient number and initials. The investigator must keep a separate log of participants' codes, names and addresses, and signed informed consent forms, all of which must be kept strictly confidential.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law. Medical information may be given to a pwPMS personal physician or other appropriate medical personnel responsible for the pwPMS welfare, for treatment purposes. Data generated by this study must be available for inspection upon request by representatives of the national and local health authorities, monitors, representatives, and collaborators, and the EC for each study site, as appropriate.

2.5 Protocol Amendments

Any protocol amendments will be prepared by the PI. Protocol amendments will be submitted to the EC and to regulatory authorities in accordance with local regulatory requirements. Approval must be obtained from the EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g. change in monitor or contact information).

3 STUDY MANAGEMENT AND MONITORING

3.1 Source documents

Source Documents are defined as original documents, data and records. These may include hospital records, medical records / outpatient data, data recorded from automated instruments, etc. Investigators should conserve all the source documents as required in the study protocol for at least two years after the end of the study.

3.2 Archiving of records

The investigator is responsible for recording and storing the essential documents of the study, according to what / and for the time required by law and by GCP. The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of EC and governmental approval.

3.3 Auditing on site

In the event that the investigator will be contacted by the Competent Authority in relation to this study, he or she will be required to immediately notify the Sponsor. The investigator must be available to respond to requests and queries by inspectors during the audit process. The investigator must provide the Sponsor copies of all correspondence that may affect the revision of the current study.

3.4 Use and Publication of Study Results

The results of the study may be presented during scientific symposia or published in a scientific journal only after review and written approval by the involved parties in full respect of the privacy of the participating subjects.

3.5 Insurance Policy

Each of the participating centers has an adequate insurance policy to cover possible damages emerging from this study.

BMJ Open

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

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

RUNNING TITLE: A resource for advance care planning in multiple sclerosis

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ABSTRACT

Introduction. Multiple sclerosis (MS) is the most common cause of progressive neurological disability in young adults. The use of Advance care planning (ACP) for people with progressive MS (pwPMS) remains limited. The ConCure-SM project aims to assess the effectiveness of a structured ACP intervention for pwPMS. The intervention consists of a training program on ACP for healthcare professionals caring for pwPMS, and a booklet to be used during the ACP conversation. Herein we describe the first two project phases.

Methods. In phase 1 we translated and adapted, to the Italian legislation and MS context, the ACP booklet of the National ACP programme for New Zealand. Acceptability, comprehensibility and usefulness of the booklet were assessed via 13 personal cognitive interviews with pwPMS and significant others, and one health professional focus group. Based on these findings, we will revise the booklet. In phase 2 we will conduct a single-arm pilot/feasibility trial with nested qualitative study. Participants will be 40 pwPMS, their significant others, health professionals from six MS and rehabilitation centers in Italy. In the six months following the ACP conversation, we will assess completion of an advance care plan document (primary outcome), as well as safety of the intervention. Secondary outcomes will be a range of measures to capture the full process of ACP; patient-carer congruence in treatment preferences; quality of patient-clinician communication; and caregiver burden. A qualitative process evaluation will help understand the factors likely to influence future implementation and scalability of the intervention.

Ethics and dissemination. The project is co-leaded by a neurologist and a bioethicist. Phase 1 has received ethical approvals from each participating center, while phase 2 will be submitted to the centers in May 2021. Findings from both phases will be disseminated widely through peer-reviewed publications, conferences and workshops.

Trial registration number ISRCTN48527663.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength of the study is the use of a mixed-methods approach
- The intervention is co-produced with users
- Study results will be key to inform the feasibility of a full-scale trial, and its design
- A limitation is that the pilot trial is a non-randomized study
- Long-term outcomes (chiefly concordance between preferred and received end of life care) are not included

KEYWORDS: Shared Decision Making; Advance Care Planning; End-of-Life Care; Multiple Sclerosis; Complex Intervention; Normalization Process Theory.

INTRODUCTION

With a lifetime risk of 1 in 400, multiple sclerosis (MS) is the most common cause of progressive neurological disability in young adults. Approximately 2.3 million people worldwide have MS, with Canada, USA and some European countries, including Italy, having the highest prevalence rates.[1] Around 15% of people with MS have a primary progressive course at diagnosis, and a further 35% develop secondary progressive disease after 15 years.[2] A mean reduction in life expectancy by 7–14 years has been reported in people with MS, with improved figures over the last two decades. [3-5]

Few treatment options are currently available to delay or prevent further clinical worsening of people with primary or secondary progressive MS (pwPMS). They may live for many years experiencing a wide range of symptoms, impairments (including cognitive impairment which affects 40-70% of sufferers [6]) and comorbidities.[5,7-10]

Advance care planning (ACP) is a process that "enables individuals who have decisional capacity to identify their values, to reflect upon the meanings and consequences of serious illness scenarios, to define goals and preferences for future medical treatment and care, and to discuss these with family and healthcare professionals (HPs)".[11]

Consistently with the Shared Decision Making model,[12-14] ACP involves both the patient and his/her HPs. Together, they make informed decisions about the patient's (future) care. Also, the family can be involved in the process, if the patient wishes. ACP differs from general medical decision-making in that it is based on an anticipated deterioration in the health of a patient. It includes a focus on the person's wishes and preferences for the time when they lose decisional capacity. In fact, it aims to align evidence-based practice and person-centered care [15] using a bioethical focus to identify the patient's values, preferences and desires. The planning process helps the patient to identify his/her personal values and goals, understand his/her health status, and the treatment and health care options available. Finally, ACP encourages discussion around end-of-life (EOL) care (a subject that is generally not considered part of health care planning, and one that can be avoided by both patients and HPs). It is up to the patient to determine the occurrence and content of any ACP discussion: if the patient does not wish to engage in conversations about his/her future care, this preference should be respected. The ACP process may result in the patient choosing to write an advance care plan document and to appoint a trustee (or else).

On December 22, 2017, the Italian Parliament approved the first law on EOL: "Provisions for informed consent and advance directives" (L. 219/2017;

http://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=62663). This law regulates advance directives (AD; Article 4) and ACP (Article 5), and a number of rights citizens have regarding healthcare issues, including the right to: be fully informed about one's health status and to give consent (or dissent) to treatment; withhold consent to lifesaving treatments; be assisted until death. Moreover, the law states that the physician has a duty to respect the patient's wishes. In a recent Italian survey, 88% (1752/2000) of citizens considered the Law 219/2017 as quite or very important, and 76% had a positive attitude towards making/registering AD or ACP.[16] Importantly, this Law triggers HPs and health care authorities in promoting educational programs on the topic, as well as programs to implement ACP in daily clinical practice.

To optimize the alignment between patient preferences and values and the care they receive, HPs should integrate best ACP practices in the care of pwPMS. A recent guideline on palliative care in MS found no evidence of the effects of ACP in pwPMS.[17] However, there is some evidence from non-neurological progressive and life-threatening illnesses that ACP decreases the use of life-sustaining treatment, increases hospice/palliative care, reduces hospitalizations and increases alignment with patients' end of life (EOL) wishes.[18] Furthermore, there is evidence that MS patients and caregivers often would like to discuss the issues of death and dying and HPs should acknowledge and encourage these discussions.[19, 20] However, often HPs leave EOL discussions until the later stages of progression in MS,[21] and caregivers may be left having to take difficult decisions.[22] A realist review identified two main barriers for ACP discussions taking place: the long and uncertain MS trajectory, with periods of stability punctuated by crisis; and lack of ACP communication skills and confidence of HPs.[23]

ConCure-SM is a project aimed to set up and evaluate the efficacy of an ACP intervention for pwPMS in Italy. The Shared Decision Making model described above is the theoretical framework of the project.[12-14] The Medical Research Council framework for developing and evaluating complex interventions is the methodological framework of the project. The framework has a phased approach, from a pre-clinical research phase to a final phase in which the intervention is introduced into the health service, leading to a theory-driven intervention: a "bottom up" development which guarantees to enter a phase III trial with an appropriate theory and pilot work.[24] Furthermore, both quantitative and qualitative methods are integrated within the framework, in order to better appraise the effects of the (complex) intervention both as a whole and on its components.

Our study hypotheses are that the intervention will produce: higher completion of an advance care plan document; increased congruence in treatment preferences between pwPMS and their carers; increased quality communication about EOL care.

METHODS AND ANALYSIS

The study protocol (FISM 2020/R-Multi/024; Version 1.0; March 15th, 2021) was designed following the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines (online supplemental appendix 1) [25] and The SPIRIT-PRO Extension.[26] The pilot/feasibility study follows the CONSORT guidance for trials on social and psychological interventions (CONSORT-SPI 2018).[27] It was registered on the ISRCTN registry (isrctn.org Identifier: ISRCTN48527663) the 30th March, 2021. Qualitative data will be reported following the Consolidated criteria for Reporting Qualitative Research (COREQ) checklist.[28]
Figure 1 outlines the two project phases and inscribed actions. The red dot identifies the current advancement status.

[Insert Figure 1 about here]

Phase 1

The first project phase involves production of the ACP booklet (Figure 1).

Provisional booklet

Early in 2020, an inter-disciplinary panel translated into Italian and adapted to the MS context and to the Italian legislation, the ACP booklet of the Health Quality & Safety Commission's New Zealand National ACP Programme (https://www.myacp.org.nz). The panel was made of five neurologists, one palliative care physician, one palliative care nurse, one psychologist, one bioethicist, one expert patient, one representative of the Italian MS Society, and the author of the original booklet. The resulting booklet in its provisional version (online supplemental appendix 2) consists of an introduction, a 'guidance' (the odd pages in most instances) and the advance care plan document (the even pages) to be completed electronically or manually by the pwPMS together with his/her referring physician. A significant other (SO), such as a family member, can participate in the process if requested by the pwPMS. The introduction explains the concepts of ACP and AD according to the Italian Law 219/2017, and describes why ACP is important in MS. Ten sections follow: 'My Advance Care Plan'; 'What matters to me'; 'What worries me'; 'Why I'm

making an Advance Care Plan'; 'How I make decisions'; 'If I were no longer able to make decisions: my trustee'; 'Thinking about my EOL'; 'My treatment and care choices'; 'Signatures'; 'Acronyms'. If the advance care plan document is completed, the pwPMS (and, when applicable, the pwPMS trustee) sign on page 29; the document is then scanned and stored, together with the completed booklet, in the (electronic) medical record.

Users' assessment and revision

Between September and November 2020, the acceptability (contents, format, envisaged administration procedure), comprehensibility and usefulness of the provisional booklet were assessed by conducting 13 personal cognitive interviews with pwPMS, pwPMS' SOs, and a focus group meeting (FGM) with HPs. Due to the COVID-19 pandemic, all the interviews and the FGM were held using digital platforms. Results of the qualitative (thematic) analysis and the revision of the booklet are underway.

Phase 2

The second project phase will be dedicated to the conduction of the multi-center, pilot and feasibility single-arm trial with a nested qualitative study. This phase (to be accomplished from May 2021 to November 2022) has three inscribed actions: intervention set up; pilot trial; and qualitative study (Figure 1).

Intervention set up

Training program - The goal of this intervention is to prime HPs to discuss goals of care and ACP. To achieve this, HPs will attend a training program (called Train-ConCure-SM) that will be Continuing Medical Education accredited, residential, and last one-and-half days (12 hours). The program aims to: improve the HP knowledge, competencies and skills in ACP based on up-to-date scientific evidence; support and guide HPs in the ACP embedment in clinical practice; improve the communication between HPs and patient promoting an effective patient-practitioner partnership in decision-making.

The training will be interactive in style. Its residential nature and the use of role-playing exercises aim at supporting group discussion and the exchange of experiences between participants.

It will consist of the following: one 2.5-hour theoretical session on the clinical, ethical and statutory principles of Shared Decision Making and ACP; two 4-hour empirical sessions (one on each day) on conducting ACP conversations in various clinical scenarios using the ConCure-SM

booklet through guided role play exercises; two 45-minute self-evaluation sessions (at the beginning and at the end of the training program).

Trainees will be physicians and other HPs from the six enrolling centers. The Italian Law 219/2017 prescribes that ACP involves the patient, his/her referring physician, and (when applicable) the trustee. We decided to train HPs other than physicians in order to promote ACP knowledge within the caring team. Each center will provide 1-3 physicians, plus one HP from the following: MS nurse, therapist, psychologist, or social worker. Thus, there will be 12-24 participants overall (2-4 from each center). Trainers will be a panel of neurologists, psychologists, a palliative care physician, a palliative care nurse, and a bioethicist. All have consolidated experience in leading training courses and workshops on patient-clinician communication and Shared Decision Making, and four on ACP and EOL conversations. These four researchers will support physicians at the centers for issues concerning the conduction of the ACP conversation during the pilot trial.

Web platform - As part of the intervention set up action, a web-based trial platform will be created containing the pseudo-anonymized trial case record form (eCRF) and the outcome measures. The platform will be ID/password protected, with dedicated accesses based on the stakeholder (pwPMS, SO, HPs, center principal investigator [PI], interviewer, data manager) and operation (completion, consultation).

Linguistic validation of measures - Two outcome measures not available in Italian will be translated and cross-culturally adapted, following accepted guidelines:[29, 30] the 4-item ACP Engagement questionnaire (4-item ACP-E),[31] and the Quality of Communication Questionnaire (QOC).[32] The main steps in this process are the following:

1) Forward translation. Two qualified translators, both living in Italy, will produce two independent translations. A panel consisting of the translators, two MS HPs and two lay persons will review the forward translations and a consensus version will be produced.

2) Backward translation. The consensus translation generated in step 1 will be independently translated back into the source language by a third qualified translator, living in the target country. The backward translation will be produced without access to the original version and without consulting the other translators.

3) Translation refinement. In a meeting between those participating in step 1 and the backward translator, the backward translation will be compared with the original, and further refinements to the Italian version will be made. Differences will be resolved by discussion.

4) Each translated questionnaire will be proof read, and then administered to/debriefed with 5 to 10 patients.

Pilot and feasibility trial

The six centers involved in the pilot trial are located in northern (four centers), central and southern Italy (one center each). Two of the centers are rehabilitation hospitals (one of which a research hospital), three are MS centers (two university hospitals, one research hospital) and one is a rehabilitation and MS center from a research hospital. Recruitment will be competitive, with no pre-specified minimum number of enrolled subjects per center. The maximum number of enrolled subjects per center is 12.

There will be a baseline assessment (T0), an ACP conversation taking place within one month from the baseline assessment, and a follow-up assessment within one week of the ACP conversation (T1) and six months (T2) thereafter. The baseline and follow-up assessments will be performed via the web-based ConCure-SM platform. The physician will record on the platform subsequent ACP conversations that should occur during follow-up. Participants (pwPMS, SOs) will be free to withdraw from the study at any time, without giving reasons and with no risk of prejudicing future care. Study personnel will make every effort to obtain, and record, information about the drop out reasons.

The objectives of the pilot and feasibility trial are reported in the Box. Trial procedures are summarized in Figure 2.

[Insert Box about here]

Eligibility and screening - PwPMS (in- or outpatients) will be included if they are: ≥18 years of age; diagnosed with primary or secondary PMS [33] one or more years before inclusion; able to communicate in Italian; and gave written consent. In addition, one or more of the following conditions that would make ACP relevant must be present: expressed desire for ACP; questions about own future; thoughts about hastening death or medically assisted suicide; high risk for death within two years using the 'Surprise Question';[34] high risk for development of severe cognitive compromise/dementia within two years; high risk for development of impairments preventing communication within two years; significant suffering (e.g. uncontrolled physical symptoms, psychosocial or existential issues). PwPMS will be excluded if they have one or more of the following: severe cognitive compromise (MMSE < 19) or impairments preventing communication; psychosis or other serious psychiatric conditions; advance care plan document completed.

PwPMS are recruited prospectively by the ACP-trained physicians involved in their care, when the potentially eligible pwPMS attends the center for an outpatient visit or hospitalization. PwPMS who show interest in participating receive full verbal and written information about the study purpose and procedures.

[Insert Figure 2 about here]

Baseline assessment (T0) - The ACP-trained physician makes an appointment with pwPMS who provided initial verbal consent to participate in the study, and checks all eligibility criteria. A written, signed informed consent is obtained, according to the Declaration of Helsinki and to the Good Clinical Practice (GCP) Guidelines of the EU. The informed consent is kept on file by the study personnel, and is available for inspection by regulatory authorities or authorized persons.
Then, the physician gives the pwPMS the credentials to the trial platform, so that the pwPMS completes the baseline set of questionnaires/instruments (completion time around 40 minutes). If the pwPMS has difficulties in using the trial platform, a telephone interview is scheduled within a week with an independent, trained interviewer who will administer the questionnaires/instruments.
The ACP conversation is scheduled at the center, within a month. It is the starting point of a process that is followed-up during the study. However, for feasibility reasons and to adapt to participant needs, subsequent conversations are recorded, but not scheduled a priori. The pwPMS is invited to involve his/her significant other (family member, relative, or friend, who is next of kin or is key decision maker as designated by the pwPMS and with whom the pwPMS shares his/her life). If the pwPMS agrees on involving his/her significant other, the significant other is contacted by a study researcher to confirm eligibility, explain the study and obtain verbal consent. Consenting significant others receive credentials to access the trial platform and complete the baseline set of questionnaires (completion time about 15 minutes). If the significant other has difficulty in using the trial platform, a telephone interview is scheduled within a week with an independent, trained interviewer who will administer the questionnaires.
Finally, the physician completes the eCRF via the trial platform.
Each center will collect information on the number of pwPMS and significant others approached, screened, and eligible prior to enrollment, with reasons for non-enrolment.

The ACP conversation - The conversation involves the pwPMS, the ACP-trained physician involved in his/her care and, when applicable, the significant other. In addition, if the pwPMS agrees, the non-physician ACP-trained HP at the center will participate. The first conversation takes place in a

dedicated room at the center, and is audio-recorded. At MS centers and rehabilitation centers, physician time and space are at premium, particularly for outpatient care. For this reason, one-hour slot is reserved for the conversation. In the case a significant other participates it is envisaged that there will be a session closed to the significant other, followed by an open session.
About one week before the scheduled ACP conversation, reminder emails (or telephone calls) are sent to pwPMS/SOs. At the end of the ACP conversation, the physician invites the pwPMS (when applicable the SO) to complete the T1 follow-up assessment within one week. The physician completes the QOC-Doc immediately after the ACP conversation ends.

Follow-up assessments (T1, T2) - The pwPMS completes the questionnaires by one week (T1, assessment time of about 20 minutes) and six months (T2, assessment time of about 30 minutes) after the first ACP conversation using the trial platform. The significant other completes the questionnaires/instruments (T1, assessment time of about 20 minutes) using the trial platform. In the event the pwPMS/significant other have difficulties in using the trial platform, a telephone interview is scheduled with an independent, trained interviewer who will administer the questionnaires/instruments.
About one week before the T2 assessment, reminder emails (or telephone calls) are sent to pwPMS. The physician completes the questionnaire (T1, QOC-Doc) and the eCRF using the trial platform. He/she records on the platform the date, duration, participants, and mode (face to face, teleconference or on the telephone) of subsequent ACP conversations that occur during follow-up.

Outcome Measures - A range of measures will be collected to capture the full process of ACP and whether the ConCure-SM intervention has any effect on completion of an advance care plan document (primary outcome measure), congruence in treatment preferences between pwPMS and their carers, quality of patient-clinician communication, and caregiver burden (Table 1). In addition, since a study-related increase in emotional burden can't be excluded, serious adverse events (SAE: admission to psychiatric ward, suicide attempt, death) will be monitored by the independent Data and Safety Monitoring Committee (DSMC).
We will use the published Italian version of the following inventories: Control Preference Scale (CPS);[35] Hospital Anxiety and Depression Scale (HADS);[36] Observing Patient Involvement in Decision Making (OPTION);[37] 29-item Multiple Sclerosis Quality of Life (MSQOL)-29;[38] Zarit

Burden Interview (ZBI).[39] The 4-item ACP-E and the QOC inventories will be translated/culturally adapted from source language (see above).

[Insert Table 1 about here]

ACP engagement - The ACP process will be assessed using the 4-item ACP-E questionnaire.[31] Originally developed and validated to measure the complex behavior of ACP, the questionnaire is available in four versions (55-item, 34-item, 9-item, 4-item). In this study, we will use the 4-item version which focuses on the readiness behavior change construct within the quality of life ACP domain. Responses are on a 5-point Likert scale (1 "I have never thought about it"; 2 "I have thought about it, but I am not ready to do it"; 3 "I am thinking about doing it in the next 6 months"; 4 "I am definitely planning to do it in the next 30 days"; 5 "I have already done it").[31]

Role preferences - The CPS is the most used instrument to assess patient preferences for involvement in decisions about their health.[40, 41] It consists of five ''cards'' on a board, each illustrating a different role in decision-making by means of a cartoon and short descriptive statement. In its original version, administration requires a trained examiner, who asks the patient to choose the preferred card, which is then covered up. The procedure continues (four choices) until one card is left. If the second preference is incongruent with the first (non- adjacent pairing, such as card A with card C), the test is explained again, and immediately re-administered. In the event of a further incongruence, the test is not re-administered, and a preference is not assigned. Six scores are possible based on the subject's two most preferred roles: active–active, active–collaborative, collaborative–active, collaborative–passive, passive–collaborative, and passive–passive. These scores are grouped as: active (active–active or active–collaborative), collaborative (collaborative–active or collaborative–passive), or passive (passive–collaborative or passive–passive).[40] We will use the electronic, Italian self-administered CPS (eCPS).[42]

Quality of the conversation – We will assess the quality of the first ACP conversation considering three perspectives: an independent observer, the pwPMS, and the physician. Each conversation will be unobtrusively audio-taped and transcribed verbatim; subsequently a specially trained third observer will evaluate the behavior of the physician in terms of patient involvement in decision-making using the OPTION (http://www.glynelwyn.com/observer-option-instrument.html).[43] The OPTION consists of 12 items, each rated on a five-point Likert scale ranging from 0 (behavior not observed) to 4 (behavior observed to high standard). A total score (range 0–48) is obtained by adding the scores of each item. After the ACP conversation, pwPMS will complete the QOC;[32] Significant others will complete the significant other version (QOC-SO), and physicians the

physician version (last two items) of the QOC. Developed from qualitative studies with patients, families, and clinicians, the QOC consists of 19 items measuring general communication (nine items) and communication about EOL care (eight items), each rated on a scale from 0 ('very worst I can imagine'/'not at all') to 10 ('very best I can imagine'/'extremely'), or identified as something the clinician did not do. The 0/10 ratings are recoded to 1/11, with 0 imputed for 'did not do' (http://depts.washington.edu/eolcare/products/instruments/).

Other outcome measures – PwPMS quality of life will be assessed using the electronic version of the MSQOL-29, which is the shortened form of the MSQOL-54.[38] MSQOL-29 includes 25 items forming 7 subscales and 4 single items, and one filter question for 3 'sexual function' items. Mood symptoms will be assessed with the HADS, a self-assessed questionnaire consisting of 14 multiple-choice (0–3 Likert scale) items probing symptoms of anxiety (7 items) and depression (7 items). HADS anxiety (HADS-A) and depression (HADS-D) scores range from 0 (no symptoms) to 21 (most severe symptoms).[44] A cutoff score of 8 or above was recommended for MS patients, since it was found to be an accurate indicator of major depression (90% sensitivity, 87% specificity) and generalized anxiety disorder (88.5% sensitivity; 81% specificity) in this population.[45] Finally, significant other burden will be assessed using the ZBI,[46] a 22-item self-report measure of subjective burden among caregivers addressing functional and behavioral impairments as well as the home care circumstances. A total 0 (low burden) to 88 (high burden) score is obtained by summing item responses, each scored on a 5-point Likert scale ranging from 0 (never) to 4 (nearly always present).

Meetings - There will be two study meetings (teleconferences): the investigators' meeting will be held before enrolment starts. Participants will be the Steering Committee, the center principal investigators (PIs), and the HPs who participated in the training program. The aim of this meeting is to provide clear information on the study procedures, and to train HPs on the use of the trial platform. A second meeting will be run about two months after enrollment starts, in order to monitor possible difficulties, top up centers' motivation and provide a safe place for peer discussion on the implementation of the intervention. Both meetings will last about two hours. Additional meetings will be organized whenever needed. In addition, the study PIs and the Training Panel will be available for inquiries about the implementation of the intervention at the participating centers.

Nested qualitative study

We will perform one-on-one semi-structured interviews with pwPMS and significant others, chosen using a maximum variation strategy, and FGMs of HPs involved in intervention delivery. For pwPMS and significant others interviews were considered most appropriate to limit interview burden and hopefully make it easier for participants to express their feelings, and recount their experiences of the intervention. For the patient referring physicians and the other HPs we chose FGMs as they promote interaction and exchange of ideas. A minimum of 10 interviews (five with pwPMS and five with significant others) and two FGMs will be held, the final number depending on the achievement of 'data saturation'.[47] Interviews and FGMs will be run via video teleconference, which will ease participation of pwPMS with severe disability and significant others with caregiving commitments, as well as HPs. If the pwPMS and/or significant others have no access to internet using personal computer or other devices, such participants will be interviewed on the telephone.

The interviews aim to provide important feedback on participant perception of the quality of the intervention provided, and will serve as a process measure. Insights from this qualitative analysis will serve to inform fine-grain intervention refinement. They will take place within two months of trial completion, and last no more than an hour. To reduce social desirability response bias, the interviewers will be researchers not involved in the ConCure-SM intervention delivery. Before starting, interviewees will be informed of study aims and requirements, and provide written consent. The interviewer will then explain that the aim of the interview is to obtain participant feedback on experience of the pilot study and stress that positive and negative experiences of, and feelings about, the intervention are welcome. Participants will be assured that the interviews are confidential, and that the audio recordings and subsequent transcripts will be fully anonymized. The interviewer will then pose each question in turn, neutrally (so as to not suggest any particular reply) and in an open-ended fashion (to allow many possible replies). As each question is discussed, follow-up questions will clarify and explore participant responses. Participants will be also encouraged to elaborate on any pertinent themes or views that emerge. The interviewer will note any potentially informative non-verbal gestures. At the end of the interview, the interviewer will verbally summarize the key points and ask the participant if the summary is full and correct.

The *FGMs* aim to collect insights and living experiences about the intervention and to identify possible barriers to its implementation; they will provide important feedback on the intervention

and on factors that can enable its implementation and adoption. For this reason, HPs other than the physicians involved in the ACP conversation will be involved. Each FGM (teleconference) will last about 2 hours; participants will be 6-10 physicians who delivered the intervention and HPs from the participating centers. All participants will provide written informed consent prior to the FGM, that will be conducted by two psychologists specifically trained in qualitative research. One will be the facilitator, whose job is to engage all participants, promote exchange, moderate conflicts, ensure that all pre-specified topics will be adequately covered, and allow exploration of any pertinent issues that arise. He/she will first explain the purpose of the meeting and ask participants to introduce themselves. He/she will then introduce each topic in turn, in an open-ended fashion. At any point the facilitator can probe for further information and ask follow-up questions to stimulate further discussion. After all pre-specified topics are fully discussed, the facilitator will summarize the main points, and ask for further feedback and whether all concerns have been fully aired. The co-moderator will take notes and oversee the audio recording. Subsequently, they will produce a report from the audio recordings/transcript and field notes, which will be submitted to participants for review (respondent validation).

Data analysis

Study power

As this is a pilot and feasibility study, a formal sample size calculation is not required. We aim to recruit at least 40 pwPMS from six centers to assess feasibility across a diverse range of participants including those with different care needs and living conditions. There are no data available on the occurrence of ACP in pwPMS: by hypothesizing a proportion in the pwPMS population of 10%, a sample size of 35 subjects achieves a power of 90%, assuming a type I error of 5%, to detect a proportion of ACP documentation of 30%. By hypothesizing a proportion in the pwPMS population of 8%, a sample size of 35 subjects achieves a power of 95%, assuming a type I error of 5%, to detect a proportion of ACP documentation of 30%. By adding 15% of drop outs or incomplete data, 40 pwPMS should be recruited.

Statistics

Descriptive statistics will be calculated for general and clinical variables. Specifically, continuous variables will be summarized by their mean and SD, or median and interquartile range; categorical variables will be summarized as numbers and percentages. Categorical variables will be compared using the chi-squared test. The normality assumption of continuous variables will be tested with

the Shapiro-Wilk test. Depending on data distribution, between-group comparisons will be carried out using either the two-sided unpaired t-test or the Wilcoxon two sided two sample test; within-group comparisons will be carried out using either the paired t-test or the Wilcoxon signed-rank test; correlations will be computed using Pearson's or Spearman's coefficients.

Our primary end-point is the proportion of pwPMS completing an ACP during the six-month period. Change in the secondary outcome measures will be also calculated. In addition, we will calculate the following feasibility outcomes: recruitment rate (enrollment per month; reasons for non-eligibility, non-enrollment); retention rate (proportion completing the intervention and study follow-up); missing data (proportion fully completed, for each scale, at each time point). Data will be analyzed according to the intention-to-treat principle. Multiple imputation of missing values will employ Rubin's approach. A p-value less than 0.05 will be considered statistically significant. No correction for multiple comparisons will be applied. All analyses will be performed using STATA 16 (College Station, Texas 77845 USA). Assumptions in determining the sample size of the main trial will be checked.

Qualitative data

Interviews and FGMs will be audio-recorded and transcribed verbatim. Data analysis will be conducted by three researchers with experience in qualitative research. Researchers will analyze interviews and FGM data using thematic analysis, with interpretation guided by the four Normalization Process Theory (NPT) components (see process evaluation below). Data will be triangulated across sources. The analytical stages can be summarized as follows:[48] 1) Each researcher will read the transcriptions and write comments and initial thoughts in a memo. 2) Each researcher will extract portions of the text individually and then share their work to reach an initial agreement. During this stage, they will conduct the thematic analysis inductively providing their insights. 3) Researchers will independently review themes and allocate portions of the text to the newly reconfigured themes. 4) Together, they will re-define themes and re-name them to achieve internal consistency. 5) One researcher will extract from the interviews and draft the final report, which will be checked and amended by the other two.

Process evaluation

We will follow the Medical Research Council guidance on process evaluation,[49] which describes three components using a mixed-methods approach: implementation or delivery; mechanisms of impact; contextual factors. We will use NPT to determine if, and in what ways, the ConCure-SM

intervention can be successfully 'normalized' (embedded) into clinical practice.[50, 51] At the feasibility and piloting stage, basic quantitative measures of implementation may be combined with in-depth qualitative data to provide detailed understandings of intervention functioning on a small scale.[49] Quantitative measures will include structured observations of audio recorded ACP conversations. These will be used to examine aspects of fidelity (such as consistency with the Shared Decision Making principles), and dose (the duration of conversations). Qualitative methods will be used to investigate mechanisms of impact and contextual factors, using NPT. NPT identifies four essential determinants of 'normalizing' complex interventions into common practice: *coherence* (the extent to which an intervention is understood as being meaningful, achievable and valuable); *cognitive participation* (the engagement of HPs necessary to deliver the intervention); *collective action* (the work that brings the intervention into use); and *reflexive monitoring* (the on-going process of adjusting the intervention to keep it in place).[51] These components are considered to be dynamic and interact within the wider context of the intervention, such as existing organizational structures and procedures.[51] Further, we will use qualitative data to identify required modifications and to develop practical strategies for enabling and sustaining intervention delivery in clinical settings.

Patient and public involvement statement

An expert MS patient and a representative of the Italian MS Society are part of SC of the project and co-authors of the present paper. These same persons were part of the inter-disciplinary panel that produced the ACP booklet, which was revised based on the results of a qualitative study with users (pwPMS, SOs and HPs).

Prior to designing and conducting a full trial, the intervention will be pilot tested in a multicenter study involving MS and rehabilitation centers across Italy, and using a mixed-method approach. We will disseminate key study findings to pwPMS via the Italian MS Society.

Ethics and dissemination

The project is co-leaded by a neurologist and a bioethicist. Phase 1 has received ethical approvals from each participating center, while phase 2 will be submitted to the centers in May 2021. Findings from both phases will be disseminated widely through peer-reviewed publications, conferences and workshops. Authorship eligibility will be based on The International Committee of Medical Journal Editors. The final trial (pseudo-anonymized) dataset will be accessed by the study principal investigators and the data management/analysis team. Details about panels and centers,

ethics and administrative considerations, and study management and monitoring are available in the online supplemental appendix 3.

DISCUSSION

One of the 10 clinical questions of the EAN guideline on palliative care of pwPMS specifically addressed ACP.[17] For this clinical question, formulated with direct patient and caregiver involvement,[52] no evidence was found and two good practice statements were produced: “It is suggested that early discussion of the future with ACP is offered to patients with severe MS”; “It is suggested that regular communication about the future progression of MS is undertaken with patients and families/caregivers”.[17] To fill this knowledge gap, we conceived the present study, which adheres to the Shared Decision Making model,[12-14] and to the Medical Research Council framework for developing and evaluating complex interventions.[24] Within this methodological context, the study follows the CONSORT guidance for trials on social and psychological interventions (CONSORT-SPI 2018),[27] as many of the guidance items (excluding items that are specific to the randomization nature of the study) are relevant for reporting other types of pilot and feasibility studies.[53] This includes the development of the study protocol following the SPIRIT guidance,[26] protocol’s publication, and the trial public registration (ISRCTN registry). The consolidated criteria for reporting qualitative research will guide the presentation of findings in the study reports and publications.[28, 54]

To increase generalizability of the study, participants (pwPMS, significant others, and HPs) will be enrolled from university hospitals, research hospitals and clinical centers from the different areas of Italy. We will not enroll from primary care practices as in Italy MS patients are followed in tertiary care centers. Moreover, previous attempts to involve the family physicians in the care of PwPMS were challenging.[55]

Personal, semi-structured interviews and FGMs will be run via video teleconference, which will ease participation of pwPMS with severe disability and significant others with caregiving commitments, as well as HPs. If pwPMS and/or significant others have no internet access, using personal computer or other devices, these participants will be interviewed on the telephone.

Other measures adopted to minimize bias include: all study personnel will be trained to conform to GCP regulation; electronic version of the study questionnaires/inventories will be used to ensure the data entered is of high quality; an IDSMC will monitor and supervise the progress of the trial, and the safety data.

The ConCure-SM intervention (booklet and HP training program) can be adapted for use in other neurological and non-neurological conditions for which consolidated ACP interventions are not available. The electronic format will ease the incorporation of the advance care plan document (and its updates) in the electronic medical record, that is currently available in some Italian regions and hopefully will be soon available all over Italy.

Study limitations

Three study limitations are noted. We used a single arm design for the pilot trial. This decision was taken as ACP is currently at premium in MS,[17,23] and designing a randomized (cluster) trial with standard care or any 'low intensity' intervention as a comparator was considered ethically and practically unviable. Another limitation is that our training program was for HPs only. A multiple-component intervention that targets clinicians and patients simultaneously has been suggested in other disciplines.[56] In the current situation regarding ACP, we preferred to have a clear focus on enhancing HP competencies.[17, 23] Finally, our pilot trial lacks long-term outcomes, chiefly the concordance between preferred and received EOL care and treatments.[57] However, the MS trajectory further challenges the collection of this outcome in the typical timeframe of a clinical trial. In line with the principles of ACP, we agreed not to narrow the inclusion criteria only to pwPMS in the late stage of the disease, deserving this relevant outcome to future studies.

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ConCure-SM Steering Committee: LDP, SV, MB, MC, MGG, PK, AL, SM, FP, EP, CS, AGi, AS. *Data Safety and Monitoring Committee*: Kevin Brazil, School of Nursing and Midwifery, Queen's University of Belfast, Belfast, Northern Ireland, UK; Bobbie Farsides, Brighton & Sussex Medical School, Falmer, Brighton, United Kingdom; Luciano Orsi, The Italian Society of Palliative Care (SICP), Milan, Italy; Carlo Peruselli, SICP, Milan, Italy; and David Oliver, The Tizard Centre,

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AUTHOR CONTRIBUTIONS

LDP, SV, and AS conceived and developed the study protocol. LDP, SV, MB, MC, AG, MGG, PK, AL, LM, SM, FP, EP, CS, AG, and AS contributed to the refinement of the study protocol. LDP, SV, and AS drafted the manuscript. LDP, SV, MB, MC, AG, MGG, PK, AL, LM, SM, FP, EP, CS, AG, and AS approved the final manuscript.

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COMPETING INTERESTS STATEMENT

AL reports grants from Novartis, during the conduct of the study; personal fees from Biogen, Merck Serono, Mylan, Novartis, Roche, Sanofi/Genzyme, Teva and FISM. FP received personal compensation for serving on advisory board and/or speaking activities by Almirall, Bayer, Biogen, Bristol Meyers & Squibb, Merck, Novartis Roche, Sanofi and TEVA; he further received research grants by Biogen Italy, Biogen Global, Merck, University of Catania, FISM and Reload Onlus Patients Association. AS reports grants from FISM and European Academy of Neurology, during the conduct of the study; personal fees from Almirall and Merck Serono. This does not alter our adherence to BMJ Open policies on sharing data. All the other authors report no competing interests.

DATA STATEMENT SECTION

Data will be available at: https://zenodo.org/communities/besta/.

FIGURE LEGENDS

Figure 1. Flow chart of the ConCure-SM project. The red dot identifies the advancement status at the time of manuscript submission. FGM, focus group meeting; HP, health professional; MS, multiple sclerosis; NPT, normalization process theory; PwPMS, people with progressive MS; SO, significant other.

Figure 2. Summary of trial procedures. ACP, Advance Care Planning; ACP-E, ACP Engagement; eCPS, Control Preference Scale, electronic; EDSS, Expanded Disability Status Scale; HADS, Hospital Anxiety and Depression Scale; MSQOL-29, 29-item Multiple Sclerosis Quality of Life; OPTION, Observing Patient Involvement in Shared Decision Making; QOC, Quality of Communication; SO, significant other; ZBI, Zarit Burden Interview.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444-52.

Mahoney FI, Barthel D. Functional evaluation: The Barthel Index. *Maryland State Med Journal* 1965; 14: 56-61.

REFERENCES

1. Browne P, Chandraratna D, Angood C, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology* 2014; 83(11): 1022-4.
2. Filippi M, Bar-Or A, Piehl F, et al. Multiple Sclerosis. *Nat Rev Dis Primers* 2018; 4: 43.
3. Kingwell E, van der Kop M, Zhao Y, et al. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. *J Neurol Neurosurg Psychiatry* 2012; 83: 61–6.
4. Scalfari A, Knappertz V, Cutter G, et al. Mortality in patients with multiple sclerosis. *Neurology* 2013; 81: 184–92.
5. Lunde HMB, Assmus J, Myhr K-M, Bø L, Grytten N. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. *J Neurol Neurosurg Psychiatry* 2017; 88: 621–5.
6. Chiaravalloti ND, De Luca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol* 2008; 7: 1139–51.
7. Higginson IJ, Hart S, Silber E, Burman R, Edmonds P. Symptom prevalence and severity in people severely affected by multiple sclerosis. *J Palliat Care* 2006; 22: 158–65.
8. Hirst C, Swingler R, Compston DA, et al. Survival and causes of death in multiple sclerosis: a prospective population-based study. *J Neurol Neurosurg Psychiatry* 2008; 79: 1016-21.
9. Sumelahti ML, Hakama M, Elovaara I, et al. Causes of death among patients with multiple sclerosis. *Mult Scler* 2010; 16: 1437-42.
10. Giordano A, Ferrari G, Radice D, et al. on behalf of the POSMOS study. Health-related quality of life and depressive symptoms in significant others of people with multiple sclerosis: A community study. *Eur J Neurol* 2012; 19: 847-54.
11. Rietjens JAC, Sudore RL, Connolly M, et al. Definition and recommendations for advance care planning: an international consensus supported by the European Association for Palliative Care. *Lancet Oncol* 2017; 18(9): e543-e551.
12. Archer J, Stevenson L, Coulter A, Breen AM. Connecting patient experience, leadership, and the importance of involvement, information, and empathy in the care process. *Healthc Manage Forum* 2018; 31(6): 252-5.
13. Coulter A, Collins A. Making shared decision-making a reality. London, United Kingdom: King's Fund. 2011. Available at: https://www.kingsfund.org.uk/publications/making-shared-decision-making-reality. Accessed March 14, 2020.

14. Elwyn G, Frosch D, Thomson R, et al. Shared decision making: a model for clinical practice. *J Gen Intern Med* 2012; 27: 1361-7.
15. Forte DN, Kawai F, Cohen C. A bioethical framework to guide the decision-making process in the care of seriously ill patients, *BMC Medical Ethics* 2018; 19: 78.
16. De Panfilis L, Giorgi Rossi P, Mazzini E, et al. Knowledge, opinion and attitude about the Italian law on Advance Directives: a population-based survey. *J Pain Symptom Manage* 2020: S0885-3924(20)30561-3.
17. Solari A, Giordano A, Sastre-Garriga J, et al. EAN guideline on palliative care of people with severe, progressive multiple sclerosis. *Eur J Neurol* 2020; 27(8): 1510-29.
18. Brinkman-Stoppelenburg A, Rietjens JAC, van der Heide A. The effects of advance care planning on end-of-life care: A systematic review. *Palliat Med* 2014; 28(8): 1000–25.
19. Golla H, Galushko M, Strupp J, et al. Patients feeling severely affected by multiple sclerosis: addressing death and dying. *Journal of Death & Dying* 2016; 74(2): 275–91.
20. Golla H, Mammeas S, Galushko M, Pfaff H, Voltz R. Unmet needs of caregivers of severely affected multiple sclerosis patients: A qualitative study. *Palliat Support Care* 2015; 13(6): 1685–93.
21. Walter HAW, Seeber AA, Willems DL, de Visser M. The role of palliative care in chronic progressive neurological diseases-a survey amongst neurologists in the Netherlands. *Front Neurol* 2019; 14; 9: 1157.
22. McCurry MK. An exploratory study of decision making by informal caregivers of individuals with multiple sclerosis. *J Neurosci Nurs* 2013; 45(1): 52–60.
23. Cottrell L, Economos G, Evans C, et al. A realist review of advance care planning for people with multiple sclerosis and their families. *PLoS ONE* 2020; 15(10): e0240815.
24. Craig P, Dieppe P, Macintyre S, et al. Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008; 337: a1655.
25. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ* 2013; 346: e7586.
26. Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. *JAMA* 2018; 319(5): 483–94.
27. Grant S, Mayo-Wilson E, Montgomery P. CONSORT-SPI 2018 Explanation and Elaboration: guidance for reporting social and psychological intervention trials. *Trials* 2018; 19: 406.

28. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32 item checklist for interviews and focus groups. *Int J Qual Health Care* 2007; 19(6): 349–57.
29. Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. *J Clin Epidemiol* 1993; 46: 1417–32.
30. Wild D, Eremenco S, Mear I, et al. Multinational trials-recommendations on the translations required, approaches to using the same language in different countries, and the approaches to support pooling the data: the ISPOR Patient-Reported Outcomes Translation and Linguistic Validation Good Research Practices Task Force report. *Value Health* 2009; 12(4): 430-40.
31. Sudore RL, Heyland DK, Barnes DE, et al. Measuring advance care planning: Optimizing the Advance Care Planning Engagement Survey. *J Pain Symptom Manage* 2017; 53(4): 669-81.
32. Engelberg R, Downey L, Curtis JR. Psychometric characteristics of a quality of communication questionnaire assessing communication about end-of-life care. *J Palliat Med* 2006; 9(5): 1086-98.
33. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology* 1996; 46: 907–11.
34. Downar J, Goldman R, Pinto R, Englesakis M, Adhikari NKJ. The “surprise question” for predicting death in seriously ill patients: a systematic review and meta-analysis. *CMAJ* 2017; 189 (13): E484–93.
35. Giordano A, Mattarozzi K, Pucci E, et al. Participation in medical decision-making: Attitudes of Italians with multiple sclerosis. *J Neurol Sci* 2008; 275: 86–91.
36. Costantini M, Musso P, Viterbori F, et al. Detecting psychological distress in cancer patients: validity of the Italian version of the Hospital Anxiety and Depression Scale. *Support Care Cancer* 1999; 7: 121–7.
37. Goss C, Fontanesi S, Mazzi MA, Del Piccolo L, Rimondini M. The assessment of patient involvement across consultation. The Italian version of the OPTION scale. *Epidemiol Psichiatr Soc* 2007; 16: 339–49.
38. Rosato R, Testa S, Bertolotto A, et al. eMSQOL-29: Prospective validation of the abbreviated, electronic version of MSQOL-54. *Mult Scler* 2019; 25(6): 856-66.
39. Chattat R, Cortesi V, Izzicupo F, et al. The Italian version of the Zarit Burden Interview: a validation study. *Int Psychogeriatr* 2010; 16: 1-9.
40. Degner LF, Sloan JA, Venkatesh P. The control preference scale. *Can J Nurs Res* 1997; 29: 21–43.

41. Kryworuchko J, Stacey D, Bennett C, Graham ID. Appraisal of primary outcome measures used in trials of patient decision support. *Patient Educ Couns* 2008;73: 497–503.
42. Solari A, Giordano A, Kasper J,et al; AutoMS project. Role preferences of people with multiple sclerosis: Image-revised, computerized self-administered version of the Control Preference Scale. *PLoS One* 2013; 8(6): e66127.
43. Elwyn G, Hutchings H, Edwards A, et al. The OPTION scale: measuring the extent that clinicians involve patients in decision-making tasks. *Health Expect* 2005; 8: 34–42.
44. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; 67: 361–70.
45. Honarmand K, Feinstein A. Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. *Mult Scler* 2009; 15: 1518–24.
46. Hérbert R, Bravo G, Préville M. Reliability, validity, and reference values of the Zarit Burden Interview for assessing informal caregivers of community-dwelling older persons with dementia. *Canadian Journal on Aging* 2000; 19: 494-507.
47. Denzin NK, Lincoln YS. Handbook of qualitative research. London, UK: Sage Publications; 2000.
48. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006; 3:77–101.
49. Moore G, Audrey S, Barker M, et al. Process evaluation of complex interventions: Medical Research Council guidance. London: MRC Population Health Science Research Network; 2014. 7.
50. Murray E, Treweek S, Pope C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. *BMC Med* 2010; 8(1): 63.
51. May CR, Cummings A, Girling M, et al. Using Normalization Process Theory in feasibility studies and process evaluations of complex healthcare interventions: a systematic review. *Implement Sci* 2018;13(1):80.
52. Kopke S, Giordano A, Veronese S, et al. Patient and caregiver involvement in formulation of guideline questions: findings from the EAN guideline on palliative care of people with severe multiple sclerosis. *Eur J Neurol* 2019; 26(1): 41–50.
53. Lancaster GA, Thabane L. Guidelines for reporting non-randomised pilot and feasibility studies. *Pilot and Feasibility Studies* 2019; 5: 114.
54. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. *Acad Med* 2014; 89(9): 1245–51.

55. Giovannetti AM, Borreani C, Bianchi E, et al; PeNSAMI project. Participant perspectives of a home-based palliative approach for people with severe multiple sclerosis: A qualitative study. *PLoS One* 2018; 13(7): e0200532.

56. Schichtel M, Wee B, Perera R. Clinician-targeted interventions to improve advance care planning in heart failure: a systematic review and meta-analysis. *Heart* 2019; 105: 1316–24.

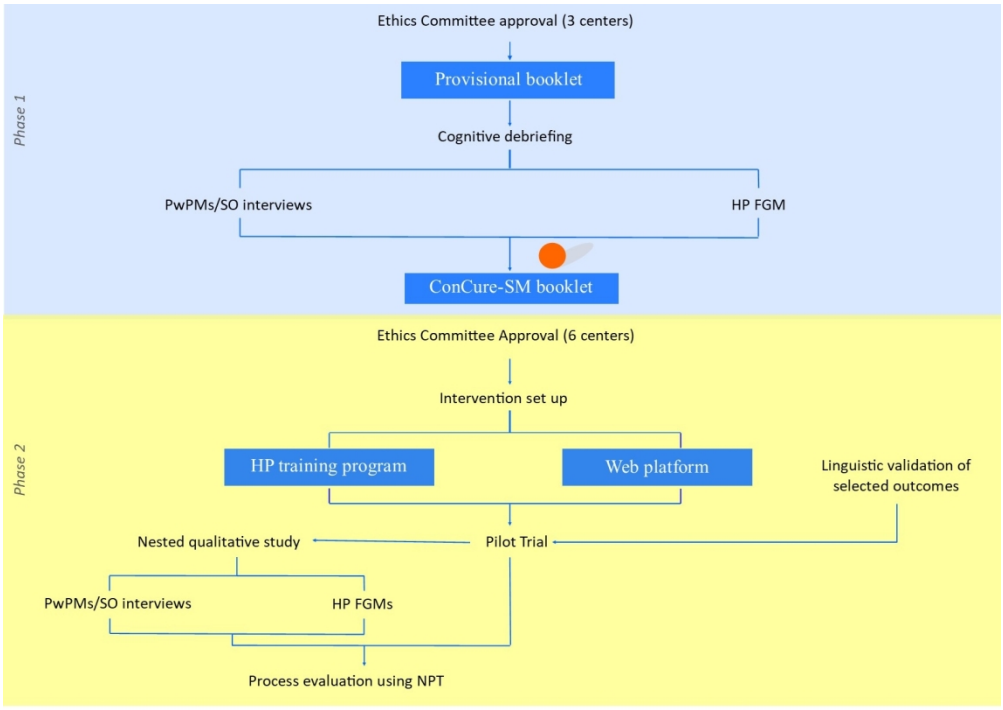
57. Higginson IJ, Evans CJ, Grande G, et al. Evaluating complex interventions in End of Life Care: the MORECare Statement on good practice generated by a synthesis of transparent expert consultations and systematic reviews. *BMC Medicine* 2013, 11: 111.

Box. Objectives of the pilot trial.

1. To determine how many people with progressive multiple sclerosis (pwPMS) accept the invitation to participate in the study
2. To determine how many participants receive the intervention
3. To estimate recruitment and refusal rates, and 6-month follow-up rates
4. To estimate advance care planning (ACP) completion during the 6-month follow-up (primary study outcome)
5. To estimate occurrence of serious adverse events and adverse events during the 6-month follow-up
6. To assess, qualitatively, the acceptability of the recruitment processes, assessments, intervention delivery and secondary outcome measures with key stakeholders
7. To measure changes in the secondary outcome measures
8. To explore the barriers and facilitators to implementing ACP in pwPMS, and the influence of the clinical setting
9. To inform the sample size estimation for a subsequent phase III trial, should this be feasible

Table 1. Secondary outcome measures of the trial (in alphabetical order). ACP-E, Advance Care Planning Engagement; eCPS, Control Preference Scale, electronic; HADS, Hospital Anxiety and Depression Scale; MSQOL-29, 29-item Multiple Sclerosis Quality of Life; OPTION, Observing Patient Involvement in Shared Decision Making; QOC, Quality of Communication; SO, significant other; ZBI, Zarit Burden Interview.

Scale name	*Assessor*	*Construct*	*Author*	*Italian version*	*Timing*
4-item ACP-E	Patient	ACP engagement	Sudore 2017	–	T0/T1/T2
eCPS	Patient	Role preferences	Degner 1997	Solari 2013	T0
HADS	Patient	Mood symptoms	Zigmond 1983	Costantini 1999	T0/T1/T2
MSQOL-29	Patient	Health-related QOL	Rosato 2019	Rosato 2019	T0/T2
OPTION	Third observer	Shared Decision Making (physician's kills)	Elwyn2005	Goss 2007	–
QOC	Patient	Communication quality (physician's skills)	Engelberg 2006	–	T1
QOC-Doc	Physician	Communication quality (physician's skills)	–	–	T1
QOC-SO	SO	Communication quality (physician's skills)	–	–	T1
ZBI	SO	Caregiver burden	Hérbert 2000	Chattat 2010	T0/T1/T2



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Eligible pwPMS:
- ► Age ≥ 18 years
- ► At least one out of seven conditions that would make ACP relevant
- ► Able to communicate in Italian
- ► Adequate cognitive and communicative ability to participate
- ► No serious psychiatric conditions
- ► No previous advance care plan document completed

Participant screening:
- ► Confirm eligibility
- ► Obtain name/contact of significant other (if applicable) and permission to contact

Baseline assessment (T0):

PwPMS
- ► HADS
- ► eCPS
- ► 4-item ACP Engagement
- ► MSQOL-29

Significant other
- ► General data
- ► ZBI

Physician
- ► PwPMS general and clinical data (EDSS [Kurtzke 1983], Barthel Index [Mahoney 1965])
- ► Physician's general data

First ACP conversation: ► OPTION scale (physician's competences)

Follow-up assessment (T1):

PwPMS
- ► HADS
- ► QOC
- ► 4-item ACP

Significant other
- ► ZBI
- ► QOC-SO

Physician
- ► QOC-Doc

Follow-up assessment (T2):

PwPMS
- ► HADS
- ► 4-item ACP Engagement
- ► MSQOL-29

Significant other
- ► ZBI

Physician
- ► PwPMS clinical/ACP update

BMJ Open

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

Ludovica De Panfilis, Simone Veronese, Michela Bruzzone, Marta Cascioli, Alberto Gajofatto, Maria Grazia Grasso, Paola Kruger, Alessandra Lugaresi, Leigh Manson, Sara Montepietra, Francesco Patti, Eugenio Pucci, Claudio Solaro, Andrea Giordano, Alessandra Solari

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ONLINE SUPPLEMENTAL APPENDIX 1 – SPIRIT CHECKLIST; DSMC CHARTER

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.

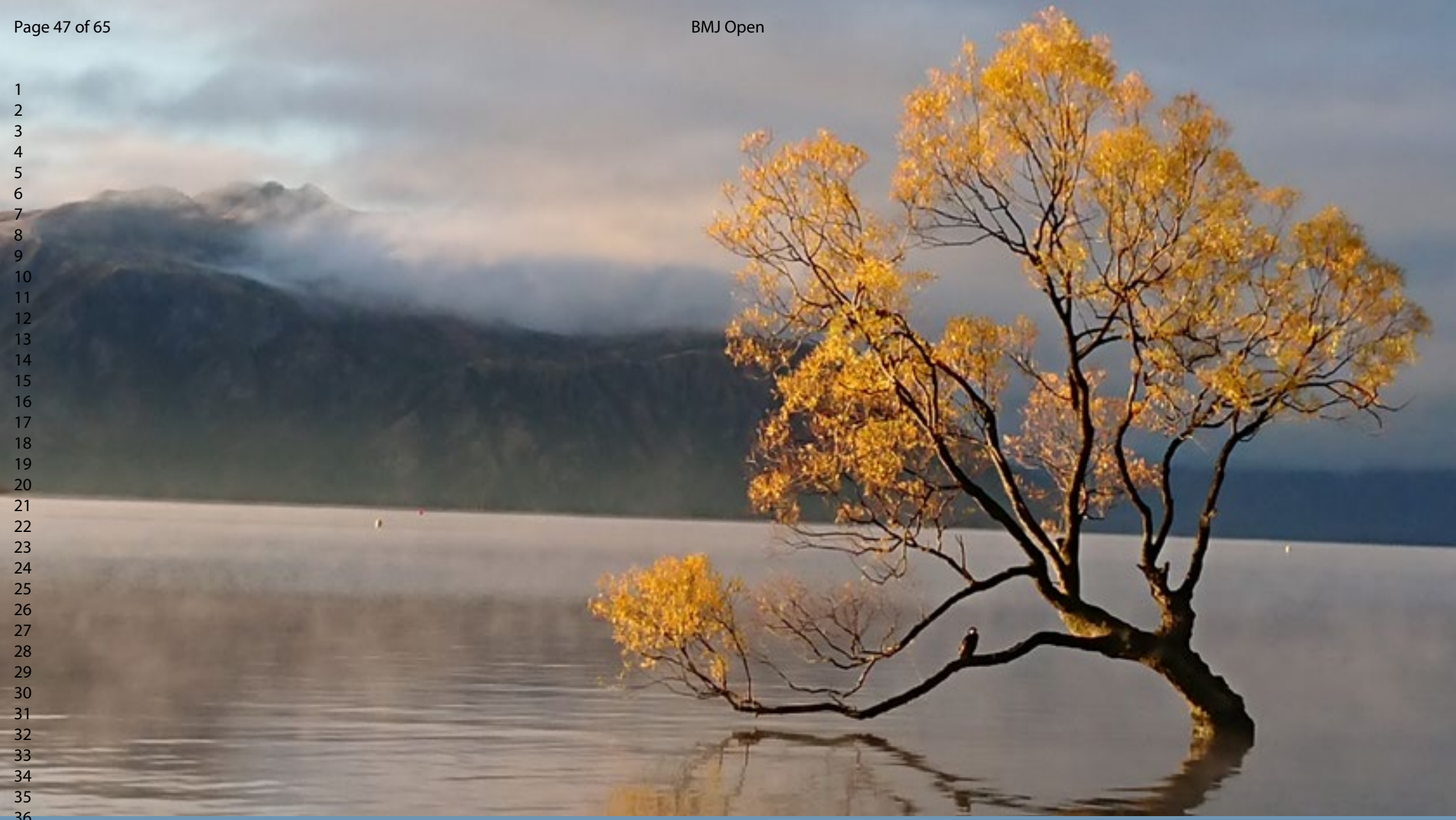
9. Reporting	
To whom will the DSMC report their recommendations/decisions, and in what form	The DSMC will report in writing to the SC, usually within three weeks of a meeting being held.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	Meeting minutes need not be 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



La mia pianificazione condivisa delle cure

Le mie scelte di cura rispetto alla mia salute e al fine vita

È importante quello che tu pensi, ciò in cui credi, quello che vorresti accadesse, o non accadesse, nel corso della tua vita. Se ne parli con i tuoi cari, con le persone importanti per te, con gli operatori sanitari, con chi pensi che ti sarà vicino quando il tuo stato di salute sarà compromesso, sarà più facile per tutti aiutarti nelle decisioni che riguardano la tua vita.

Se però vuoi assicurarti che le tue preferenze vengano rispettate ed abbiano un valore vincolante, devi metterle per iscritto o videoregistrarle. Questo permetterà ai medici di consultarle e di comportarsi in modo da soddisfare i tuoi desideri.

La legge italiana 219/2017 prevede la possibilità di fare delle scelte per situazioni future tramite due differenti modalità. La prima è rivolta a chi sta bene e non ha una malattia progressiva, ma desidera esprimersi rispetto a scelte di cura future, nell'ipotesi in cui perdesse la capacità di decidere o di esprimersi, e si chiama Disposizioni Anticipate di Trattamento (DAT). Le DAT possono essere redatte da qualunque cittadino adulto, adeguatamente informato e capace di decidere. Nelle DAT il cittadino può indicare le sue preferenze e volontà rispetto ai trattamenti sanitari che desidera, o non desidera ricevere, e stabilire se è disposto ad accettare condizioni come l'intubazione, la nutrizione "artificiale", la respirazione meccanica e così via. Le DAT devono essere depositate presso il comune di residenza o presso un notaio. Entrambi si occuperanno di trasmettere il documento ad un registro nazionale consultabile dai medici che entrano in contatto con il cittadino.

La seconda modalità si chiama Pianificazione Condivisa delle Cure (PCC), riguarda chi ha una malattia progressiva, che nel tuo caso è la sclerosi multipla (SM), e viene redatta insieme al proprio medico di fiducia (per esempio il neurologo, il palliativista o il medico di medicina generale). La PCC è un documento che permette al paziente di pianificare le scelte di cura in modo graduale rispetto all'andamento della sua malattia. Essa viene registrata nella cartella clinica o, nelle regioni in cui è attivo, nel fascicolo sanitario elettronico, in modo da poter essere condivisa tra tutti i sanitari che si prendono cura della persona malata. Una copia del documento di PCC rimane al paziente, che potrà conservarla nella sua documentazione sanitaria.

In entrambi i casi la nostra Legge prevede che si possa nominare un fiduciario, ovvero una persona di fiducia che rappresenterà e farà le veci del paziente nelle relazioni con il personale di cura e con le strutture sanitarie, nel caso in cui la persona malata perdesse la capacità di decidere (a causa del peggioramento della malattia, per la comparsa di un evento acuto, o un incidente) e i medici dovessero prendere una decisione importante sulle terapie da iniziare (o non iniziare, o sospendere). In questa evenienza, il fiduciario potrà partecipare alla decisione discutendone con i medici, portando il punto di vista del paziente e le sue preferenze. Si può anche scegliere più di un fiduciario, anche perché non è possibile sapere se la persona identificata in questo compito sarà necessariamente disponibile al momento del bisogno, ma dovrà essere chiaro un ordine di preferenza, per evitare che insorgano contrasti tra i fiduciari rispetto alle scelte. È auspicabile che una copia della PCC sia consegnata anche al fiduciario.

Sia le DAT che la PCC possono essere riviste, ripensate e ridiscusse nel corso del tempo. Questo perché le preferenze e la visione della vita possono cambiare, così come la scelta della persona che si vuole indicare come fiduciario.

Per questo è importante aggiornare regolarmente la PCC, per ripensare alle scelte e ridiscuterle con il medico curante e gli altri professionisti sanitari.

Questo opuscolo è destinato alla persona con SM che desidera redigere la propria PCC. A fianco del **documento di PCC** è presente una **guida** che ha lo scopo di facilitare la compilazione, che deve sempre avvenire attraverso una discussione e condivisione con il proprio medico di fiducia. La guida ti aiuterà a pensare e ad esprimerti su:

- Cosa è importante per te adesso
- Come desideri prendere le decisioni
- Che tipo di assistenza e di cure vorresti per il futuro
- Come vorresti essere assistito alla fine della tua vita

Non devi necessariamente riempire tutti gli spazi di compilazione del **documento di PCC**, ma solo le parti che ti interessano. Ciò che deve essere compilato in ogni parte è la sezione "Firme".

Questo spazio è a tua disposizione per descrivere le tue idee, i tuoi valori, la tua visione della vita e del tuo futuro.

In questo spazio puoi scrivere le tue domande sulle scelte per il futuro, le cure o altre scelte per le quali necessiti di risposte da parte dei medici o di chi si prende cura di te:

La SM è una malattia cronica, caratterizzata da una riduzione variabile dell'aspettativa di vita (tra 7 e 14 anni) rispetto alla popolazione generale, e da un decorso altrettanto variabile. Nella forma progressiva di malattia, i sintomi e le limitazioni funzionali coinvolgono, in modo e con gravità variabile, diversi aspetti, come l'autonomia nei movimenti, la vista, il controllo degli sfinteri, la capacità di alimentarsi, di comunicare, e le funzioni mentali. Questi disturbi possono stabilizzarsi anche per lunghi periodi, permettendo un adattamento personale ed una qualità della vita accettabili, se non soddisfacenti. Ulteriori peggioramenti, come la comparsa di complicanze o di altri problemi di salute e le mutate condizioni familiari che possono verificarsi rendono più difficoltoso questo adattamento continuo. Può accadere di dover condividere la scelta di ricorrere, talvolta in emergenza, a trattamenti di supporto vitale per evitare la morte. Questi trattamenti sono, ad esempio, la tracheostomia (che consente la respirazione facendo passare l'aria direttamente in trachea attraverso un foro chirurgico praticato alla base del collo), oppure la gastrostomia percutanea o PEG (che consente l'alimentazione attraverso un foro chirurgico praticato nell'addome). I trattamenti di supporto vitale possono assicurare anni di vita, tuttavia possono causare ulteriori sofferenze. È utile interrogarsi per tempo sul significato personale di una qualità di vita accettabile.

Lo scopo della PCC è di condividere col proprio medico di fiducia e riportare per iscritto le decisioni rispetto alle scelte terapeutiche ed assistenziali che potranno essere necessarie nel corso della malattia.

Essa costituisce uno strumento vincolante rispetto a queste specifiche decisioni ed aiuterà i tuoi curanti e i tuoi cari a prendere le decisioni qualora tu non potessi più esprimerle.

Questa PCC è tua, ma potrai modificarla in accordo con il tuo medico di fiducia ogni volta che vorrai, avendo cura di condividere il nuovo piano anche con il tuo fiduciario che potrà avere la possibilità di confermare il suo ruolo o meno, a seconda delle indicazioni e preferenze che indicherai.

Contenuti:

1. La mia pianificazione condivisa delle cure

Questa è la mia Pianificazione Condivisa delle Cure e contiene le mie scelte.

Per favore, seguitela qualora non fossi più in grado di esprimere quello che desidero:

Nome _____ **Cognome** _____

Nato/a il: _____ **a:** _____

Indirizzo: _____

_____

Telefono: _____

E-mail _____

2. Cosa è importante per me

Alcune domande che possono aiutarti a definire cosa sia importante per te:

- Cosa ti rende felice?
- Cosa ti reca piacere e gioia?
- Che cosa ti piace fare?
- Quali sono i tuoi hobby e i tuoi interessi?
- Ci sono delle abitudini alle quali sei affezionato?
- Che cosa dà senso alla tua giornata?
- Con chi ti piace trascorrere il tempo?
- Hai principi spirituali, religiosi, o riti che sono importanti per la tua vita?

Ecco alcune altre cose che potrebbero essere importanti o significative per te:

- Parlare e stare vicino alle persone
- Renderti conto di chi sei e dove ti trovi
- Sentire l'amore e l'affetto degli altri
- Vivere esperienze significative
- Avere vicino il cane o l'animale di compagnia
- Partecipare al culto della mia religione
- Sentirti attivo culturalmente
- Contribuire al bene della società
- Sentire che qualcuno ti abbraccia e ti tiene per mano
- Mantenere il più possibile l'autonomia
- Avere momenti di intimità o sessualità

Questo è ciò che voglio che i miei curanti ed i miei cari sappiano di me, e di cosa è importante per me:

Questi sono i valori culturali, spirituali, religiosi e i riti importanti per me:

Per onorare questi valori desidero che i miei curanti e i miei cari:

3. Cosa mi preoccupa

Ci sono cose che ti preoccupano quando pensi al tuo futuro?

Per esempio, ti preoccupi quando pensi:

- Che la tua salute potrà compromettere le tue scelte
- Che la tua salute potrà causare problemi ai tuoi cari
- Dove sarai assistito in futuro
- Di provare dolore o sofferenza
- Di non essere più in grado di comunicare
- Di perdere la capacità di ragionare
- Di essere di peso per gli altri
- Di venire ricoverato in struttura
- Di morire da solo
- Di come le persone che ami possano andare avanti senza di te
- Di rimanere bloccato in un letto
- Che le tue scelte non siano rispettate
- Che i tuoi valori non siano considerati
- Di avere problemi economici

Questo è ciò che voglio che i miei curanti e i miei cari sappiano rispetto a ciò che mi preoccupa:

Segna le caselle corrispondenti

☐ **Soffrire. La sofferenza per me significa:**

☐ **Non poter comunicare, ad esempio:**

☐ **Non poter far cose, ad esempio:**

☐ **Mi preoccupo per i miei cari perché:**

☐ **Altre cose che mi preoccupano:**

4. Perché voglio fare una Pianificazione Condivisa delle Cure

Alcune cose a cui pensare:

- Come è stato l'andamento della tua SM e della tua salute in generale nell'ultimo anno?
- Il tuo stato di salute ti limita fortemente in attività che sono importanti per te?
- Sei aiutato e sostenuto da familiari e più in generale da persone care?
- Sei di aiuto e sostegno a familiari e persone care?

Per comprendere meglio che impatto potrà avere il tuo stato di salute sul tuo futuro, parlane con i professionisti sanitari che si prendono cura di te.

Per esempio, potresti chiedere loro: Se la mia SM dovesse peggiorare...

- Che livello di indipendenza potrò avere?
- Cosa è bene/giusto pianificare ora?
- Cosa accadrà al mio corpo e alla mia mente?
- Che impatto potrebbe avere il mio stato di salute sulle persone che si prendono cura di me?

Ecco perché voglio fare una PCC:

Se penso al mio futuro mi viene in mente:

Se penso al mio futuro mi sento:

Se il tempo davanti a me fosse breve allora vorrei:

5. Come prendo le decisioni

Pensa alle decisioni che potresti dover prendere nel corso della malattia.

Pensa a come sei abituato a prendere le decisioni.

Hai bisogno di tempo? Ti piace essere molto informato sulle possibilità di scelta, o preferisci che siano altri a decidere per te?

Hai mai pensato che nella vita possano verificarsi eventi improvvisi, come incidenti o eventi acuti, in cui debbano essere prese rapidamente delle decisioni importanti?

Chi vorresti che decidesse per te, se tu non fossi in grado di farlo?

Ricorda che, qualora non fossi più in grado di esprimerti, altri dovranno decidere per te. Prenditi dunque del tempo per pensare e per parlare di questo con le persone che ti sono vicine.

Se decidi di nominare una persona come tuo fiduciario, perché pensi che possa rappresentare adeguatamente il tuo punto di vista nelle decisioni che riguardano la tua salute, potrebbe essere il momento giusto per farlo. Potrai revocare questa scelta in ogni momento. Il tuo fiduciario deciderà per te solo in caso tu non possa esprimere la tua preferenza.

Rispondendo a ciascuna delle affermazioni riportate di seguito potrai chiarire meglio le tue preferenze relative alle scelte di cura che ti riguardano.

Segna la casella che più corrisponde alla tua preferenza

Voglio avere...

Solo le informazioni strettamente necessarie	☐ ☐ ☐ ☐ ☐	Tutti i dettagli sulla mia malattia e le terapie

Voglio che i miei curanti...

Facciano quello che pensano sia meglio per me	☐ ☐ ☐ ☐ ☐	Mi consentano di dire la mia in ogni circostanza

Se la mia SM raggiungesse una fase avanzata vorrei...

Sapere quanto mi resta da vivere	☐ ☐ ☐ ☐ ☐	Non sapere quanto mi resta da vivere

Voglio che i miei cari…

Decidano rispettando esattamente la mia volontà, anche se questo li facesse stare male	☐ ☐ ☐ ☐ ☐	Prendano la decisione che li faccia sentire in pace, anche se dovesse essere contraria alla mia volontà

Voglio che i miei cari…

Non sappiano nulla sul mio stato di salute	☐ ☐ ☐ ☐ ☐	Ricevano ogni informazione sul mio stato di salute

6. Se non fossi più in grado di decidere: il mio fiduciario

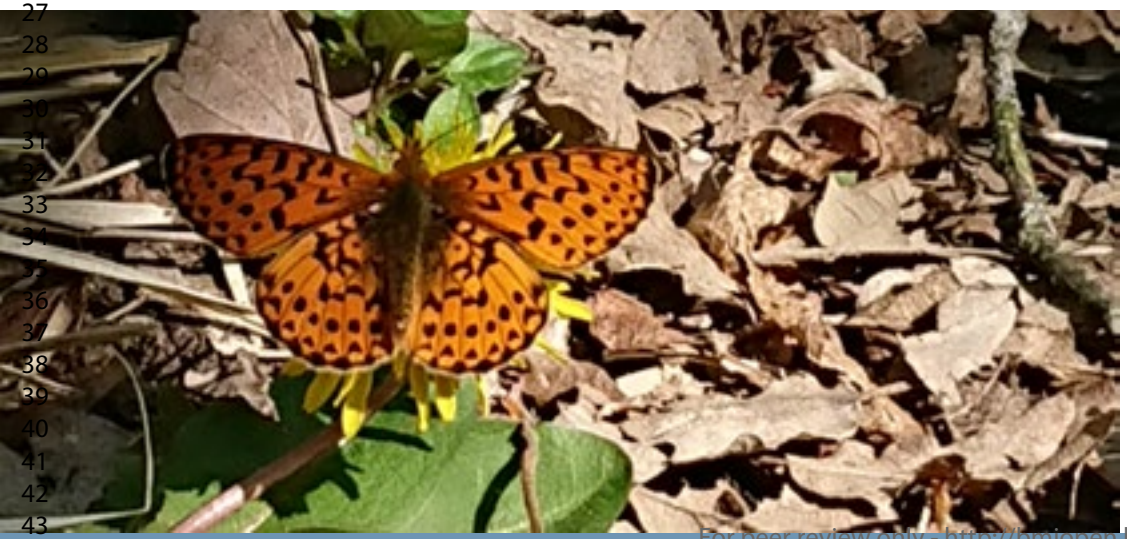
Se hai deciso di nominare un fiduciario, devi coinvolgerlo nelle tue scelte future.

Parla con lui, o con lei, del tuo piano di cure e consegna al fiduciario una copia del documento di PCC, dopo che l'avrai compilato.

Se non hai ancora deciso di nominare un fiduciario, prova a pensare se non sia il caso di farlo ora.

Se devi scegliere una persona, o più persone, che dovranno decidere per la tua salute nel momento in cui tu non fossi più in grado di farlo, scegli qualcuno che:

- Ti conosca bene
- Si preoccupi di cosa è importante per te
- Sia disponibile a parlare di questi aspetti con te
- Ti ascolti e sia rispettoso
- Sia disposto a difendere le tue volontà affinché vengano esaudite.



Se perdessi la capacità di decidere, vorrei che:

Segna la casella che corrisponde alla tua preferenza

☐ **Le decisioni riguardanti le mie cure future venissero concordate con il mio fiduciario di seguito indicato:**

Nome e Cognome

Indirizzo

Telefono e-mail

Se il mio fiduciario fosse impossibilitato a svolgere il suo ruolo, indico come seconda, terza persona di fiducia:

Nome e Cognome

Telefono e-mail

Nome e Cognome

Telefono e-mail

Oppure:

☐ **Non ho scelto un fiduciario.**

Vorrei inoltre che la persona di seguito indicata sia comunque informata dai sanitari che prenderanno decisioni sulle mie cure future in base alle indicazioni contenute in questo documento ed in funzione del mio migliore interesse.

Nome e Cognome

Indirizzo

Telefono e-mail

7. Pensando alla fine della mia vita

Morire è parte del vivere, ma ci preoccupa e spaventa. È desiderabile che la fine della vita avvenga nel rispetto della propria dignità e autonomia, in un luogo adeguato e possibilmente di nostra scelta, in presenza delle persone a noi care, se lo vogliamo, e limitando ogni tipo di sofferenza. Non esiste un percorso uguale per tutti alla fine della vita, esso infatti può essere influenzato dall'età, dalle malattie di cui soffriamo e da altre circostanze. In questa fase, potrebbe essere necessario ricevere farmaci e trattamenti con l'obiettivo di controllare sintomi che possono presentarsi quali dolore, mancanza di fiato, nausea, ansia, agitazione. Nei rari casi nei quali la sofferenza non fosse gestibile con terapie ordinarie potrebbe essere indicata una sedazione palliativa profonda, ovvero un trattamento che annulla gradualmente la coscienza, con lo scopo di ridurre la sofferenza sino al sopraggiungere della morte (la sedazione palliativa profonda infatti non anticipa né procrastina il momento della morte).

Pensando a cosa significhi per te mantenere una buona qualità della vita, in questa fase cosa credi che sarebbe importante?

- Restare vigile e mantenere il controllo il più a lungo possibile
- Non sentire alcuna sofferenza anche a costo di essere sonnolento o addormentato
- Avere accanto chi amo
- Stare da solo

Dovendo pensare alla fine della tua vita:

- Quale sarebbe la tua morte ideale?
- Pensando alla morte ed al morire, cosa ti preoccupa di più?
- Chi vorresti avere accanto?
- Che tipo di assistenza spirituale o religiosa vorresti?
- In prossimità della morte, cosa vorresti e cosa non vorresti?

Per me una buona qualità della vita in prossimità della morte significa:

Vorrei anche aggiungere:

Quando starò morendo desidero essere curato e accudito nel rispetto della mia persona e della mia dignità. Inoltre desidero:

Segna la casella che corrisponde a ciò che desideri

☐ **Che vengano rimossi tubi ed altri presidi che possano ostacolare il contatto con le persone che mi sono care**

☐ **Che vengano interrotti trattamenti non più utili**

☐ **Avere un sostegno spirituale o religioso**

7. Pensando alla fine della mia vita

Dove vorresti trascorrere le tue ultime settimane o giorni?

- Cosa ritieni necessario affinché questo possa avvenire?

Chi dovrà essere informato del fatto che stai per morire?

- Dove conservi i contatti (nome, telefono) di queste persone?
- C'è qualcuno che potrà contattarle?

Nel caso non fosse possibile soddisfare la tua scelta sul luogo dove morire, hai altre preferenze da esprimere?

Quali altre cose sarebbero importanti per te? (Per esempio, mantenere la tua privacy, ascoltare una musica particolare, poter vedere alcune persone significative, ecc.)

Il luogo nel quale morire è importante per me:

Segna la casella che corrisponde alla tua preferenza

☐ **Sì** ☐ **No**

Quando starò morendo vorrei essere assistito:

☐ **A casa, che per me significa:**

☐ **In ospedale**

☐ **In una struttura (comunità, casa di riposo)**

☐ **In hospice**

☐ **Non è rilevante il luogo dove sarò assistito**

Altri aspetti che vorrei venissero considerati:

8. Le mie scelte di cura

Questa parte del documento va compilata con l'aiuto del tuo medico di fiducia.

I trattamenti di supporto vitale possono mantenerti in vita nelle stesse condizioni in cui ti trovi ora. Altre volte essi possono consentire condizioni di vita per te inedite e difficili da immaginare, o risultare fastidiosi o dolorosi. Tra questi trattamenti vi sono l'idratazione/nutrizione 'artificiale' (per sondino naso-gastrico, PEG, per via parenterale/endovenosa), la rianimazione cardiopolmonare (RCP), la ventilazione meccanica con o senza tracheostomia, la dialisi. I trattamenti di supporto vitale in sé non sono né buoni né cattivi, dipende da come e quando vengono utilizzati. È importante, inoltre, ricordare che questi trattamenti non devono essere considerati irreversibili e che si può tornare indietro anche in queste scelte.

Puoi decidere se ricevere, o meno, questi trattamenti. I tuoi curanti ti proporranno solo trattamenti utili per la tua condizione, come per esempio la RCP, che potrebbe riattivare la funzione del cuore o dei polmoni. In tal caso sei chiamato a decidere se vuoi che venga fatta o meno.

Pensa a cosa è importante per te. Per esempio, la qualità della tua vita (non soffrire) o la durata della tua vita (poter vivere il più a lungo possibile). La tua PCC serve in particolare nelle condizioni di emergenza, ove tu non sia in grado di prendere delle decisioni per facilitare i curanti a mettere in atto o meno, trattamenti nel tuo miglior interesse. Trattamenti appropriati sul piano strettamente tecnico, potrebbero infatti essere inappropriati alla luce delle tue preferenze.

Ci sono circostanze nelle quali non vorresti essere mantenuto in vita e preferiresti non iniziare o sospendere terapie di supporto?

Se mi trovassi in condizioni di estrema gravità, in pericolo di vita ed incapace di decidere per me, ciò che segue descrive al meglio le mie preferenze di cura. Sono consapevole di non poter pretendere trattamenti che i medici giudichino inappropriati per le mie condizioni. Estrema gravità per me significa:

Scrivi nel riquadro in fondo alla pagina il numero corrispondente alla tua scelta di cura e, dove applicabile, indica con un segno i trattamenti specifici (punto 2).

1 Vorrei ricevere **tutti i trattamenti disponibili** ritenuti necessari e appropriati dai medici che mi cureranno, per mantenermi in vita il più a lungo possibile.

2 Vorrei ricevere **solo quei trattamenti** mirati non solo a prolungare, ma anche a preservare una qualità di vita ancora accettabile per me.

Nello specifico, accetto di ricevere i seguenti trattamenti:

- ☐ idratazione/nutrizione per sondino naso-gastrico
- ☐ PEG
- ☐ idratazione/nutrizione parenterale/endovenosa
- ☐ rianimazione cardiopolmonare
- ☐ ventilazione meccanica senza tracheostomia
- ☐ ventilazione meccanica con tracheostomia
- ☐ dialisi

3 Vorrei ricevere solo le cure mirate al **controllo dei sintomi e al mio comfort**, nel rispetto della mia dignità. Non voglio alcun trattamento finalizzato solo a prolungare la mia vita.

4 Non sono in grado di decidere adesso. **Delego i medici** che mi cureranno a prendere le decisioni migliori per me, tenendo in considerazione il parere delle persone che ho indicato nella sezione 6.

Ho scelto l'opzione numero: ☐

Ho già redatto le mie **Disposizioni Anticipate di Trattamento**, depositate presso il comune

di ☐ in Data ☐

e reperibili presso il Registro Nazionale DAT.

Questo documento:

☐ Aggiorna le mie DAT ☐ Conferma le mie DAT

9. Firme

La firma di questo documento è necessaria affinché esso sia ritenuto valido e sia applicato. Se non puoi firmare, è sufficiente una videoregistrazione in cui i sanitari leggeranno le sezioni 6, 7 e 8 del documento e registreranno le tue scelte.

Se hai nominato un fiduciario, è necessaria anche la sua firma.

Anche il tuo medico di fiducia, ed eventuali altri professionisti sanitari che ti hanno in cura dovrebbero firmarlo, perché questo garantisce che la PCC è avvenuta in modo informato e condiviso.

Firmando questo documento io confermo:

1. **Di avere compreso la finalità dello stesso e che esso rispecchia le mie volontà**
2. **Di averlo compilato in piena libertà e dopo essere stato adeguatamente informato**
3. **Di acconsentire alla conservazione delle informazioni nei registri, nelle cartelle cliniche e nei fascicoli elettronici previsti, secondo la normativa sulla privacy (Regolamento UE 2016/679) e relativa normativa italiana di adeguamento (D.Lgs. n. 196 del 30 Giugno 2003, così come modificato dal D.Lgs. n. 101 del 10 Agosto 2018).**

Nome e Cognome _____

Indirizzo _____

Telefono _____ **e-mail** _____

Data _____ **Firma** _____

☐ **Ho scelto come fiduciario:**

Nome e Cognome _____

Indirizzo _____

Telefono _____ **e-mail** _____

Data _____ **Firma** _____

☐ **Non ho scelto un fiduciario**

Ho condiviso con il mio medico di fiducia questo documento:

Dr

Telefono e-mail

Data Firma

E, dove applicabile, con il professionista sanitario:

Dr

Telefono e-mail

Data Firma

10. Abbreviazioni

DAT: Disposizioni anticipate di trattamento

PCC: Pianificazione condivisa delle cure

PEG: Gastrostomia percutanea endoscopica

RCP: Rianimazione cardiopolmonare

SM: Sclerosi multipla

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BMJ Open

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

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ONLINE SUPPLEMENTAL APPENDIX 3 – EXCERPTS FROM THE STUDY PROTOCOL VERSION 1.0

1 PANELS AND CENTERS

1.1 Trial Steering Committee (TSC)

The TSC is the executive body for the study. Members are from the Gruppo di Studio di Bioetica e Cure Palliative of the Società Italiana di Neurologia (L De Panfilis, MG Grasso, A Giordano, A Lugaresi, E Pucci, A Solari, S Veronese), from the National ACP programme for New Zealand (L Manson), and from patient associations (M Bruzzone, P Kruger).

1.2 Data Safety and Monitoring Committee (DSMC)

The independent DSMC has been established to: (1) oversee the progress of the pilot study and the safety data, and ensure that it is conducted, recorded, and reported in accordance with the protocol, GCP, and the applicable regulatory requirement(s); (2) monitor and supervise the progress of the pilot study, and the safety data. Members are: K Brazil, B Farsides, L Orsi, C Peruselli, and D Oliver (Chair). The DSMC is scheduled to meet (teleconference) before enrollment starts, at the end of the enrollment, and at the end of the follow-up, and depending on the needs of the trial. One week prior to each teleconference, the trial PI will send each DSMC member a report with trial data

(overall and by site) such as recruitment rates, reasons for exclusion, reason for drop out, plus other information if needed. The DSMC should report in writing to the TSC, usually within 3 weeks after the teleconference.

1.3 Data Management and Analysis Committee (DMAC)

The DMAC is responsible for data entry, quality assurance, and the statistical analyses. Members are M Farinotti (data manager) and A Giordano. DMAC will be in charge of the data protection to respond to the European and Italian law on privacy and data storage and conservation.

1.4 Qualitative Analysis Panel (QAP)

The QAP devised the design, procedures and analysis plan of the qualitative study. QAP members will conduct the personal interviews and the FGMs, and the analysis. Members are: M Cascioli, L De Panfilis, L Ghirotto, K Mattarozzi, and S Veronese.

8.5 HP Training Panel (HTP)

The HTP devised the HP training program. HTP members will have responsibility of conducting the residential program, and revise it based on training findings. Members are: M Cascioli, L De Panfilis, K Mattarozzi, E Pucci, M Rimondini, A Solari, and S Veronese.

1.6 Linguistic validation Panel (LP)

The LP was appointed to translate and adapt the outcome measures not available in Italian. Members are M Farinotti, A Giordano, A Solari, S Veronese and three independent translators (section 5.3.8).

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2 ETHICS AND ADMINISTRATIVE CONSIDERATIONS

2.1 Ethical Considerations

This clinical study was designed and shall be implemented and reported in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for GCP, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki.

2.2 Ethics Committee Approval

The protocol, Subject Information Sheet, Informed Consent Form must be reviewed and approved by an appropriately constituted Ethics Committee (EC), as required in chapter 3 of the ICH E6 Guideline. Written EC approval must be obtained by the Sponsor prior to shipment of study agent or subject enrolment.

2.3 Subject Information and Informed Consent

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), EC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents. No study procedure can be performed before the written informed consent has been provided.

2.4 Confidentiality

The investigator must ensure participant anonymity. On database and other documents, participants must not be identified by name but by patient number and initials. The investigator must keep a separate log of participants' codes, names and addresses, and signed informed consent forms, all of which must be kept strictly confidential.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law. Medical information may be given to a pwPMS personal physician or other appropriate medical personnel responsible for the pwPMS welfare, for treatment purposes. Data generated by this study must be available for inspection upon request by representatives of the national and local health authorities, monitors, representatives, and collaborators, and the EC for each study site, as appropriate.

2.5 Protocol Amendments

Any protocol amendments will be prepared by the PI. Protocol amendments will be submitted to the EC and to regulatory authorities in accordance with local regulatory requirements. Approval must be obtained from the EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g. change in monitor or contact information).

3 STUDY MANAGEMENT AND MONITORING

3.1 Source documents

Source Documents are defined as original documents, data and records. These may include hospital records, medical records / outpatient data, data recorded from automated instruments, etc. Investigators should conserve all the source documents as required in the study protocol for at least two years after the end of the study.

3.2 Archiving of records

The investigator is responsible for recording and storing the essential documents of the study, according to what / and for the time required by law and by GCP. The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of EC and governmental approval.

3.3 Auditing on site

In the event that the investigator will be contacted by the Competent Authority in relation to this study, he or she will be required to immediately notify the Sponsor. The investigator must be available to respond to requests and queries by inspectors during the audit process. The investigator must provide the Sponsor copies of all correspondence that may affect the revision of the current study.

3.4 Use and Publication of Study Results

The results of the study may be presented during scientific symposia or published in a scientific journal only after review and written approval by the involved parties in full respect of the privacy of the participating subjects.

3.5 Insurance Policy

Each of the participating centers has an adequate insurance policy to cover possible damages emerging from this study.