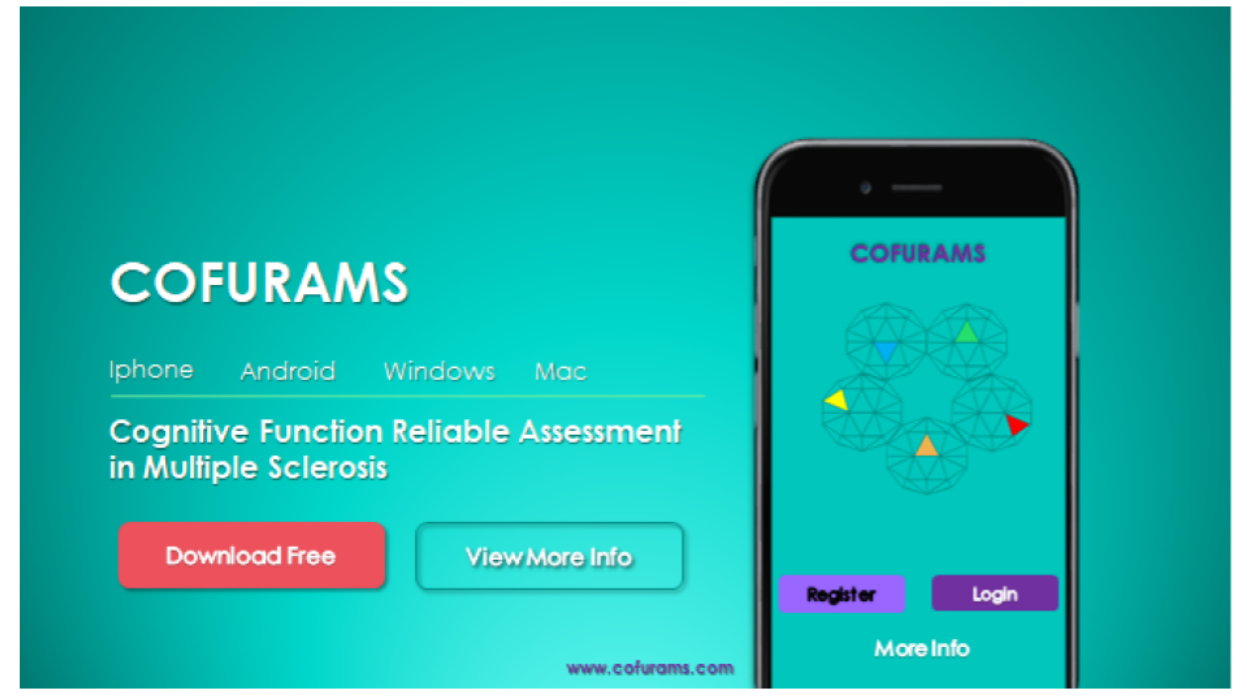
COFURAMS

Assessing your future

Reliable Assessment of Cognitive Function in Multiple Sclerosis: COFURAMS



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ABSTRACT

COFURAMS (Cognitive Function Reliable Assessment in Multiple Sclerosis) is an Artificial Intelligence (AI) multitool developed for reliable assessment of cognitive function in Multiple Sclerosis (MS).

The solution **COFURAMS** integrates with the mobile phone of the patient in order to assess cognitive deficits specifically in terms of attention and concentration by the eye tracker; information processing by interaction - response analysis; memory through visual - auditory and writing tool; problem - solving by interaction with multiple Apps; verbal fluency by Android - Bixbi or Apple - Siri; and visual-spatial ability by picture mode performance.

We have created a solution which whilst targeted at patients with MS over the age of 18 years, can also be used by patients at any age with quick, objective and pragmatic results. The areas of evaluation remain consistent over time for each individual but at the same time they can be comparable across multiple individuals.

COFURAMS targets relapsing - remitting multiple sclerosis (RRMS) patients but can be used by other patients with multiple sclerosis. The cognitive functionality is not only being assessed in real time, but it is also trackable over an extended period of time.

Results obtained in **COFURAMS** can also be applied for clinical trials, allowing for multiple other uses for all the data collected, which will allow for improvements to be rapidly made in many aspects of research.

COFURAMS does not require supervision by a healthcare professional, however, the results can also be evaluated by the specialized team if needed. This means that there are no particular technological skills needed to operate the system, allowing it to be implemented and used by anyone.

COFURAMS is better than any other assessment in the market because there is no application easier to use than this one. It has incredible ease of use, since part of the system is fully integrated, meaning that for a large part of the data collected, the patient does not need to be consciously answering questions or filling out forms, the user would simply have to use his device as a user normally would.

COFURAMS is also partly integrated as a widget, ensuring the user does not feel any abnormalities with device functionality, whilst data is being collected through various ergonomic registries. An example of this would be in the case of eye tracking, touch screen

scrolling or in typing on a digital keyboard. This would not only ensure that the user feels engaged, but also ensures that **COFURAMS** is able to provide information and data in real time, demanding to the patient with MS only assessments when an impairment is detected.

The main aspect of **COFURAMS** is its dynamic system, something no other similar software or application in the market such as Emilyn, Companion or MS Cognition are capable of.

COFURAMS can use its integrated system to find areas in which the patient may be lacking, and therefore request a more targeted test for the patient to complete. This dynamic aspect is why this software must be the go to helper for MS patients.

INTRODUCTION TO COGNITIVE DYSFUNCTIONS AND ASSESSMENTS IN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a disease characterized by a large variability of symptoms arising from focal inflammation of the central nervous system (typical white matter lesions that are best visualized with magnetic resonance imaging) that may occur at various points in time. Symptoms generally last for several days to weeks, but occasionally persist for many months, with subsequent full or partial recovery. These periods are referred to as relapses. The occurrence of clinical relapses or new white matter lesions is used to estimate disease activity. The occurrence of relapses is the dominant clinical picture in the vast majority of patients during the earlier disease stages and is defined as relapsing-remitting MS (RRMS). When there is a disease progression independent from relapses, this is referred to as secondary-progressive MS (SPMS).

Swift action to prevent or slow damage to the brain is crucial. Clinicians must act before the disease causes irreparable damage to the brain and before the brain's limited mechanisms for repair are damaged. There is increasing consensus about the importance of early intervention to maximize lifelong brain health[1]. Due to the heterogeneous nature of the disease, it is a challenge to capture disease activity of multiple sclerosis (MS) in a reliable and valid way.

Cognitive Dysfunction

Cognitive problems in MS are the result of nerve damage in the brain interrupting the transmission of electrical messages, reducing the speed and accuracy of the information. Cognitive problems can be made worse by:

- **Fatigue or poor sleep** - which slows everything down. Try to pace yourself and plan demanding activities for times when you've got the most energy.
- **Physical effort** - if you have difficulties with your balance or your mobility you may find that you need to concentrate more when you are moving about to ensure you don't fall. This means you have less capacity to concentrate on other things, such as carrying on a

[1] Giovannoni G, Butzkueven H, Dhib-Jalbut S, et al. . Brain health: time matters in multiple sclerosis. UK: Oxford PharmaGenesis, 2015.

conversation at the same time as walking. Try to balance physical and cognitive activities so you only have to concentrate on one thing at a time.

- **Emotions** - stress, anxiety and depression can all impact cognition. They can also be difficult to distinguish from other MS symptoms. Proper assessment by a psychologist may help in this situation.
- **Infections** - and other illnesses can worsen cognitive problems.
- **Medications** - including some that are commonly used to treat MS symptoms such as bladder problems, spasticity and pain. A GP, pharmacist or MS nurse can advise on the likely effects of all medications.
- **Other things that generally worsen symptoms** - such as heat, or tense or exciting situations. Try to stay cool in hot weather, or use relaxation techniques to cope.

The disease could be affecting cognition 5–10 years before any clinical manifestation can be seen[2]. If cognitive decline starts so early, we need to begin treating MS with disease-modifying drugs as soon as we are aware of it.

The areas which have commonly shown more deficits are: information processing speed, episodic memory, complex attention, and executive function[3],[4].

Clinicians often think of MS progression in terms of walking ability and judge the progress of MS by performance on tests such as the timed 25-foot walk. However, for people with MS, cognitive health is of major importance and is impaired before walking ability. Cognitive deficit, not walking ability, has the biggest impact on the employment status of people with MS[5].

The most common cognitive areas affected are:

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[2] Sinay V, Perez Akly M, Zanga G, et al. School performance as a marker of cognitive decline prior to diagnosis of multiple sclerosis. Mult Scler. 2015 Jun; 21(7):945-52.

[3] Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. Lancet Neurol. 2008 Dec; 7(12):1139-51.

[4] De Luca J, Chelune GJ, Tulsky DS, et al. Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? J Clin Exp Neuropsychol. 2004 Jun; 26(4):550-62.

[5] Celia Oreja-Guevara, Teresa Ayuso Blanco, Luis Brieva Ruiz, et. al. Cognitive Dysfunctions and Assessments in Multiple Sclerosis. Front Neurol. 2019 June 4; 10: 581.

Memory

You may find that your memory isn't as good as it used to be. Usually memory problems in MS revolve around difficulties remembering recent events or information and forgetting to carry out plans. Diaries, smartphones or notice boards are useful tools to record information and act as reminders. Have a set place to keep things like your keys and glasses to make it easier to find them and stay organised.

Word finding

Do you feel like a word is 'on the tip of your tongue' but you can't quite recall it? This is a common problem, even for people without MS. It can be helpful to try and describe the word you are struggling with in other terms, for example 'the building with teachers and children' could be used to describe 'a school'.

Concentration and attention

You may find it difficult to concentrate or find your mind wanders, particularly if lots of people are talking at once. This can make it harder to follow the thread of a conversation or give you a feeling of 'information overload' if only some of what you are being told is relevant. Try to reduce distractions such as turning the TV off before making a phone call, or dividing large tasks into more manageable chunks.

Information processing

This is when you experience difficulties with following a series of complex instructions. This can particularly be a problem if information is given rapidly. Reducing distractions and trying to avoid interruptions can help.

Visuospatial abilities

This refers to the way you relate to visual information, for example accurately judging speed and distance when driving, or judging where things are in relation to the space around you. It is the skill you use when you walk through a door rather than bumping into the door frame, or when you use a map to find your way somewhere. You might need to slow down and concentrate on moving around, or enlist a sat-nav to guide your journeys.

Planning and problem solving

Planning and solving problems are known as 'executive skills', and these may be impaired. It can be harder to see how your actions or decisions may affect you beyond the immediate future.

This means that your decisions may not be as sound as they used to be. If your executive skills are affected it can be more difficult to manage your day, or even your healthcare.

Often, it is a family member or friend who picks up on this kind of issue before you recognise it yourself. It can be helpful to get another person's insight and talk through the implications before you make any important decisions.

Assessments in Multiple Sclerosis

Several approaches can be used to quantify and measure disease activity in a patient with MS. Within clinic-based metrics these include (e.g. annualized clinical relapse rate, timed walking and cognitive tests, and sustained increases in the Expanded Disability Status Scale (EDSS) score). These tests are important outcomes utilized within the realm of clinical trials in MS. In clinical practice, these measures can be beneficial in assessing treatment response to a given therapy and defining or prognosticating an individual's disease course.

For the design of **COFURAMS**, we evaluated all the evidence base tools currently in use for multiple sclerosis and the accuracy as described in the literature. Moreover, we asked a group of patients with MS about certain features (from their experience) about these tests.

Despite several limitations, the traditional clinical measures are still the mainstay for assessing treatment efficacy. Newer and potentially valuable outcome measures increasingly used or explored in MS trials are, clinically, the MS Functional Composite and patient-reported outcome measures. Several limitations of these measures have been addressed and further improvements will probably be proposed. Major improvements are the coverage of additional functional domains such as cognitive functioning and assessment of the ability to carry out activities of daily living. The development of multidimensional measures is promising because these measures have the potential to cover the full extent of MS activity and progression[6].

[6] van Munster CE, Uitdehaag BM. Outcome Measures in Clinical Trials for Multiple Sclerosis. CNS Drugs. 2017;31(3):217-236.

Expanded Disability Status Scale

The Expanded Disability Status Scale (EDSS)[7] is a method of quantifying disability in multiple sclerosis and monitoring changes in the level of disability over time. It is widely used in clinical trials and in the assessment of people with MS. The EDSS scale ranges from 0 to 10 in 0.5 unit increments that represent higher levels of disability. EDSS steps 1.0 to 4.5 refer to people with MS who are able to walk without any aid and is based on measures of impairment in eight functional systems (FS):

- Pyramidal – muscle weakness or difficulty moving limbs.
- Cerebellar – ataxia, loss of balance, coordination or tremor.
- Brainstem – problems with speech, swallowing and nystagmus.
- Sensory – numbness or loss of sensations.
- Bowel and bladder function.
- Visual function - problems with sight.
- Cerebral functions - problems with thinking and memory.
- Other.

A functional system (FS) represents a network of neurons in the brain with responsibility for particular tasks. Each FS is scored on a scale of 0 (no disability) to 5 or 6 (more severe disability).

EDSS steps 5.0 to 9.5 are defined by the impairment to walking. The scale is sometimes criticised for its reliance on walking as the main measure of disability.

Although the scale takes account of the disability associated with advanced MS, most people will never reach these scores. A large study that looked at people with MS at a clinic in Ontario (prior to the development of the expanded version) found that 51% of people had a DSS score of 5 or lower. 88% had a score of 7 or lower.

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[7] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33(11):1444-1452.

Despite being the most widely used outcome measure for disability progression in MS, the EDSS has been criticised for having some limitations. For instance, EDSS scores can vary due to the complex scoring rules and the subjective nature of the neurological examination. Some argue that the changes between steps on the scale (e.g. 1.0 to 2.0 and 4.0 to 5.0) are unequal and that from 4.0 upwards the scale focuses too much on walking ability, and underestimates how important upper body function is in self-care and independence. It's also been highlighted that some functional areas are not sufficiently assessed, such as cognitive function, mood, energy levels and quality of life[8]. In summary, we could say that a successful solution should resolve the following EDSS limitations:

- High intra- and inter-observer variability.
- Non-linearity (bimodal distribution).
- Limited responsiveness.
- Necessity to use non-parametric statistics (ordinal scale).
- Uneven distribution of relapsing–remitting and progressive patients.
- Several functional domains not assessed.

MS Functional Composite (MSFC)

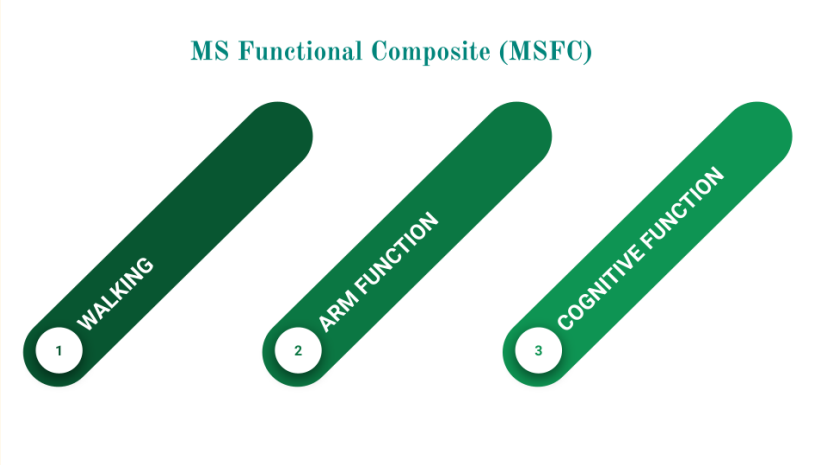
Because of the limitations of the EDSS and assessment of relapses and improved clinical outcome methods, the MSFC was developed to improve clinical assessment[9].

The National Multiple Sclerosis Society (NMSS) convened an international task force in 1994 to recommend improved clinical outcome measures. As the result of a two-year process of discussion and data analysis, the task force recommended the Multiple Sclerosis Functional Composite (MSFC) as a new clinical outcome measure for future MS trials. MSFC consists of

[8] Expanded Disability Status Scale (EDSS). In Multiple Sclerosis Trust. https://mstrust.org.uk. Accessed 03/07/2021.

[9] Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Cutter GR, Baier ML, Rudick RA, Cookfair DL, Fischer JS, Petkau J, Syndulko K, Weinshenker BG, Antel JP, Confavreux C, Ellison GW, Lublin F, Miller AE, Rao SM, Reingold S, Thompson A, Willoughby E. Brain. 1999 May; 122 (Pt 5)():871-82.

timed tests of walking, arm function, and cognitive function, expressed as a single score along a continuous scale. The task force recommended that MSFC be included in future MS trials, and recommended a series of validation studies. Subsequent studies have provided evidence that MSFC correlates moderately with Expanded Disability Status Scale (EDSS), and that correlation is driven by strong correlations with the ambulatory function component; arm function and cognitive function correlate at lower levels with EDSS. The MSFC correlates better than EDSS with magnetic resonance imaging (MRI) variables, including brain atrophy, and shows significant correlation with patient-reported disease-related quality of life (QOL)[10].



This type of assessment has the following limitations:

- Moderate reliability, sensitivity and responsiveness of the PASAT
- The PASAT often disliked by patients, requirement of mathematical ability and ceiling effect
- Several important functional domains are not assessed
- Lack of a clear dimension of the overall score (resulting in difficult interpretability)
- Z scores are influenced by results of the reference population and obscure the meaning of crude scores

Patient-reported outcome measures (PRO)

Multiple patient-reported outcomes (PROs) are currently being used in multiple sclerosis (MS) but their application is inconsistent and guidance on the appropriateness of each tool is lacking.

[10] Rudick RA, Cutter G, Reingold S. The multiple sclerosis functional composite: a new clinical outcome measure for multiple sclerosis trials. Mult Scler. 2002 Oct;8(5):359-65.

Most PRO measures are categorized as either generic or targeted[11]. Generic measures include questions that are general enough for use with both healthy and clinical populations. Generic measures used in MS include the Medical Outcomes Study Short Form-36 (SF-36)[12], the Sickness Impact Profile[13], and versions of the Health Utilities Index[14].

Targeted measures are comprised of questions aimed towards specific diseases (e.g., MS), domains (e.g., cognition, fatigue), or interventions (e.g. use of biological response modifiers). Examples of symptom-focused, domain-specific measures include the Brief Pain Inventory[15], and the pain, fatigue, depression, sleep, and other symptom measures included in the Patient-Reported Outcomes Measurement Information System (PROMIS)[16] and the Neurology Quality of Life (Neuro-QoL) measurement system[17].

Disease-specific measures for MS are numerous, and include:

- Multiple Sclerosis International Quality of Life (MusiQoL)[18],
- Multiple Sclerosis Quality of Life-54 (MSQOL-54)[19],

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[11] Nowinski CJ, Miller DM, Cella D. Evolution of Patient-Reported Outcomes and Their Role in Multiple Sclerosis Clinical Trials. Neurotherapeutics. 2017 Oct;14(4):934-944.

[12] The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Ware JE Jr, Sherbourne CD. Med Care. 1992 Jun; 30(6):473-83.

[13] The Sickness Impact Profile: development and final revision of a health status measure. Bergner M, Bobbitt RA, Carter WB, Gilson BS. Med Care. 1981 Aug; 19(8):787-805.

[14] The Sickness Impact Profile: development and final revision of a health status measure. Bergner M, Bobbitt RA, Carter WB, Gilson BS. Med Care. 1981 Aug; 19(8):787-805.

[15] Cleeland C. Measurement of pain by subjective report. Adv Pain Res Ther. 1989;12:391–403.

[16] Becker H, Stuifbergen A, Zhang W. Functional and health promotion predictors of PROMIS® scores in people with multiple sclerosis. Health Psychol. 2019 May;38(5):431-434.

[17] Matza LS, Phillips G, Dewitt B, et al. A Scoring Algorithm for Deriving Utility Values from the Neuro-QoL for Patients with Multiple Sclerosis. Med Decis Making. 2020 Oct;40(7):897-911.

[18] Simeoni M, Auquier P, Fernandez O, et al. Validation of the Multiple Sclerosis International Quality of Life questionnaire. Mult Scler. 2008 Mar; 14(2):219-30.

[19] Vickrey BG, Hays RD, Harooni R, et al. A health-related quality of life measure for multiple sclerosis. Qual Life Res. 1995 Jun; 4(3):187-206.

- Functional Assessment of Multiple Sclerosis (FAMS)[20],
- Multiple Sclerosis Impact Scale (MSIS-29)[21],
- Patient Reported Impact of Multiple Sclerosis (PRIMUS)[22],
- Hamburg Quality of Life Questionnaire in Multiple Sclerosis[23],
- MS Quality of Life Inventory[24],
- Multiple Sclerosis Impact Profile[25],
- Leeds Multiple Sclerosis Quality of Life scale[26],
- Disability and Impact Profile[27], and
- RAYS scale[28].

Some PRO measures, like the Disability and Impact Profile, also incorporate patients' perceptions of how important each effect of MS is on their lives. Generic PROs, usually normed against general/healthy populations, are appropriate for cross-disease comparisons, and are useful in resource allocation and cost-effectiveness analyses. In contrast, targeted measures can provide more in-depth and comprehensive coverage of a specific domain or area, are thought to

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[20] Cella DF, Dineen K, Arnason B, et al. Validation of the functional assessment of multiple sclerosis quality of life instrument. Neurology. 1996 Jul; 47(1):129-39.

[21] Hobart J, Lamping D, Fitzpatrick R, et al. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain. 2001 May; 124(Pt 5):962-73.

[22] Doward LC, McKenna SP, Meads DM, et al. The development of patient-reported outcome indices for multiple sclerosis (PRIMUS). Mult Scler. 2009 Sep; 15(9):1092-102.

[23] Gold SM, Heesen C, Schulz H, et al. Disease specific quality of life instruments in multiple sclerosis: validation of the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS). Mult Scler. 2001 Apr; 7(2):119-30.

[24] Fischer JS, LaRocca NG, Miller DM, et al. Recent developments in the assessment of quality of life in multiple sclerosis (MS). Mult Scler. 1999 Aug; 5(4):251-9.

[25] Wynia K, Middel B, van Dijk JP, et al. The Multiple Sclerosis impact Profile (MSIP). Development and testing psychometric properties of an ICF-based health measure. Disabil Rehabil. 2008; 30(4):261-74.

[26] Ford HL, Gerry E, Tennant A, et al. Developing a disease-specific quality of life measure for people with multiple sclerosis. Clin Rehabil. 2001 Jun; 15(3):247-58.

[27] Lankhorst GJ, Jelles F, Smits RC, et al. Quality of life in multiple sclerosis: the disability and impact profile (DIP). J Neurol. 1996 Jun; 243(6):469-74.

[28] Quality of life in multiple sclerosis: development and validation of the 'RAYS' scale and comparison with the SF-36. Rotstein Z, Barak Y, Noy S, Achiron A. Int J Qual Health Care. 2000 Dec; 12(6):511-7.

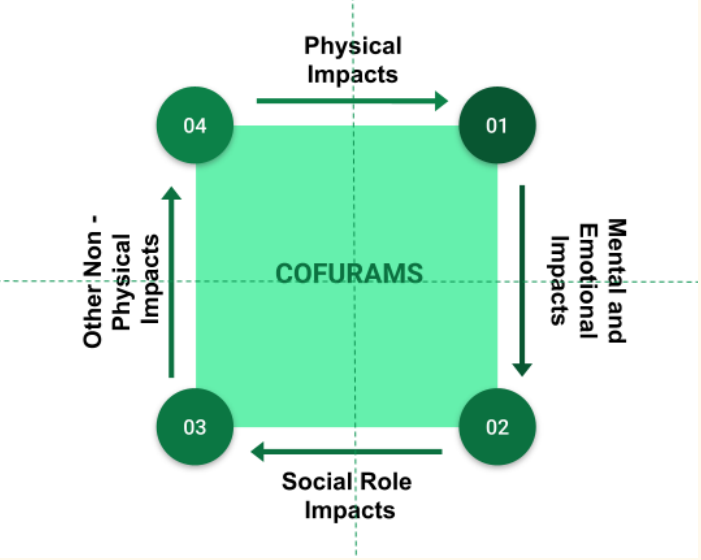
be more sensitive to changes in health status or function, and questions may seem more relevant and therefore more acceptable to patients[29]. This has led to recommendations for using a combined approach (generic and targeted) when feasible. The MSQOL-54, for example, includes the generic SF-36 along with 18 MS-specific questions. PROs also differ in whether they measure a single dimension of health or multiple dimensions. Multidimensional, or profile measures, typically provide separate scores for each dimension rather than a summary score. Some, such as the FAMS, provide both individual dimension scores and a total summary score.

The limitations showed with these tests are:

- Unblinded nature.
- Potential expectancy bias.
- Assessment of quality of life may be influenced by multiple factors.
- Possible response shifts over time.

Multiple Sclerosis Impact Scale (MSIS-29)

The MSIS-29 is a widely used measure of HRQOL in MS with strong psychometric properties. It consists of a physical subscale of 20 items and a psychological subscale of 9 items. Respondents are requested to report the impact of MS on their day-to-day lives over the preceding 2 weeks. The amended version, MSIS-29-v2, has four response levels per item: "not at all," "a little," "moderately," and "extremely." The content of the instrument was based on qualitative work with people with MS



[29] Ozakbas S, Akdede BB, Kösehasanogullari G, Aksan O, Idiman E. Difference between generic and multiple sclerosis-specific quality of life instruments regarding the assessment of treatment efficacy. J Neurol Sci. 2007 May 15; 256(1-2):30-4.

and is designed to be suitable for all types of MS[30].

Subscale	Conceptual dimension	Code	Item description
Physical	General/other physical functioning	IS01	Do physically demanding tasks
		IS02	Grip things tightly (e.g., turning on taps)
		IS03	Carry things
		IS04	Problems with your balance
		IS06	Being clumsy
		IS07	Stiffness
		IS08	Heavy arms and/or legs
		IS09	Tremor of your arms or legs
		IS10	Spasms in your limbs
		IS11	Your body not doing what you want it to do
		IS15	Difficulties using your hands in everyday tasks
	Mobility	IS05	Difficulties moving about indoors
		IS14	Being stuck at home more than you would like to be
		IS17	Problems using transport (e.g., car, bus, train, and taxi)
	Bladder/bowel	IS20	Needing to go to the toilet urgently?

[30] J. Hobart, S. Cano. Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods. Health Technol Assess, 13 (2009) iii, ix–x, 1–177

	General/other social and role functioning	IS13	Limitations in your social and leisure activities at home
	Independence	IS12	Having to depend on others to do things for you
	Employment	IS16	Having to cut down the amount of time you spent on work or other daily activities
	Unallocated items	IS18	Taking longer to do things
		IS19	Difficulty doing things spontaneously (e.g., going out on the spur of the moment)
Psychological	General/other mental and emotional well-being	IS24	Worries related to your MS
		IS25	Feeling anxious or tense
		IS26	Feeling irritable, impatient, or short tempered
		IS28	Lack of confidence
	Depression	IS29	Feeling depressed
	Fatigue	IS23	Feeling mentally fatigued
	Cognition	IS27	Problems concentrating
	Sleep quality	IS22	Problems sleeping
	Unallocated items	IS21	Feeling unwell

DETAILED DESCRIPTION OF REQUIREMENTS

COFURAMS (Cognitive Function Reliable Assessment in Multiple Sclerosis) is an Artificial Intelligence (AI) multitool developed for reliable assessment of cognitive function in Multiple Sclerosis (MS).

The solution **COFURAMS** integrates with the mobile phone of the patient in order to assess cognitive deficits specifically in terms of attention and concentration by the eye tracker; information processing by interaction - response analysis; memory through visual - auditory and writing tool; problem - solving by interaction with multiple Apps; verbal fluency by android - bixbi or apple - siri; and visual - spatial ability by picture mode performance.

COFURAMS is the future of integration the most used tool in our life (mobile phone) with human ergonomics to detect necessities and impairment in each area of cognitive function[31].

In the detailed description of requirements below we indicate how **COFURAMS** assesses the cognitive deficits and how is implemented into the mobile phone.

1. Must measure one or more of the following cognitive deficits

The main aspect of **COFURAMS** is its dynamic system, something no other software or application in the market such as Emilyn, Companion or MS Cognition are capable of. **COFURAMS** can use its integrated system to find areas in which the patient may be lacking, and therefore request a more targeted test for the patient to complete. This dynamic aspect is why this software must be the go to helper for MS patients.

COFURAMS can use its integrated system to find areas in which the patient may be lacking

COFURAMS is divided into two parts, the main application, where tests are done, results can be viewed, and you can access the Support Networks, and the integrated portion. This latter section works as a widget would, running in the background of the device's operations, it is able

[31] João J Cerqueira, D Alastair S Compston, Ruth Geraldes, et. al. Time Matters in Multiple Sclerosis: Can Early Treatment and Long-Term Follow-Up Ensure Everyone Benefits from the Latest Advances in Multiple Sclerosis? J Neurol Neurosurg Psychiatry. 2018 August; 89(8): 844-850.

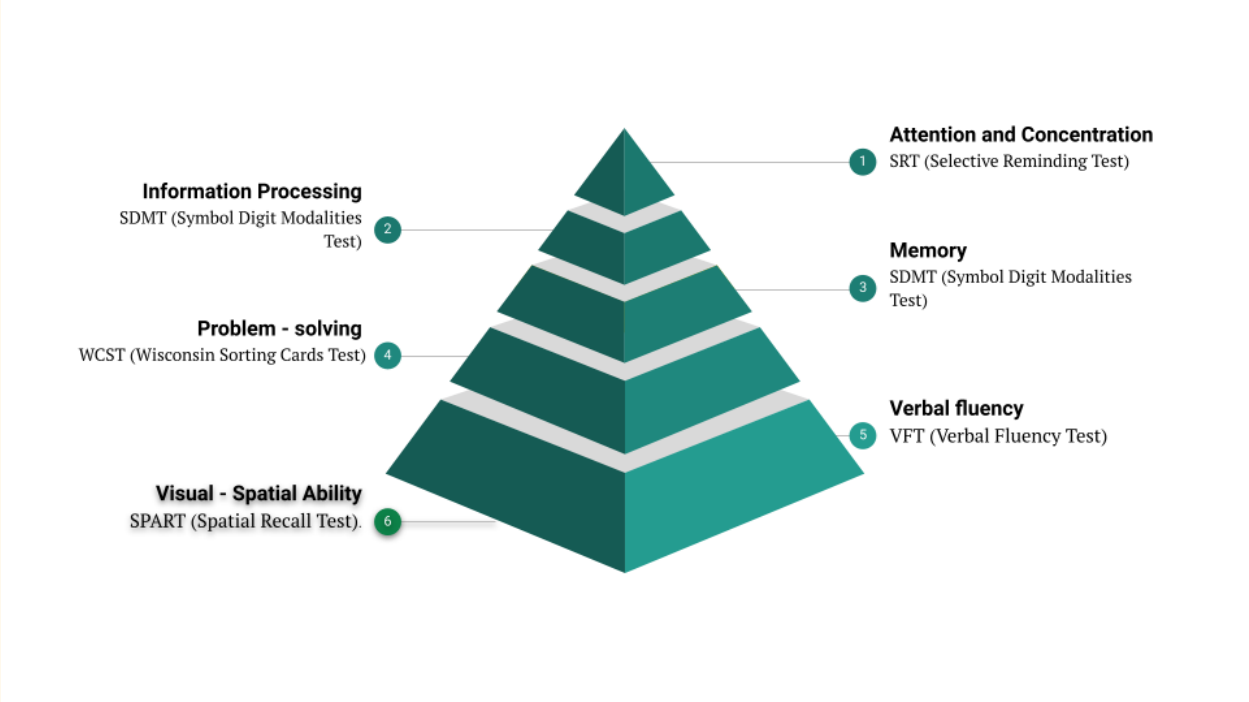
to do things such as detect touchscreen inputs, use eye tracking software, etc. The software is capable of analysing normal device functions and inputs, and then, if it finds any possible issues in the cognitive ability of the user, it can direct the patient to carry out a more specific test, and combine the results of the test along with the findings of the integrated software to give a prognosis.

For example, if the integrated portion of **COFURAMS** had been detecting that for one week, the patient has repeatedly increased the volume output of his device. With this, the system is able to analyse a change in behaviour, and thereby request the patient to carry out a test that would be able to give it more data on issues related to auditory neurological focality. Once the patient has carried out this test, more light would be shed on the issue, and we would be able to see whether there is an issue with the patient's hearing, in which case, an appointment could be booked with the appropriate specialist.

Once the integrated portion of **COFURAMS** has detected a deficit in Attention and Concentration, Information Processing, Memory, Problem Solving, Verbal Fluency or Visual-Spatial Ability, it may request the patient to carry out the most sensitive tests for detecting cognitive impairment in MS which have been considered to be: Selective Reminding Test (SRT),10/36 Spatial Recall Test (SPART), Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test (PASAT) and Word List Generation (WLG)[32],[33].

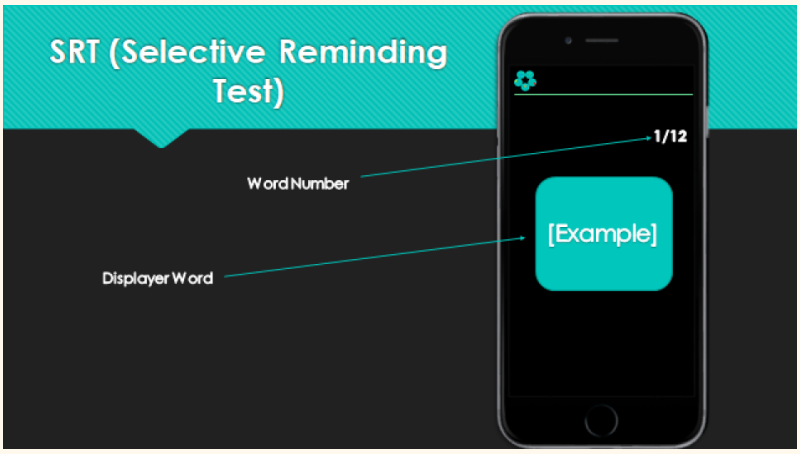
[32] Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology. 1991;41(5):685-91. doi:10.1212/WNL.41.5.685

[33] Strober L, Englert J, Munschauer F, Weinstock-Guttman B, Rao S, Benedict, RH. Sensitivity of conventional memory tests in multiple sclerosis: comparing the Rao Brief Repeatable Neuropsychological Battery and the Minimal Assessment of Cognitive Function in MS. Mult Scler. 2009;15(9):1077-84.



COFURAMS can measure the following cognitive deficits by its specific tools described below.

- ## Attention and concentration

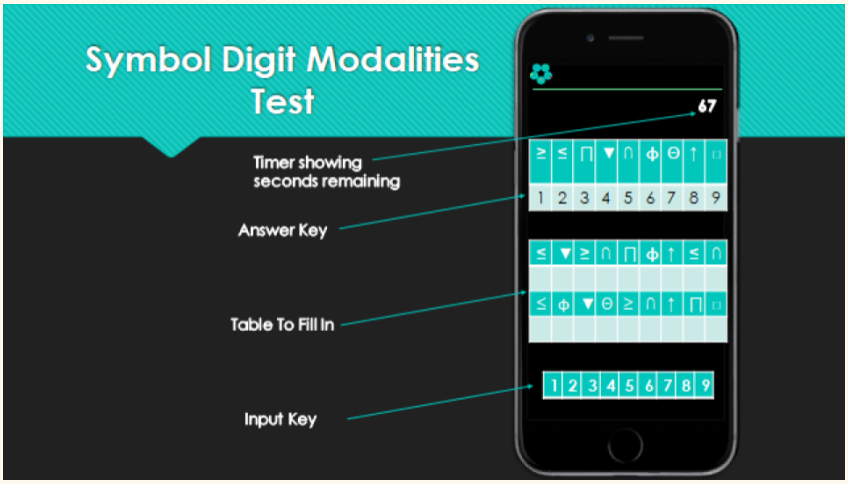


In this case, the integrated portion would consider a deficit in this cognitive area if the patient was: taking too long to read text, responding late to notifications or prompts, etc. If this was the case, **COFURAMS** would prompt the patient to carry out the following test: SRT (Selective Reminding Test) can be easily implemented into a device format, along with both voice reception and digital keyboard. The device will output 12 words at a rate of one every two seconds, a time regulated by the application itself. Then, it

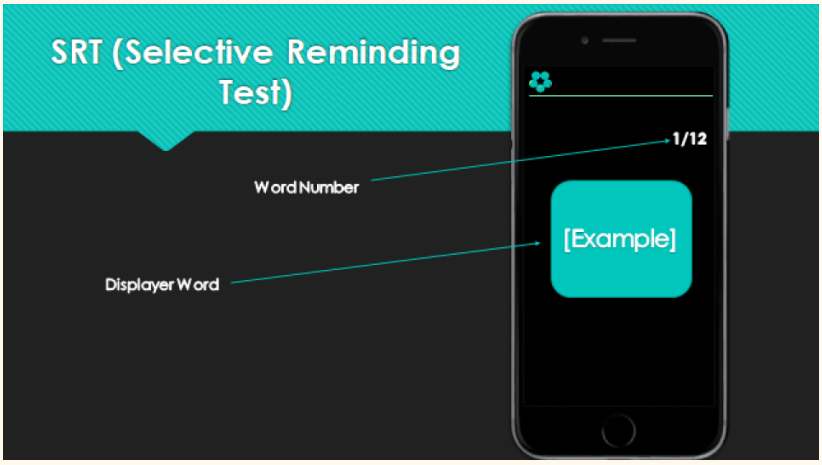
will ask the patient to recall these words. The patient can either choose to speak them out, in which case the voice recognition software will detect them, or write them out. This ends the first round, every round, only the words that the patient has missed in the previous one are given out. Then, once fifteen minutes have passed, the patient is asked to recall all 12 words.

- ## Information processing

The integrated portion would consider a deficit in Information Processing if the patient was: taking too long to switch off alarms, slower typing than usual, slow scrolling speed, fixing sight on particular sections of the screen for an extended period of time, etc. Then, **COFURAMS** would prompt the patient to carry out the following test: SDMT (Symbol Digit Modalities Test) also has an automated version, which would be the one used in this case for devices, responses can both be written and given orally, which would also facilitate giving answers. The screen will display both the symbol key along with the numbers to replace. Then, it is up to the patient to carry out the task, replacing the symbols with numbers, either orally or by selecting them/typing them out on a keyboard. The patient has 90 seconds to pair specific numbers, and a small timer would be displayed in a corner of the screen, for the patient's ease of use.

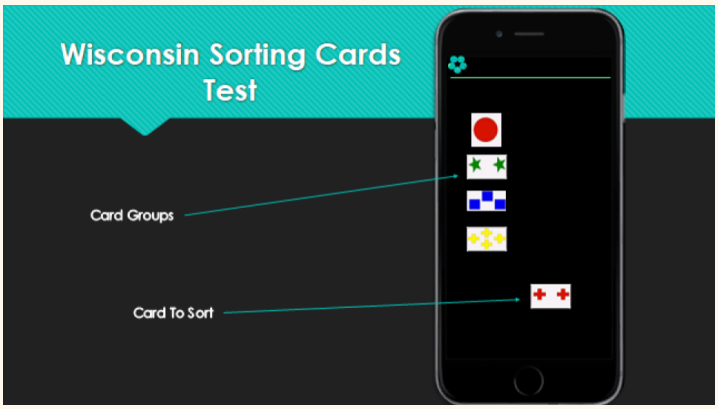


- **Memory**



In this case, the integrated portion would consider a deficit in this cognitive area if the patient was:repeatedly switching between tabs when filling out information, repeatedly selecting the same application after exiting in a short span of time, unusual writing form, unusual number of searches for the same sort of information, etc. If this was the case, **COFURAMS** would prompt the patient to carry out the following test: SRT, can be easily implemented into a device format, along with both voice reception and digital keyboard.The device will output 12 words at a rate of one every two seconds, a time regulated by the application itself. Then, it will ask the patient to recall these words. The patient can either choose to speak them out, in which case the voice recognition software will detect them, or write them out. This ends the first round, every round, only the words that the patient has missed in the previous one are given out. Then, once fifteen minutes have passed, the patient is asked to recall all 12 words.

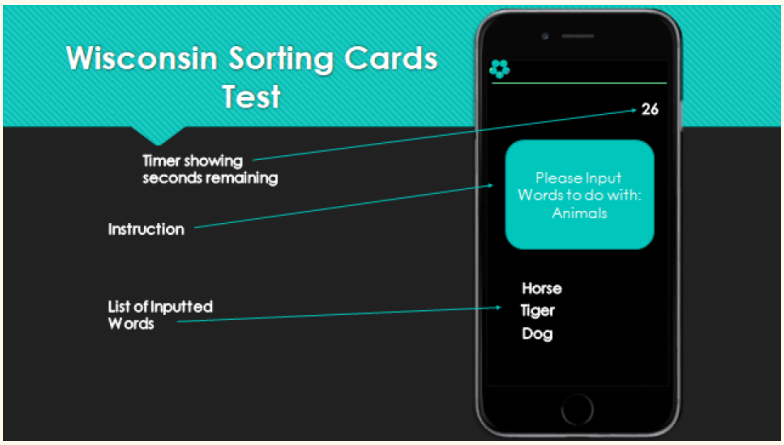
- ## Problem-solving



In this case, the integrated portion would consider a deficit in this cognitive area if the patient was: taking to achieve menial tasks like opening certain windows, when filling out information, not doing so in a logical manner, etc. If this was the case, **COFURAMS** would prompt the patient to carry out the following test:WCST (Wisconsin Sorting Cards Test), easily implemented in mobile devices, and does not need much external prompting for results to be accurate. Cards will be displayed at the top of the device's screen, along with the card to sort at the bottom corner. Then, it is up to the user to figure out the rules for sorting out the cards, with the only feedback being given whether the card has been sorted correctly or incorrectly. Furthermore, the rule may be changed, after a random number of sorts, but no less than 7.

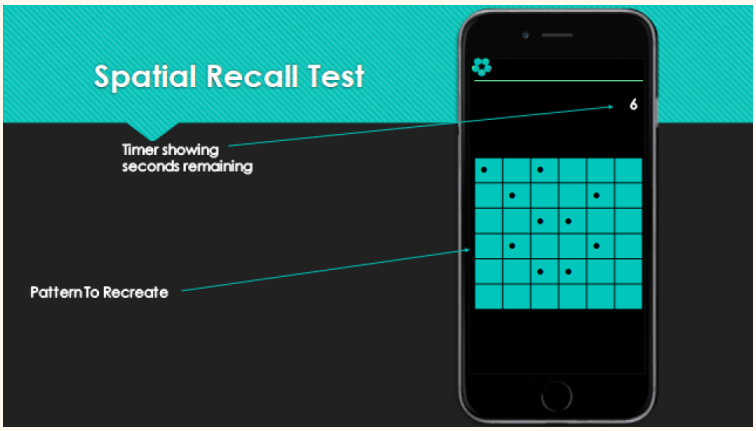
- ## Verbal fluency

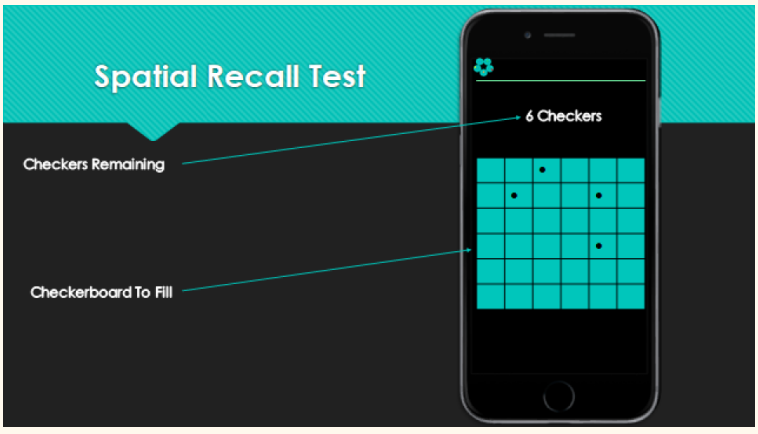
In this case, the integrated portion would consider a deficit in this cognitive area if the patient was: weird formation of sentences when typing, unusual spelling mistakes or vocabulary use etc. If this was the case, **COFURAMS** would prompt the patient to carry out the following test: VFT (Verbal Fluency Test) while this test is usually used for Dementia patients, it can also be used for MS patients, due to similarities in the fields which we look to test for. **COFURAMS** is able to use two variations of the Verbal Fluency



Test. Variation one, the device will display an instruction, whereby it will give the patient 60 seconds to speak out as many words related to a topic, (e.g. vegetables or animals), then, the test will add up all the words the patient has been able to come up with. In the second variation, the device will display an instruction, asking the patient to come up with as many words as he can that begin with a specific letter of the alphabet, having 60 seconds to do so. In both variations, a timer will be displayed to inform the patient of the time remaining in their task.

- **Visual-spatial ability**





In this case, the integrated portion would consider a deficit in this cognitive area if the integrated software campimetry analysis resulted in unusual data or, the patient was: mistakenly tapping the screen in incorrect places, responding late to prompts, unable to find certain options or applications within the main screen, etc. If this was the case, **COFURAMS** would prompt the patient to carry out the following test: SPART (Spatial Recall Test) by implementing both an eye tracker as well as a modified version of the test, which has been developed for mobile devices and computers. The device will reproduce a 6×6 checkerboard, which will have a pattern formed of 10 checkers placed on it. This pattern will be visible to the patient for 10 seconds, after which, the patient will have to attempt to recreate the pattern, with the device displaying a blank checkerboard and ten movable checkers, he will be able to use touchscreen display

to place. This constitutes one round, of which there are three total, before the results are tallied up.

2. May include a module to track changes related to employment status and work capacity

In **COFURAMS**, the system will have a collection of pre-loaded requirements for the most common of jobs. With a database of information, the system will be able to compare it to the results of the tests in real time. With this in consideration, the system will be able to track the changes in the patient's physical, mental and emotional capabilities, and then make informed decisions on the employment capabilities and work capacity of each specific patient. This information will be made available to both the patient as well as the legal and medical guardian, which will have been placed at the start of the testing process.

COFURAMS will have a collection of pre-loaded requirements for the most common of jobs

For this purpose, it is very important that we define in **COFURAMS** the most frequent employment capabilities, so that the system can define which cognitive functions are needed to accomplish the job role, and to what capacity they will be required. For example an accountant that suffers a cognitive deterioration in regards to mental calculus, **COFURAMS** will advise the patient as to this deficit, and will inform them they may not be suitable for the job role, or that they may need to receive advice as to ways to get around their limited capabilities.

COFURAMS is able to store the measured cognitive levels needed for each job, and can then compare them to the received results, thereby informing the patient whether they are fit for the job, or if certain modifications must be made for them to operate at peak efficiency.

Job	Memory	Verbal Fluency	Information Processing	Concentration & Attention	Problem Solving
Policeman	88%	96%	89%	92%	86%
Teacher	88%	97%	87%	99%	86%
Doctor	96%	89%	92%	99%	90%
Programmer	93%	85%	98%	92%	97%
Translator	97%	98%	98%	93%	86%

Minimum Percentage needed in order to be efficient at the job, with 100% being the baseline of the average professional

3. May include a module for the partner, a family member or caregiver to track changes in cognition according to points 1 and 2

When first the patient is registered into **COFURAMS**, he names a next of kin (NOK) or legal guardian and medical in charge who will be able to see the information the patient gives permission to. In its most basic form, the person named as responsible will have access to any glaring issues, whether it be rapidly degenerating qualities or concerning mood situations. In this way, a secondary responsible adult will be able to track any changes found in the patient, and will also be able to offer some more background to the specialist or team responsible for the patient's care. The person

The person responsible will be able to view a variety of obtained data

responsible will be able to view a variety of obtained data.

The simple module will be able to display more or less, depending on the permissions given to the person by the patient. On the most basic of situations, a screen will be available that will display any concerning developments found by the tests. If anything truly concerning is found or suspected by the system, it will also notify the person responsible, with a warning message and a short description of the issue, from here, the person responsible will also be able to notify the doctor of this, and book an appointment or consultation at the nearest possible time.

If a patient gives the person responsible more permissions, then the module will also display the more specific results for each test, along with the results for each specific subsection the system can test for. In this way, the person responsible for the patient, would be able to see a much more intimate array of results, which may be found useful when dealing with the patient in the day to day.

Furthermore, our system can also provide with many other utility uses, which may be favoured by both the patient and their legal carer, all of these options, can also be toggled on or off, depending on what the patient and legal carer, as well as the team of doctors/specialist in charge of the patient feel is necessary.

1. **COFURAMS, can alert the legal carer in case of inaction for a period of time, which can be preset before hand, this could be useful in case a patient was to suddenly suffer from an attack or rapid deterioration in their body functions**

2. **COFURAMS, can alert the legal carer in case the patient forgets to complete a required test, furthermore, reminders can be programmed to be sent to the patient to ensure that they do not forget to complete tests when necessary**

3. **COFURAMS, permits users to view the current percentage of functions, as well as view whether a patient is suitable for a certain profession**

4. **COFURAMS, can also allow the patient to set an 'emergency button' on their phone, in case of emergency, it would serve to contact the emergency services**

5. **COFURAMS, can allow for the configuration of negative or adverse effects of medication, to ensure early detection in case the treatment is not effective (and vice versa), as well as to ensure that any complications that come up can be dealt with before they become a more severe issue**

4. **Must be suitable for self-administration by the patient, or usable with the help of a partner, caregiver or family member, as well as for administration by a non-specialist health care professional.**

COFURAMS has multiple ways for a patient to access its system, from facial or tactile recognition, to a simple password or PIN that may also be shared with the person that will be legally and medically responsible over the patient. In this way, there will always be a manner of accessing the system. **COFURAMS** itself is a simple system, with a clear, concise layout. This means that it is easy to navigate, and the tutorial leaflet that will be freely accessible would only make the task even easier, so that anyone can help administer the test if necessary. Of course, due to its simplicity, it's obvious to say that the patient itself would also be able to self-administer their own test. They would only have to select the appropriate button to begin a test, and then follow the set of instructions displayed on the screen, specific to each test. These instructions are more informative than anything, since they mostly highlight time limits, answer format, and so on. All of these things are things which the system automatically takes care of.

COFURAMS itself is a simple system, with a clear, concise layout

COFURAMS is divided into parts, the testing application, and the integrated data collecting system, the latter of which only needs to be set up once. The application is where the patient will carry out all the necessary tests at the required time. Once one opens the application, he is met with a login screen, it is imperative that there are multiple ways to get through it, to ensure it can be done not only by the patient, but also by a family member or carer. Once the application has been accessed, the main screen would display a button, which would make it clear it is the button that needs to be pressed to begin a test. After this,they only have to continue going through each test, as all the necessary tests they have to complete will happen

one after another, automatically sequenced by the system, in order to ensure that no test is missed.

Furthermore, a window of the application allows access to a sort of public forum, where groups (called Support Networks) of patients and volunteers that have gone through appropriate training and vetting, can interact and talk to each other, offering another solution to any queries or concerns a patient or care may have. This allows for worries to be dealt with in a more informal manner, ensuring that above all, the patient and the carer all feel comfortable and ready to operate within the system, and beyond.

5. Must provide accurate measurements using one or more tests that cannot be learned.

The idea of **COFURAMS** is that we do not only test by regular learnable methods, we analyse features of behaviour and actions of daily life. This is specifically shown in the second part of our system, the integration analysis. What this would do, is apply various existing pieces of software to the device, so that when the patient is using it, data can be collected. This data will be combined with the appropriate tests, which will allow the system to give a set of accurate measurements using testing features that could not be learned.

The idea of COFURAMS is that we do not only test by regular learnable methods, we analyse features of behaviour and actions of daily life

In addition to this, **COFURAMS** only uses specialised tests, such as the SRT test, which target specific cognitive aspects, and cannot be learned by the patient. In this way, we are able to collect a wide array of results, which can then be collected and grouped together appropriately, creating a database and tabulising them in an easy-to-understand manner.

In addition to this, within the more 'social' tab, patients can access appropriate games such as Sudokus, which they can play, to improve and maintain their cognitive capabilities. It is also possible for patients to share their scores within a public ranking, a completely optional part of the more 'social' aspect of the application, that may offer patients an extra incentive to improve upon their capabilities.

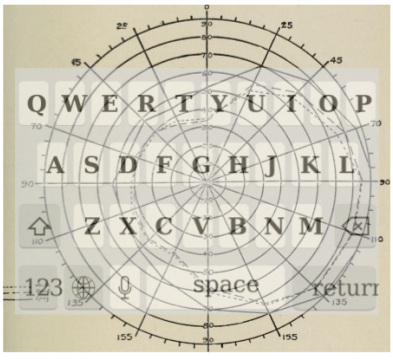
6. Must collect time-coded data, with the option to download results in a format that can be forwarded to a clinician if the patient opts to do so.

COFURAMS has the ability to collect data from both the integrated system, as well as the testing itself. All of these results and data are collected in a database, and also displayed in a tabular format. This database can easily be downloaded in various easy-to-access formats such as PDF. These downloads can then be easily forwarded to a clinician through a file sharing system, or an emailing platform. All of this data that is being stored and analysed is time-coded. With separate columns for dates and times of when the data was gathered, being created as an integral part of the database.

COFURAMS has the ability to collect data from both the integrated system, as well as the testing itself

For example, part of **COFURAMS** integrated system works by giving the patient a simple campimetry analysis based on the touch screen of the mobile according to errors, this can be displayed on its lonesome, or also displayed as part of the finalised and combined results.

MS CAMPIMETRY INTEGRATED TOUCHSCREEN KEYBOARD



However, a more detailed analysis of this campimetry data can be obtained, were anything suspicious or out of the norm be found, by forwarding the data to a person with access to a more powerful statistical analysis tool such as the SPSS (Statistical Package for Social Sciences).

7. Must be user-friendly and incentivize repeated use.

The patient will be able to use **COFURAMS** without noticing that it is registering data from daily activities. Real examples include:

Since the moment that the patient wakes up in the morning, and snoozes the alarm, once or several times, this is registered. If the patient has an integrated watch with the phone, heart rate is monitored and crossed with the information of standing up and taking the first steps. This will immediately provide to the patient a quick evaluation of basic functions, as well as ensure that much of the data is collected without the patient having to worry about carrying out specific actions, he would simply have to go about his day normally.

The patient will be able to use COFURAMS without noticing that it is registering data from daily activities

This, along with the short burst of tests the patient would have to complete throughout the week, would ensure that the system is as user-friendly as it can be. Furthermore, the incentive to repeatedly use the system is the system itself. As it will be mainly integrated with a mobile device, it means that a lot of use will be given, simply due to how prone we are to use our mobile phones. Another feature that would be incredibly user-friendly is the mood tracking. The short question is displayed as a notification, and the user only needs to find a short period of free time to complete it, there is no need to sit down and fill in a questionnaire.

In addition to this, within the more 'social' tab, patients can access appropriate games such as Sudokus, which they can play, to improve and maintain their cognitive capabilities. It is also possible for patients to share their scores within a public ranking, a completely optional part of the more 'social' aspect of the application, that may offer patients an extra incentive to improve upon their capabilities. Furthermore, it is also the perfect aspect to incentivise further use of the software, whilst offering rewards that will become tangible once they see an improvement in their following test results, or at least, a reduction in their decline.

8. Must incorporate symptom (RRMS only) and mood tracking (Depression/Anxiety)

There is a test in MS that is used to evaluate depression / anxiety that can be quickly evaluated along the day, that is the DMQ (Daily Mood Question) test.

This test is simple: throughout the day, the patient is required to answer a short question, which would serve to track their mood. This becomes even simpler when using **COFURAMS**, as the system can display the question as a simple notification on their device. There is no need to stop and fill in a questionnaire, just a short moment where the patient has access to their phone. Furthermore, this test can also be improved by asking more questions spaced out throughout the day, the patient (or if necessary, doctor/team in charge of patient), can define the number of times that he/she wants **COFURAMS** to ask them about their mood.

COFURAMS can display the question as a simple notification on their device

9. Must be targeted to people 18 years of age or older.

COFURAMS is integrated into the mobile phone/device of a patient - normally one that is 18 years old or older. However, there is an option to also add the system and application into the device of someone that is younger, as long as there is parental consent, or the legal guardians have agreed to do so. In this case, while we may expect a less rigorous attempt at tests, it may be balanced by the comparatively higher device usage.

COFURAMS is integrated into the mobile phone/device of a patient

Furthermore, someone not being of age means that a legally responsible adult would always have to be present for tests, analysis... This means that a large part of the self-administration

and independence **COFURAMS** offers would be nullified. This would mean that the system is targeted at legal adults, who can self-administer tests, and can quickly change aspects of their tests with their doctor's advice.

10. May be used to inform clinical decision making

When **COFURAMS** is first implemented, the patient provides permission to the Neurologist or to the team involved in the patient's care to observe the results and data gathered by the system. This large collection of data, which over time could also be used to create trend lines, predictions, and so on, would be of great use for clinical decision making.

This large collection of data, would of great use for clinical decision-making

Furthermore, it could also serve the purpose of giving the patient an orientation about the necessity of getting a doctor appointment based on the results, where they do not have one booked in the near future. This feature works particularly well early on, due to the fact that as soon as the system observes something unusual, it would inform both the patient and the doctor of the need to have an appointment in order to discuss these results.

There is of course an option of emergency referral, in the case that the system detects a sudden deterioration of more than 5% in one area. In this case, an alert would be sent to the doctor or specialist in charge, and an immediate request would be made for the patient to visit the doctor.

In addition to this, it is also possible to create a specific clinical trial configuration, with the specific results one would expect, along with possible side effects. In this way, the system would be able to inform the team in charge of the trials of any developments, and also have an option to reassure the patient of any side effects they may or may not be having.

For example, it would be possible to set up a trial for Drug 'X'. The team would be able to input data into the system, informing it that it is possible receivers of the drug may feel slight dizziness when waking up, along with toggling an option to inform all participants of this. In this way, the system would send an alert every morning, informing all participants that some

slight dizziness when waking up was to be expected. In this way, patients would be reassured, and the number of queries they would have to deal with would be reduced, lightening their workload, and ensuring that the trial would overall run in a much smoother manner.

SUCCINCT RATIONALE

Evidence suggests that generic measures may not be appropriate for MS. We developed with COFURAMS an MS-specific preference-based measure to quantify the impact of MS and its treatment: deriving a health state classification system, which is amenable to valuation, from the 29-item Multiple Sclerosis Impact Scale (MSIS-29), a widely used patient-reported outcome measure in MS.

The main aspect of **COFURAMS** is its dynamic system, something no other similar software or application in the market such as Emilyn, Companion or MS Cognition are capable of. **COFURAMS** can use its integrated system to find areas in which the patient may be lacking, and therefore request a more targeted test for the patient to complete.

This function of our system can be easily explained with an example:

If the integrated portion of **COFURAMS** had been detecting that for one week, the patient has repeatedly increased the volume output of his device. With this, the system is able to analyse a change in behaviour, and thereby request the patient to carry out a test that would be able to give it more data on this issue. Once the patient has carried out this test, more light would be shed on the issue, and we would be able to see whether there is an issue with the patient's hearing, in which case, an appointment could be booked with the appropriate specialist.

Another example of this would be the following:

For some time now, the campimetry analysis has shown that whilst sending messages and typing on the keyboard, the patient makes repeated and numerous spelling errors. At this, the system is alerted, and therefore requests the patient to take a more appropriate test, in hopes of dealing with this particular issue.

While developing the initial versions of the software, we carried out some queries, in order to gather data on what was considered important, as well as having some overall feedback, these were some of the responses received, when surveying a closed test group of 147 patients, along with their carers.

- 67% considered that being able to track and therefore rectify their mood daily was the most relevant aspect of the system.
- 74% considered that belonging to a support group, allowed them to alleviate concerns they may have when using the software, or in their daily lives.

- 54% favoured insulating their family from their usage of the app, only wishing to confide in the person legally and medically responsible for them, as well as their support group.
- 34% considered that having the option of an emergency button made them feel safer, and only 3% felt it was unnecessary.
- 94% of carers felt that being able to also be part of a support group, made them feel more confident in helping their respective.
- 97% were grateful to the targeted and dynamic aspect of the system, as it allowed them to find and solve issues much faster than they normally would

SUPPORTING INFORMATION

Privacy Policy COFURAMS

We describe an overview of the main subjects related to the privacy policy of **COFURAMS**:

- Data protection. Data is encrypted and only associated with the user when providing a unique login credentials.
- An external Data Protection Officer is required.
- **COFURAMS** will only collect, use and/or pass on personal data if this is permitted by law or if the user gives consent.
- Applicable legal provisions are, in particular, those of the regulation (EU) 2016/679 of the European Parliament and Council of 27 April 2016, repealing the directive 95/46/EC, on the protection of individuals with regard to the processing of personal data, on the free movement of such data ("General Data Protection Regulation").
- Analysis of Data. **COFURAMS** uses the information collected, including personal data of the user, in order to improve and analyze the functional use of the App based on the Art. 6 (1) b.

RESOURCES FOR IMPLEMENTATION

Budget

We can separate the budget for **COFURAMS** into the main parties:

a) **Team:**
   - Manager: 30.000 $
   - Programmer: 25.000 $
   - Secretary - Call center: 12.000 $
   - Secretary - Call center: 12.000 $

b) **Software:**
   - Website: 3.000 $
   - Mobile App: 2000 $
   - Server - site: 1000 $

c) Support:

- Legal advice: 3.000$
- Design: 2.000 $
- Marketing: 3.000 $
- Statistical analysis and validation: 6.000$

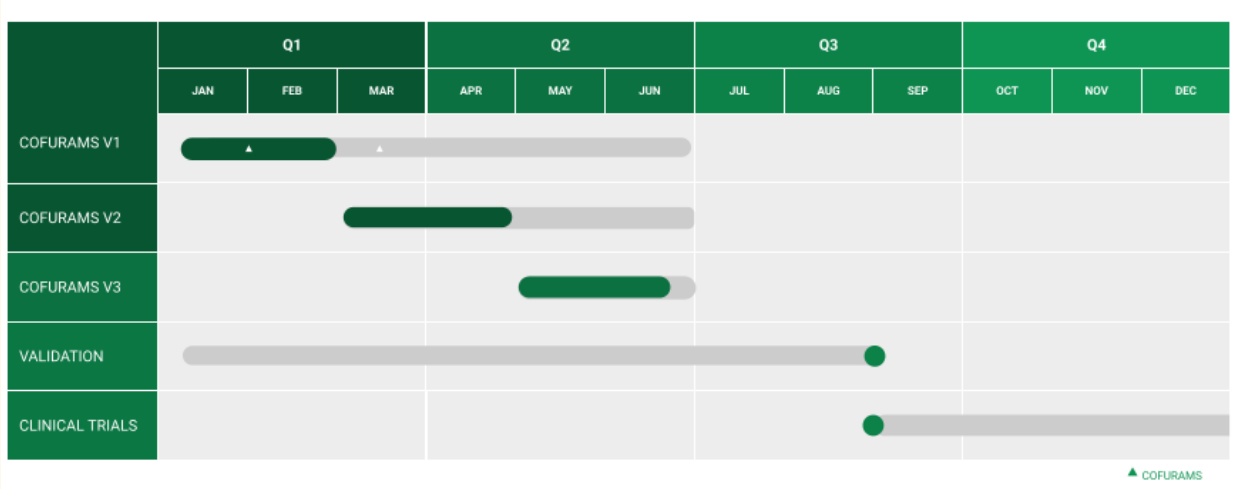
Teams		**79.000$**
	Manager	30.000 $
	Programmer	25.000 $
	Secretary - Call Centre	12.000 $
	Secretary - Call Centre	12.000 $
Software		**6.000$**
	Website	3.000 $
	Mobile App	2.000 $
	Server - Site	1.000 $
Support		**15.000$**
	Legal	3.000 $
	Design	2.000 $
	Marketing	4.000 $
	Statistical Analysis - Validation	6.000 $
TOTAL		**100.000$**

We have designed **COFURAMS** in a way that not only is useful to the final user, the patient, but also to the Pharmaceutical Companies which will be using the data in the future clinical assays and to the response to new therapies. This way, the Pharmaceutical Companies will have to pay for the data provided to sustain the project with the final result of providing the best cognitive function reliable assessment in MS for free.

Timeline

- Launching V1 - 2 months. Cognitive Function Assessment with 1 task per functional area.
- Launching V2 - 2 months. Cognitive Function Assessment with 2 more tasks per functional area.
- Launching V3 - 2 months. Full functionality and social interaction.
- Statistical Assessment and validation. After the first 6 months.

- Clinical trials application in the 8th - 10th month. Once data has been processed and validated.



Personnel

We have designed the structure of **COFURAMS** with a specific budget for the main members of the team: manager, programmer and two secretaries in charge of the call centre. The rest of the team will be based on specific support when needed.

We need to take into account that the moment we can incorporate **COFURAMS** to the clinical trials, each Pharmaceutical Company will provide the resources for a Research Nurse or monitor of the clinical assay that will evaluate the application.

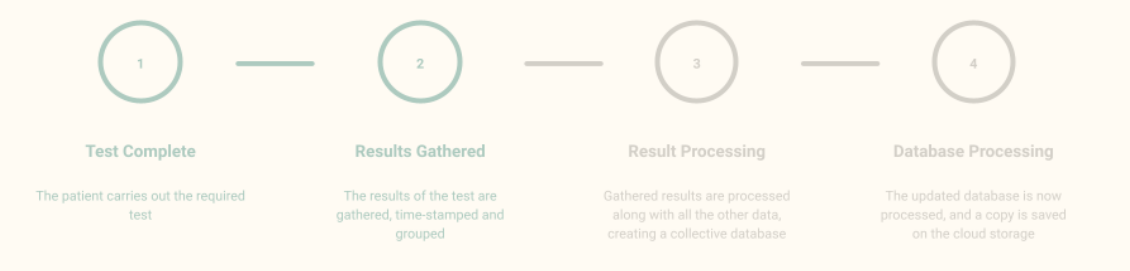
Moreover, after 6 months, with the "Social Integration" we will create the following structure for users, who belong and are active within their Support Networks. Users will be able to react to comments or posts in multiple ways, and all of these reactions will serve separate purposes, to either increase (likes, high ratings...) or decrease (reports, flags for inappropriate content...) their points, an internal quantified structure of the app that will allow users to increase or decrease in 'rank'. In this structure, these would be the initially proposed 'ranks':

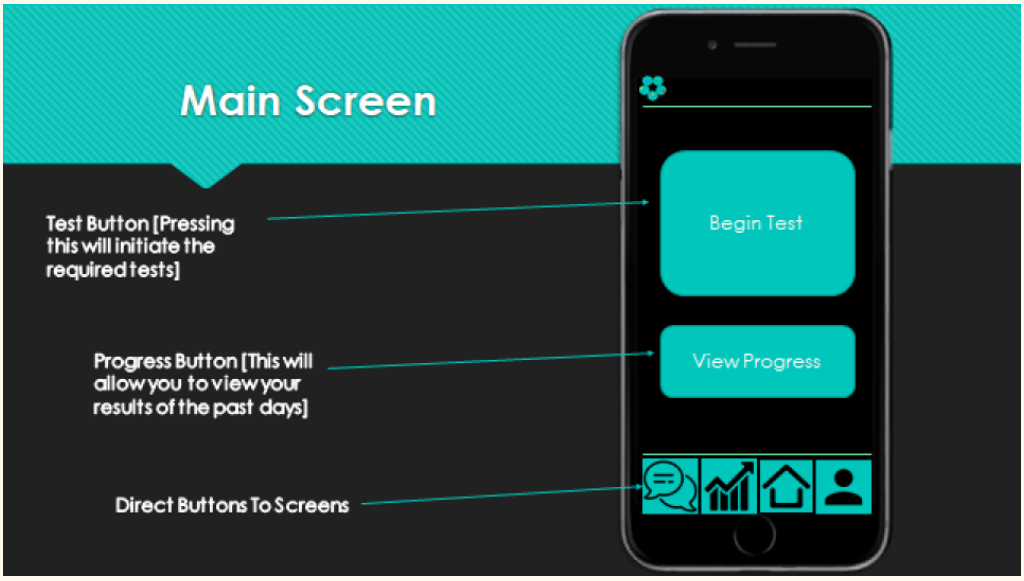
- Platinum Supporter
- Gold Supporter
- Silver Supporter
- Basic Supporter

In the initial testing, it was found that new users appreciated having users who were more ‘reputable’ guiding them, as it eased worries of being mislead, whilst also creating a mentee-mentor relationship which was found to be extremely helpful - particularly to those users that were not confident in their use of more modern technologies and mobile devices.

VISUAL ELEMENTS

Diagrams





OTHER BENEFITS OF COFURAMS

Clinical Trials Evaluation

In clinical trials of MS, the EDSS is the most widely used outcome measure to determine disability worsening and define relapse-related change in neurological function. Furthermore, it is used as an inclusion criterion and to characterize study populations[34],[35]. However, the value of the EDSS as a surrogate outcome measure for future disability is limited.

Another difficulty is that disability often accumulates slowly. Consequently, long-term follow-up is needed to assess treatment effect, which makes trials time-consuming and expensive. Lastly, disability is influenced by confounding factors that may not be directly related to disease activity (e.g. fatigue, mood disturbances, deconditioning, spasticity and side effects of medication).

Correlation to MRI and Areas Affected

This means that the team of doctors or specialists in charge of the patient, would be able to use MRI results, and correlate them with the data gathered by **COFURAMS** . The main benefit of this is that it would allow for a direct correlation to be created between imagery from the MRI scans and graphical or numerical data from the system. This would allow a team to both quantify and diagramify their findings.

Other Neurological Deficits

COFURAMS can be implemented in any patient's phone to detect cognitive deficits as in dementia, multisystemic atrophy, or other degenerative diseases.

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