NICE advice

icobrain ms for active relapsing–remitting multiple sclerosis

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is icobrain ms. It is used to assess disease activity or early signs of disease progression from brain MRI scans in people with active relapsing–remitting multiple sclerosis (MS).
- The **innovative aspects** are that icobrain ms quantifies the brain MRI scans and summarises clinically relevant findings in concise structured electronic radiological reports with annotated images.
- The intended **place in therapy** would be when monitoring disease activity in people with active relapsing–remitting MS, including when making a clinical decision to switch therapy.

- The **main points from the evidence** summarised in this briefing are from 6 studies (3 non-randomised comparative studies and 3 technical validation studies). They show that icobrain ms has comparable accuracy for brain volume assessment compared with Structural Image Evaluation using Normalisation of Atrophy (SIENA) analysis in people with relapsing–remitting MS. The evidence suggests that the technology reduces staff reporting time.
- **Key uncertainties** around the evidence or technology are that the evidence is limited in quantity and quality and primarily assesses the technical validity of the technology. There is no evidence for its use in the NHS.
- **Experts advised** that icobrain ms is innovative, but can only be used in addition to current practice. They added that there is evidence for system benefits because of reductions in staff time, but more evidence is needed to verify the claimed patient benefits.
- The **cost** of icobrain ms ranges from £30,000 to £60,000 per year (excluding VAT). This is in addition to standard care.

The technology

icobrain ms (icometrix) supports the objective tracking of disease progression in people with active relapsing–remitting multiple sclerosis (MS). The software quantifies brain MRI scans and summarises clinically relevant findings related to white matter lesions and brain atrophy.

icobrain ms allows objective assessment of lesion dissemination in space and time by detecting, quantifying, and tracking the evolution of FLAIR/T2 white matter hyperintensities and T1 white matter hypointensities. It also contrast-enhances T1 hyperintensities to evaluate disease activity and reports the distribution following the McDonald criteria (juxtacortical, periventricular and infratentorial).

The technology provides precise and relevant brain atrophy measures by tracking yearly brain volume changes for whole brain and grey matter. It compares brain volumes and volume changes to a population without MS matched for age and gender.

Innovations

The technology aids the quicker detection of sub-optimal response to treatment in people with active relapsing–remitting MS. It could therefore enable earlier switching to an alternative more efficacious agent. icobrain ms summarises the findings in structured electronic radiological reports with annotated images. This may reduce the time a radiologist needs to make an assessment and could allow assessment by staff working at lower grades.

Current care pathway

People with MS who have had 2 or more clinical relapses in the last 2 years are diagnosed with active relapsing–remitting MS. Individuals with active relapsing–remitting MS start disease-modifying therapy (DMT). This can be with a drug of moderate efficacy (interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate) or with a drug of high efficacy. People are then monitored, and their MS may be reclassified as more active by frequent clinical relapses or MRI activity, or both. Criteria for disease activity are based on MRI (white matter lesions) and clinical evidence (relapses and disability progression). The MRI evidence is qualitatively assessed by the clinician. Structural Image Evaluation using Normalisation of Atrophy (SIENA) analysis is a validated method for automatic analysis, but has only been used in research settings and assesses brain atrophy only. If people on a low efficacy drug continue to experience disease activity, a switch to a drug of higher efficacy is considered (ocrelizumab, cladribine, natalizumab, fingolimod, ofatumumab, alemtuzumab).

The following publications have been identified as relevant to this care pathway:

- NHS England's Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies (2018)
- NICE's topic page on multiple sclerosis
- NICE's guideline on multiple sclerosis in adults.

Population, setting and intended user

icobrain ms is intended for people with active relapsing–remitting MS, based on radiological and clinical grounds. Relapsing–remitting MS is the most prevalent form of MS

with up to 85% of cases of that phenotype (GP Notebook, 2020). A delay to switching from an ineffective DMT may result in disability. The company specifically acknowledges that the technology can be used for other forms of MS, but because of the lack of multiple DMTs it will not have a high clinical value.

icobrain ms is for use in secondary care. Specifically, the technology is for use in radiology departments by a radiologist or neuroradiologist to assist in analysing and reporting of MRI scans during the assessment of disease activity in people with active relapsing–remitting MS. The radiological report is to be used by the neurologist or care teams during follow-up visits to evaluate patient disease activity status and to inform decisions about DMTs. The company states that a training manual is provided that gives guidance on how to use the software and interpret reports. It further states that it does a clinical and technical test phase before using the technology in clinical practice. The duration is estimated to vary from 1 to 3 months, as 30 to 40 cases are needed to complete the test phase.

Costs

Technology costs

The cost of icobrain ms ranges from £30,000 to £60,000 per year depending on volume (excluding VAT). This covers the licence fee only, but the company states that there are no additional costs. The company estimates a broad patient volume range of 100 to 1,000, but states that there is no linear correlation between the volume and price range. User training and customer support are included in the licence fee, with training estimated to take 3 to 6 hours of radiologist time. The company states that there are no additional costs for software updates or any other intervention for the correct functioning of the software, except for installation of the icobridge software used for data pseudonymisation and transferring. The company estimates that the cost of installing this software is minimal.

Costs of standard care

The cost of icobrain ms will be in addition to standard care.

Resource consequences

The company states that the technology is currently not routinely used in the NHS. It suggests that adopting icobrain ms will reduce the time needed to assess MRI results and

the level of expertise needed to assess MRI scans, therefore releasing clinician resource. The technology enhances the detection of lesions and brain atrophy, which signal disease progression. This would lead to better patient outcomes because of the timelier switch to more effective DMTs and could contribute to additional cost savings. This claim is supported by an early cost–utility analysis done by the company (Sima et al. 2021). The study estimated quality-adjusted life-year gains of 0.23 and 0.37 over 10 and 15 years respectively, and average cost savings of $1,500 to $2,200 per patient in the US. The effects of uncertainty were not assessed.

Adopting icobrain ms does not need any changes in facilities or infrastructure. The software does not need any additional equipment to be purchased.

Regulatory information

icobrain ms is a CE-marked class I medical device regulated under 93/68/EEC.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Multiple sclerosis (MS) disease progression and disease-modifying therapies can lead to sustained disability. Women are at a greater risk of MS, and the condition is most likely to be diagnosed in people aged 20 to 40. Disability, sex and age are protected characteristics under the Equality Act 2010. People with MS are automatically protected under the Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement for medtech innovation briefings. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

There are 6 studies summarised in this briefing, selected as the most relevant and best quality evidence relating to the technology. The studies comprise evidence on a range of people, including 160 with relapsing–remitting MS. Four studies did not clearly state the number of people with relapsing–remitting MS and 1 did not state the number of people at all. The selected studies report on an earlier version and the current version of icobrain ms (previously MsMetrix).

The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

Overall, the quantity and the quality of the technical evidence for the technology is moderate, but limited in terms of the clinical benefits, particularly for patients. There is no evidence in the NHS. The comparator in the technical validity studies is a reference (gold) standard, which is suitable. But in some cases, a different comparator could be more appropriate, for example, patient outcomes with and without the technology. The evidence comes from 5 papers and 1 conference abstract that report on multiple outcomes and often include people with different MS phenotypes. It was unclear how many people had relapsing–remitting MS in 4 studies. More prospective comparative studies are needed to evaluate the patient benefits of the technology. These should include assessment of icobrain ms in the NHS.

Van Hecke et al. (2021)

Study size, design and location

An observational study assessing the performance of radiologists with different levels of experience in terms of effect on diagnostic findings and reporting time.

Intervention and comparator

icobrain ms lesion segmentations assessed by a non-specialised neurologist compared with experienced neuroradiologists; MRI results assessed by a radiologist twice, once with a computer-aided report with icobrain ms and once without.

Key outcomes

Performance of radiologists with different levels of experience. Intra-rater test-retest lesion count agreement on scan and rescan images was significantly improved for non-specialised neurologists, but the effect was not observed for experienced neuroradiologists. Inter-rater lesion count agreement was significantly better when icobrain ms was used. The mean time for conventional radiological reporting was 7 minutes 28 seconds (standard deviation [SD] 3 minutes 6 seconds). The median computer-aided reporting time was 5 minutes 49 seconds (SD 2 minutes 15 seconds). People with relapsing–remitting MS and people with clinically-isolated syndrome showed significantly higher whole brain and grey matter volumes and lower ventricular volumes compared with other groups.

Strengths and limitations

The study provides direct evidence for the potential system benefits of the technology. Not all people in the study had relapsing–remitting MS. All authors were affiliated with the company. Some of the results were also reported in abstract form (Sima et al. 2020).

Beadnall et al. (2019)

Study size, design and location

An observational study of a cohort of 102 people with MS in a real-world setting (99 with relapsing–remitting MS) assessing longitudinal percentage brain volume change (PBVC) in Australia.

Intervention and comparator

Automated assessment with icobrain ms compared with Structural Image Evaluation using Normalisation of Atrophy (SIENA) analysis (gold standard).

Key outcomes

Agreement of PBVC measurements between the 2 technologies and assessment of correlation between lesion volume and PBVC. Annualised PBVC as measured by icobrain ms correlated strongly with SIENA measurements (Pearson's correlation coefficient, r=0.805), with excellent consistency (Intraclass Correlation Coefficient, ICC=0.801) and

agreement (ICC=0.800). Agreement between non-annualised PBVC measurements was very similar (correlation coefficient, r=0.797; consistency ICC=0.793; and agreement ICC=0.793). Change in total FLAIR lesion volume weakly correlated with annualised PBVC for icobrain only (Kendall Tau rank correlation analysis, tau=0.134; p=0.046).

Strengths and limitations

The technology evaluated was compared with the current gold-standard method for the measurement of PBVC (SIENA). A limitation is that not all people in the study had relapsing–remitting MS and that brain atrophy is currently not used as an indicator in the NHS. Three of the authors were affiliated with the company.

Smeets et al. (2016)

Study size, design and location

A technical validation study of 167 separate scan pairs (from 10 people with MA in dataset 1, 3 healthy subjects in dataset 2, and 20 people in dataset 3) evaluating the measurement error, robustness toward physiological processes and consistency of icobrain ms.

Intervention and comparator

Automated assessment with icobrain ms compared with SIENA analysis (gold standard).

Key outcomes

Measurement error, robustness and consistency of the technology, measured by PBVC. icobrain ms showed measurement errors comparable to, or lower than, SIENA. The test–retest PBVC computed by icobrain ms differed in absolute value from the expected 0% by a median of 0.13% (interquartile range [IQR] 0.09% to 0.29%). Those of SIENA differed from 0% in absolute value by 0.17% (IQR 0.08% to 0.22%). However, the difference between the technologies was not significant (p=0.54, paired t-test; p=0.60, Wilcoxon signed-rank test). icobrain ms showed robustness toward daily physiological processes. icobrain's overall error for whole-brain atrophy was significantly smaller than SIENA's (median absolute value of 0.19% for icobrain ms and of 0.31% for SIENA). The longitudinal consistency of the technology was assessed by the correlation between whole-brain atrophy measurements obtained with icobrain ms and SIENA. A Pearson correlation

coefficient r=0.91 and an intraclass correlation coefficient ICC=0.90 suggested relatively high consistency. No significant differences were seen between the technologies in terms of the consistency index for 6-month intervals compared with the 1-year interval of the whole-brain atrophy.

Strengths and limitations

The technology evaluated was compared with the current gold-standard method for the measurement of PBVC (SIENA). However, this technical validity study gives little evidence for the clinical validity of the technology. A further limitation is that it is unclear which people in the study had relapsing–remitting MS. Also, the data used is heterogenous and comes from 3 countries (Belgium, the US and the Czech Republic). Eight of the authors were affiliated with the company.

Wang et al. (2016)

Study size, design and location

A technical validation study of 63 MRI scans (61 from people with relapsing–remitting MS, 2 from people with clinically-isolated syndrome) evaluating cross-sectional whole-brain volume (WBV) in people with MS in Australia.

Intervention and comparator

Automated cross-sectional assessment with icobrain ms compared with SIENAX (structural image evaluation using normalisation of atrophy-cross-sectional) analysis (version for cross-sectional analysis; gold standard).

Key outcomes

Precision and accuracy of WBV for icobrain ms compared with SIENAX. The statistical precision and accuracy of WBV estimation for icobrain ms compared with SIENAX were 0.992 ($p<0.001$) and 0.994, respectively. There was statistical agreement between the methods. icobrain ms showed a 1.0% volume overestimation compared with SIENAX.

Strengths and limitations

This technical validity study provides little evidence for the clinical validity of the technology. A p value for the statistical accuracy of icobrain ms compared with SIENAX has not been reported.

Steenwijk et al. (2017)

Study size, design and location

A technical validation study on 20 simulated brain images, as well as in vivo data from 100 people with MS and 20 people without MS to act as controls. The study evaluated cross-sectional and longitudinal WBV and grey matter volume in the Netherlands.

Intervention and comparator

Automated cross-sectional assessment with icobrain ms compared with SIENAX analysis (gold standard) and longitudinal assessment with icobrain ms compared with SIENA analysis (gold standard).

Key outcomes

icobrain ms displayed bigger average deviation than SIENAX when compared with the reference WBV in the simulated data and in vivo. In longitudinal assessment, mean difference percentage brain volume change was low between icobrain ms and SIENA. icobrain ms suffered proportional errors in some cross-sectional and longitudinal methods.

Strengths and limitations

The sample size for longitudinal assessment was smaller than that for cross-sectional assessment. Another limitation is that the hardware for MRI was upgraded between baseline and follow up. The literature suggests that this may lead to substantial reduction in the reliability of the results.

Van Hecke et al. (2019)

Study size, design and location

A comparative study of standard clinical radiological reports, neuroradiologist review, and automated software reports in 100 people with MS.

Intervention and comparator

New and/or enlarging lesion count was assessed between baseline and 1-year follow-up MRI scans and summarised in reports. Standard clinical radiological reports were compared with structured neuroradiologist review and automated software reports produced with icobrain ms.

Key outcomes

Both clinical radiological and neurologist review reports indicated the same 33% of people having new or enlarging lesions, yet incomplete separate counts. The proportion was 45% when using icobrain ms. Clinical radiological and neurologist review reports specified a presence of enlarging lesions in only 5% of people, while icobrain ms detected such lesions in 39% of people.

Strengths and limitations

The study suggests that automated techniques agree well with manual lesion counts in people with MS having MRI scans. However, the setting of the intervention and the number of people with relapsing–remitting MS in the study were unclear. This study is reported in conference abstract form only so is limited in detail. Three of the authors were affiliated with the company.

Sustainability

There are no sustainability claims about the technology made by the company.

Recent and ongoing studies

Clinical disease activity with long-term natalizumab treatment: a retrospective

observational study of 2 cohorts investigating the proportion of people free of new or enlarging fluid-attenuated inversion recovery (FLAIR) lesions assessed by semiautomatic lesion count by icobrain ms. ClinicalTrials.gov identifier: NCT02677077. Status: completed, no results published. Indication: new or enlarging FLAIR lesions. Medicine: natalizumab, Biogen. Date: 4 January 2019. Countries: Belgium and Czech Republic.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

All experts were familiar with the analysis and interpretation of MRI scans in the context of multiple sclerosis (MS), 2 were familiar with the particular technology, and 1 had used icobrain ms before. Two of the experts were actively involved in research related to the technology.

Level of innovation

All experts agreed that the technology is the first in a new class of procedures. One further expanded that it is novel, but sufficiently mature to be tested for real-world implementation. All experts acknowledged that although the technology may have both patient and system benefits, it will be in addition to standard care. One expert mentioned ongoing research on implementation of the technology in the UK context and research on another, competitive technology. One expert was familiar with competitive technologies, but suggested they are at a less advanced development stage than icobrain ms.

Potential patient impact

Only 2 of the experts agreed that there would be potential benefits to patients from using the technology. The third expert felt that currently there is evidence for indirect patient benefits only, stemming from the system benefits of the technology (discussed below). It was not clear if there would be any subgroups who would particularly benefit from the technology. The experts generally did not specify using the technology in the context of relapsing–remitting MS. One expert estimated that 50,000 to 60,000 people would currently be eligible for it.

Potential system impact

A key benefit to the healthcare system would be a reduction in the use of NHS resources. All experts thought that the technology would result in reductions in staff time spent on reporting a scan, whereas 2 of them thought it could lead to increases in the sensitivity of counting lesions. Two experts expressed concerns that implementation of icobrain ms would need to be cleared with governance and PACS administration because of the icobridge software. One of them further expanded that since brain atrophy measurement is not routinely used in the NHS, using it to guide treatment choice should not be done before there are clear guidelines.

General comments

Only 1 expert suggested that there might be safety and efficacy issues, more specifically mistakes in the automatic count of lesions. In terms of impact, 1 expert thought that the technology would be used in most or all district general hospitals. One expert thought it would be used in a minority of specialist centres, and 1 could not provide an estimate. The experts agreed that further research is needed to address uncertainties in the evidence base, but 2 of them expressed a view that such research is currently being done. In terms of the needed evidence, all agreed and 1 specifically stressed that it would be particularly valuable to assess if the technology leads to better patient outcomes.

Expert commentators

The following clinicians contributed to this briefing:

- Professor Olga Ciccarelli, National Institute for Health Research research professor of neurology, University College London. Professor Ciccarelli declared involvement in imaging analysis and post-processing projects, including a project on developing automatic lesion segmentation using MRI images.
- Professor Klaus Schmierer, professor of neurology, Queen Mary University of London and Barts Health NHS Trust. Professor Schmierer declared that they are a joint lead investigator on a grant application together with the company and that they are involved in a joint working project using the technology and led by Dr Ashok Adams.
- Dr Ashok Adams, consultant in neurology, Barts Health NHS Trust. Dr Adams declared that they are a lead in a joint working project using the technology.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement for medtech innovation briefings sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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