

Reveal LINQ insertable cardiac monitor to detect atrial fibrillation after cryptogenic stroke

Medtech innovation briefing

Published: 16 February 2018

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Summary

- The **technology** described in this briefing is Reveal LINQ insertable cardiac monitor (ICM) with CareLink service for detecting suspected asymptomatic atrial fibrillation (AF) after cryptogenic stroke.
- The **innovative aspects** are: a proprietary AF detection algorithm, which is designed to reduce false positive detections; small device size, which allows insertion outside a catheterisation lab; and memory capacity offering sufficient recording time to establish symptom–rhythm correlations.
- The **intended place in therapy** is in addition to standard care for patients after cryptogenic stroke whose AF remains undiagnosed by standard stroke care. It could also be used to replace repeated longer-term external cardiac monitoring.
- The **main points from the evidence** summarised in this briefing are from 5 studies (1 randomised controlled trial [RCT] and 4 observational studies) including 1,821 adults who have had cryptogenic stroke. The observational studies show that Reveal devices can detect AF and the RCT shows a significantly higher rate of AF detection and subsequent treatment compared with conventional electrocardiogram (ECG) monitoring.
- **Key uncertainties** around the evidence are a lack of studies comparing Reveal LINQ with standard care and whether evidence generated using the predecessor device is generalisable to the current technology.

- The cost of Reveal LINQ with MyCareLink patient monitor is £1,800 per unit (excluding VAT). The resource impact will be greater than standard care because of the device cost and adopting the device would require redesign of current pathways for cryptogenic stroke. These additional costs could be offset from using a less resource-intensive setting for device implantation compared with other continuous ECG monitors, and from the remote monitoring function. In addition, an increased rate of AF detection leading to effective treatment and a reduction in stroke risk would be expected to result in downstream savings.

NICE is in the early stages of planning diagnostics guidance on implantable devices for detecting AF after cryptogenic stroke. Please contact diagnostics@nice.org.uk to register an interest.

The technology

Reveal LINQ ICM (Medtronic) is an insertable cardiac monitoring device (also known as a cardiac event recorder or implantable loop recorder). It is indicated for people with clinical symptoms of cardiac arrhythmias and for people who have transient symptoms that suggest cardiac arrhythmia.

This briefing focuses on the Reveal LINQ ICM for detecting AF in people who have had cryptogenic stroke (which includes cryptogenic transient ischaemic attack [TIA] and embolic stroke of undetermined source [ESUS]). Other uses of the device, such as cardiac monitoring after transient loss of consciousness, are beyond the scope of this briefing.

Reveal LINQ ICM is a small (45 mm × 7 mm × 4 mm) wireless device that is inserted under the skin on the chest wall using an incision of less than 1 cm. The device weighs 2.5 g and has 2 electrodes, which monitor the patient's subcutaneous ECG, and an embedded accelerometer, which measures patient activity. Reveal LINQ ICM has a dedicated AF detection algorithm that detects true AF based on incoherence in the R–R interval of an ECG wave over a minimum of 2 minutes.

Cardiac information is recorded by the device in response to either automatically detected arrhythmias or patient activation. The memory capacity of the device can store up to 27 minutes of ECG recordings from automatically detected arrhythmias, up to 30 minutes of ECG recordings from patient-activated episodes and 2 minutes of the longest AF episode stored since the last interrogation. New ECGs overwrite older ones when the storage capacity is met. Reveal LINQ ICM is a magnetic resonance (MR)-conditional device; this feature allows the safe scanning of a patient implanted with Reveal LINQ in an MR system.

The system also includes a patient assistant and a patient monitor, which patients can use unsupervised when not in hospital. The patient assistant is a battery-powered, hand-held radiofrequency device, which when held in front of an implanted ICM can activate the ICM to

record cardiac data. When the patient monitor is plugged in within 2 metres of the patient and has adequate cellular signal, data from the ICM is wirelessly sent to the patient monitor and uploaded via the Medtronic CareLink network service (see NICE's advice on [CareLink for remote monitoring](#)) for review by a physician.

Current care pathway

Some people with cryptogenic stroke will have AF, which puts them at increased risk of subsequent stroke. If AF is diagnosed, anticoagulant therapy can be offered to reduce this risk. People with cryptogenic stroke are routinely assessed for undiagnosed AF. This typically involves using a standard ECG device to monitor heart rhythm over a short period (typically a few seconds). This can be effective at detecting permanent AF, but may miss intermittent AF.

If a person with cryptogenic stroke is suspected to have intermittent AF, they may be offered heart-rhythm monitoring using a 24-hour ambulatory ECG or a 24-hour event recorder. Extended ECG monitoring may be done for 7 or 30 days. In some cases, longer-term monitoring using an implantable cardiac monitor may be needed; this is put into the person's chest by a cardiologist in a catheterisation laboratory.

Currently there is variation in NHS care pathways on how long an episode of AF should last for the person to be diagnosed as having AF. Some clinicians diagnose and treat an AF episode of any length of time; others will only consider treatment if an AF episode has exceeded a threshold varying from 30 seconds to 6 hours. The most common threshold used in NHS care pathways is 2 minutes. This variation means that the number of false positives (people diagnosed with AF who do not actually have the condition) and the number of false negatives (people who do have AF, but is it 'missed' by the monitoring device) varies.

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

- [Atrial fibrillation: management](#) (NICE guideline CG180).
- [Stroke and transient ischaemic attack in over 16s: diagnosis and initial management](#) (NICE guideline CG68, update in progress).

Innovations

Reveal LINQ has a proprietary AF detection algorithm with an enhanced p-wave evidence score, which is designed to reduce the false positive detection rate. Reveal LINQ ICM is also smaller than

other implantable monitoring device and can be implanted in an outpatient setting rather than in a cardiac catheterisation laboratory.

Reveal LINQ ICM has a memory capacity of 59 minutes. It can provide continuous monitoring for up to 3 years.

Population, setting and intended user

Reveal LINQ ICM is intended to be used to detect AF in people who have had cryptogenic stroke including TIAs and ESUS. The device can be inserted in an outpatient or day-case setting. The procedure is done by a healthcare professional such as a doctor or nurse in cardiology, neurology or stroke medicine, or a cardiac physiologist. Reveal LINQ ICM is intended to replace ICMs that need implanting in a catheterisation laboratory and non-invasive ECG monitoring methods used to detect AF in people who have had cryptogenic stroke.

Costs

Technology costs

Table 1 Estimated technology costs*

Description	Cost
Cost of Reveal LINQ with MyCareLink patient monitor (excluding VAT)	£1,800
Follow-up costs; 2 per year over 3 years	£474
Estimated daily cost over 3 years of continuous monitoring	£3.05

* Additional procedure costs are: cost of implant plus consumables, £96; cost of explant plus consumables, £889.

Costs of standard care

Electrocardiogram monitoring or stress testing (EY51Z) costs are £122 on the outpatient tariff or £369 for a day case.

Costs of implantable loop recorders (same cost for day-case and outpatient procedures):

- £3,982 for implanting electrocardiography loop recorder with critical care (CC) score 3+ (EY12A)
- £3,878 for implanting electrocardiography loop recorder with CC score 0–2 (EY12B).

Resource consequences

Using Reveal LINQ ICM would lead to increased costs compared with non-invasive cardiac rhythm monitoring. This could be offset if the device can diagnose AF more effectively than existing heart-rhythm monitors, which in turn could prevent more strokes. Diamantopoulos et al. (2016) estimated the cost effectiveness from an NHS perspective of ICMs for detecting AF in people with cryptogenic stroke; this was done using a lifetime Markov model. The analysis used data from literature and a multicentre RCT comparing Reveal XT (a predecessor model) with conventional ECG monitoring (CRYSTAL-AF trial; Sanna et al. 2014). Patients monitored with an ICM had fewer recurrent strokes and reduced costs related to stroke and the post-stroke period. However, overall costs remained higher than standard care (£19,631 compared with £17,045). The base-case incremental cost-effectiveness ratio (ICER) when patients with AF were treated with non-vitamin K oral anticoagulants (NOACs) was £17,175 per quality-adjusted life year (QALY) and £13,296 per QALY when warfarin replaced NOACs.

If the device can be implanted by a specialist nurse or other healthcare professional, and if it can be used in place of an invasive heart-rhythm monitor – which are implanted in a catheterisation laboratory – it may lead to cost savings. Kanters et al. (2016) did a cost comparison in hospitals in the UK, France and the Netherlands. It looked at the costs of implanting Reveal XT in a catheterisation laboratory compared with inserting Reveal LINQ outside a catheterisation laboratory. The estimated cost savings were: €662 in the UK; €781 in France; and €682 in the Netherlands.

Reveal LINQ ICM is used in NHS cardiology departments for other indications, including transient loss of consciousness. These services may need expanding if use of the device was extended to people with cryptogenic stroke. The cost of training a person to insert and program the Reveal LINQ ICM device is included as part of the Reveal LINQ ICM with CareLink service.

According to the company, 17 NHS organisations currently use Reveal LINQ ICM for detecting AF in cryptogenic stroke. If adopted it would be used alongside a range of non-invasive heart-rhythm monitors.

Regulatory information

The Reveal LINQ ICM (Model LNQ11) with CareLink service is a CE-marked class III medical device. The incision and insertion tools are covered by the CE mark of the device.

A search of the Medicines and Healthcare products Regulatory Agency website revealed no adverse events. However, a Reveal LINQ field safety notice in 2016 addresses a performance issue that affects the recommended replacement time alert. The manufacturer resolved this issue and the file was closed in 2017.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

There is anecdotal evidence suggesting that cardiologists in England are less likely to offer the precursor model Reveal XT to women, older and frail people. Failing to offer the technology to women could stem from concerns about visible scarring on the chest in younger women and subjective evidence on discomfort from the device when wearing a bra.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the [interim process and methods statement](#). 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

This briefing summarises 4 observational studies and 1 RCT with a total of 1,821 people with cryptogenic stroke.

The evidence base for Reveal LINQ ICM in detecting AF in cryptogenic stroke patients is limited. Validation studies of the AF detection algorithm for Reveal LINQ ICM against its precursor device (Reveal XT) show that the LINQ device has improved AF detection capacity (Purerfellner et al. 2014; Sanders et al. 2016). The company suggests that evidence of the clinical ability of the precursor device is generalisable to the LINQ device. Evidence generated by the precursor device in cryptogenic stroke patients have been included in this summary. Table 2 summarises the clinical evidence as well as its strengths and limitations.

Overall assessment of the evidence

The RCT and observational studies included in this briefing may have limited generalisability to the NHS. Only 1 observational study was done in the UK.

All studies applied rigorous screening methods in classifying people with cryptogenic stroke. However, there are variations in the methods applied by each study. These rigorous inclusion criteria can make people's results quite similar at baseline and can minimise any confounding factors, but this could imply that the evidence generated is only generalisable to patients who have had similar extensive testing.

There were variations in the duration of AF episodes used to define the final endpoint across studies. Three studies analysed AF episodes lasting 2 minutes or more; 1 study analysed episodes lasting 30 seconds or more; and 1 study analysed episodes lasting 6 minutes or more.

Table 2 Summary of selected studies

<u>Sanna et al. (2014)</u>	
Study size, design and location	A randomised prospective study of 441 people diagnosed with cryptogenic stroke, after extensive testing. Multinational trial across Europe, Canada and US.
Intervention and comparator(s)	Longer-term monitoring with Reveal XT ICM (n=221). Conventional follow-up with ECG monitoring (220).

<p>Key outcomes</p>	<p>Primary endpoints at 6 months:</p> <p>The rate of detection of AF was significantly higher in the ICM group: 8.9% versus 1.4% in the control group (hazard ratio, 6.4:95% CI 1.9 to 21.7; $p < 0.0010$).</p> <p>The median time from randomisation to detection of AF was 41 days (interquartile range 14 to 84) in the ICM group and 32 days (interquartile range 2 to 73) in the control group.</p> <p>19 first AF episodes were detected in the ICM arm versus 3 in the control arm.</p> <p>The rate of use of anticoagulants in the ICM arm was 10.1% versus 4.6% in the control group.</p> <p>Endpoints at 12 months:</p> <p>The rate of detection of AF was significantly higher in the ICM group: 12.4% versus 2.0% in the control group.</p> <p>The median time from randomisation to detection of AF was 84 days in the ICM group and 53 days in the control group.</p> <p>An additional 10 first AF episodes were detected in the ICM arm compared with 1 in the control arm.</p> <p>The rate anticoagulant use in the ICM arm was 14.7% versus 6.0% in the control group and there was a lower rate of stroke recurrence in the ICM arm.</p> <p>2.4 % of inserted ICMs were removed because of infection or pocket erosion.</p>
<p>Strengths and limitations</p>	<p>This multicentre prospective randomised study had a rigorous exclusion methodology to classify a stroke as cryptogenic. Although 18 patients left the study before 6 months and 18 patients crossed over (12 in ICM arm, 6 in control), the intention-to-treat approach used in the analysis ensured randomisation was not broken.</p> <p>The study was supported by Medtronic and limited by lack of blinding. Also, AF events that might have occurred within the time lapse between randomisation and insertion of the ICM were not accounted for.</p>
<p><u>Ziegler et al. (2015)</u></p>	
<p>Study size, design and location</p>	<p>Retrospective cohort study using anonymised data from a database. Study involved 1,247 people who had an ICM for the detection of AF following cryptogenic stroke.</p> <p>US.</p>

Intervention and comparator(s)	6 months of follow-up with Reveal LINQ ICM in clinical practice (n=1,247). None.
Key outcomes	<p>At 30 days' follow-up, AF detection rate was 4.6% for AF episode with a threshold of 2 minutes.</p> <p>At 6 months, AF detection rate was 12.2% for AF episode with a threshold of 2 minutes.</p> <p>When compared with detection rates at 6 months in the ICM arm of the RCT by Sanna et al. (2014), this represents a 37% increase in AF detection in clinical practice.</p> <p>In this cohort study, 70.7% of patients with AF detected had a minimum of 1 episode lasting longer than 1 hour; 37.4% had at least 1 episode lasting longer than 6 hours; and 12.2% had at least 1 episode lasting longer than 24 hours.</p> <p>There was a significant age-related difference in AF detection rates in people aged 60 and over compared to those under 60 (15% versus 6%, p<0.001) and a non-significant difference in the duration of an AF episode.</p>
Strengths and limitations	<p>This study included a large number of patients and provided insight into the real-world incidence of AF in people with cryptogenic stroke who have had a Reveal LINQ ICM.</p> <p>The study was funded by Medtronic.</p> <p>The work-up before classifying a stroke as cryptogenic was based on the discretion of the treating physician rather than a specified criteria.</p>
<u>Cotter et al. (2013)</u>	
Study size, design and location	<p>A cohort study of 51 people with cryptogenic stroke implanted with ILRs for investigating ischaemic stroke.</p> <p>UK.</p>
Intervention and comparator(s)	<p>Reveal XT.</p> <p>None.</p>

Key outcomes	<p>Among patients with at least 50 days of continuous monitoring, AF was detected in 25.5% (95% CI; 13.1% to 37.9%) of the cohort. Median time to AF detection was 48 days (IQR 34 to 118; range 0 to 154). The remaining patients were followed up with continuous monitoring for a mean (SD) duration of 229 (116) days with no AF detected.</p> <p>People in whom AF was detected were significantly older than patients with no AF (48.9 versus 59.2 years p=0.018).</p>
Strengths and limitations	<p>Based on the geographical location for this study, its results can potentially be generalised to people with cryptogenic stroke within the NHS.</p> <p>This study is limited in its failure to make reference to the total number of stroke cases from which the sample was recruited.</p>
<u>Ritter et al. (2013)</u>	
Study size, design and location	<p>A prospective observational study. 60 people with acute cryptogenic stroke were implanted with an ICM for detecting iAF. All people had 7-day Holter monitoring after ICM was inserted.</p> <p>Germany.</p>
Intervention and comparator(s)	<p>Reveal XT.</p> <p>7-day ECG.</p>
Key outcomes	<p>Implantation took place after a median of 13 days (IQR 10 to 67) after qualifying event.</p> <p>The ICM detected iAF in a significantly higher number of patients 17% (95% CI, 7% to 26%), whereas the 7-Day ECG monitoring detected iAF in only 1.7% (95% CI, 0% to 5%) of patients.</p> <p>The average time from implanting the device to detecting iAF episode was 64 days (range 1 to 556 days).</p>
Strengths and limitations	<p>This study states the population from which the eligible sample was taken and had a well-defined criteria for excluding patients with cryptogenic stroke caused by factors other than AF.</p> <p>This was a single-centre study.</p>
<u>Etgen et al. (2013)</u>	

Study size, design and location	A single-centre retrospective cohort study of 22 people with cryptogenic stroke. Germany.
Intervention and comparator(s)	Reveal XT. None.
Key outcomes	At the end of a 1-year follow-up period, 27.3 % of the cohort had AF detected and secondary preventive treatment was changed to anticoagulant treatment.
Strengths and limitations	This study had a rigorous inclusion criteria, which involved including only patients with MRI proven ischaemia. A single-centre study with a small sample size.
AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; iAF, intermittent atrial fibrillation; ICM, insertable cardiac monitor; ILR, implantable loop recorder; IQR, interquartile range; RCT, randomised controlled trial; SD, standard deviation.	

Recent and ongoing studies

No ongoing clinical trials for use of Reveal LINQ ICM for cryptogenic stroke have been identified. The following relates to ischaemic stroke of known origin.

- [Rate of Atrial Fibrillation Through 12 Months in Patients With Recent Ischemic Stroke of Presumed Known Origin](#). ClinicalTrials.gov identifier: NCT02700945. Status: Ongoing, currently recruiting. Started: March 2016. Estimated primary completion date: November 2018. Estimated study completion date: February 2021. Device: Reveal LINQ insertable cardiac monitor. Indication: Stroke, Acute. Comparator: Standard care. Location: US.

Specialist commentator comments

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

Comments were received from 8 specialists, 1 of whom had not used the Reveal LINQ device but was aware of its use in clinical practice. Another specialist uses the older Reveal XT device in clinical practice but is familiar with the functioning of the LINQ device.

Level of innovation

All experts agreed that the technology is innovative, with 1 describing it as a novel concept for an unmet need to investigate people with cryptogenic stroke. Another expert described the potential pathway the technology fits into as being innovative. Three experts noted that the technology is a marked improvement to standard care because of its ability to monitor AF over a long period. One clinical expert noted that the technology is a minor variation to the older model with improved size and usability.

Potential patient impact

All experts agreed that there are potential patient benefits from the device including a reduction in the risk of stroke (noted by 4 experts).

Two experts noted that the small size of the device would likely to be cosmetically acceptable to people. The experts noted other patient benefits including: fewer hospital visits; less need for rehabilitation; reassurance that AF will be detected in a timely manner; avoiding the loss of life quality; avoiding losing income following a second stroke.

One clinical expert highlighted that people would have the choice not to have the device explanted at the end of the battery life and this could be cost saving.

One expert noted that the technology may not be suitable for older people because of fragile skin, another expert disagrees with this opinion. Another expert highlighted that patient selection would be important for the device to be cost effective.

Potential system impact

Seven experts considered that detecting AF and then starting anticoagulation will prevent strokes, resulting in less use of health resources for stroke-related events.

Five experts noted that Reveal LINQ would cost more than standard care and 1 of them considered that the initial higher cost would be offset by fewer hospital admissions, less need for rehabilitation and longer-term social care savings. Another expert felt the device would cost less than standard care only if it is implanted outside a catheterisation laboratory and the cost of patient journeys are taken into account. One expert noted that device implantation is easy to learn and do in routine clinical settings and that they had been able to do more angioplasties as using Reveal LINQ had

released catheterisation laboratory resources. Another expert considered that the high cost of clot retrieval resulting from blocked vessels in AF patients could be avoided.

Four experts noted that with adequate training, nurses and allied health professionals could implant the device. One expert felt that implanting the device outside a catheterisation laboratory could reduce waiting times and release cardiologist time. One expert felt there would be a significant resource impact if the technology is adopted, as current facilities and the existing pathway for patients with unexplained syncope need to be expanded. Another expert felt the resource impact would be minimal as most hospitals have trained cardiac physiologists for ICM interrogation.

One expert noted the need to involve primary care in patient follow-up and another expert felt that adopting the device would lead to closer liaison between cardiology and stroke doctors.

General comments

One expert noted that early in their experience with the LINQ device they had an increase in downloads of a variety of reports (ad hoc alerts, patient-activated events, routine reports) from the device. This had in turn increased workload. They have used an in-house multidisciplinary team approach to significantly reduce this workload; they now focus on monitoring only AF, unless there is an indication to monitor other arrhythmias. Another expert noted the importance of training staff within stroke services to pick up referrals as the number of eligible patients is rapidly increasing. One expert also noted that the device does not interfere with clothing such as bra straps as the older device did.

Patient organisation comments

Responses were received from Syncope Trust and Reflex Anoxic Seizures (STARS), Arrhythmia Alliance and AF Association on the Reveal LINQ ICM, and have been summarised below.

All 3 organisations expressed that people will feel relieved that Reveal LINQ ICM can record their symptomatic episodes and enable an accurate diagnosis of AF, particularly when diagnosis with other ECG monitors has failed.

Giving recommendations on Reveal LINQ will be a significant change to the way AF is diagnosed and will open up opportunities for using technologies such as pacemakers.

Groups of patients who would benefit from Reveal LINQ are those with undiagnosed AF which cannot be captured by 12-lead ECG or Holter monitoring and younger patients (under 65) who would have their quality of life affected by atrial fibrillation.

All organisations agreed that infection could be a possible problem with the device and Arrhythmia Alliance stated that the likelihood of being diagnosed with other arrhythmias in addition to AF might also be a problem.

Arrhythmia Alliance expressed that people with disability and communication difficulties might have more trouble understanding the functioning of the device.

Specialist commentators

The following clinicians contributed to this briefing:

- Dr Klaus Witte, associate professor and consultant cardiologist, NIHR clinical scientist, University of Leeds and Leeds Teaching Hospitals NHS Trust. Dr Witte provided consultation to Medtronic on the design and features of a new range of defibrillators, co-authored the health economic assessment quoted in this briefing and is working with a research fellow on a project on a different technology class funded by a grant from the company.
- Dr Alastair Sandilands, consultant cardiac electrophysiologist and honorary senior lecturer, University Hospitals Leicester. No relevant conflict of interest.
- Dr Anand Dixit, consultant physician in stroke and general medicine, Newcastle Hospitals NHS Foundation Trust, honorary senior lecturer at University of Newcastle upon Tyne . Dr Dixit was on the advisory board of the company in the past.
- Dr Jenny Chuen, consultant cardiologist with subspecialty interest in devices and heart failure, Nottingham University Hospitals NHS Trust. Dr Chuen has provided speaker services to the company.
- Professor Gregory Lip, professor of cardiovascular medicine, University of Birmingham. Professor Lip has provided consultancy and speaker services to the company.
- Dr Mathew Patteril, consultant anaesthetist with special interest in cardiothoracic anaesthesia, University Hospitals of Coventry and Warwickshire. No relevant conflict of interest.

- Dr Sajid Alam, consultant in stroke, geriatric and general medicine, Ipswich Hospital NHS Trust. Dr Alam has provided consultancy and speaker services to the company.
- Mr Alun Roebuck, consultant nurse for cardiology/associate chief nurse, United Lincolnshire Hospitals NHS Trust. Mr Roebuck has provided speaker services for Medtronic.

Representatives from the following patient organisations contributed to this briefing:

- Syncope Trust and Reflex anoxic Seizure
- AF Association
- Arrhythmia Alliance.

Development of this briefing

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

ISBN: 978-1-4731-2852-1