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SUMMARY OF SAFETY AND CLINICAL PERFORMANCE

BRAINLAB

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- Clinical Evaluator
- Regulatory Affairs AG

Change Log

Sept 2022	Inserted reference number in section 2
March 2022	Inserted device identifiers, modified standards table
October 2021	Updated clinical information section (aligned with CEP, CER and DD); updated references to CER; added Change Log and References section

EM DISPOSABLE STYLET

TABLE OF CONTENTS

1 PURPOSE

This Summary of Safety and Clinical Performance (SSCP) is following MDCG 2019-9 “Summary of safety and clinical performance - A guide for manufacturers and notified bodies” and is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.
The SSCP is not intended to replace the Instructions For Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients. The following information is intended for users/healthcare professionals

2 DEVICE IDENTIFICATION AND GENERAL INFORMATION

Table 1 – Device description

Device Name	EM Disposable Stylet
Article number(s)	18097-01 (Single Box), 18097-10 (Dispenser Box with 10 pcs.)
Basic UDI-DI	4056481EMStylet4C
Reference number	0000282488
Manufacturer	Brainlab AG Olof-Palme-Str. 9 81829 München
Manufacturing site (s)	RAUMEDIC AG, Am Mühlgraben 10, 08297 Zwönitz, Germany - RAUMEDIC AG (contract manufacturer and supplier, Design, Development (Phase 1-8) / Testing, Assembly & Packaging) o Address: Hermann-Staudinger-Str. 2, 95233 Helmbrechts, Germany - Rose GmbH (ETO sterilization, sub-contractor of RAUMEDIC AG) o Address: Gottbillstr. 25-30, 54294 Trier, Germany - NDI Europe GmbH (Critical Component: EM Sensor, sub-contractor of RAUMEDIC AG) o Address: Güttinger Str. 37, 78315 Radolfzell am Bodensee, Germany - ADROIT Mfg Co (critical component: guide wire manufacturing, subcontractor of RAUMEDIC) o Address: 24, SVS Rd, RBI Colony, Dadar West, Prabhadevi, Mumbai, Maharashtra 400025, India
SRN	DE-MF-000006183
Medical Device Description nomenclature	• GMDN: 63570: Intracranial catheter navigation transmitter stylet • EMDN: Z12011485 (surgical navigation instruments – consumables) • MDN 1203 (Non-active non-implantable guide catheters, balloon catheters, guidewires, introducers, filters, and related tools)

	• MDS 1005_1 (Devices in sterile condition) • MDT 2001 (Devices manufactured using metal processing) • MDT 2002 (Devices manufactured using plastic processing) • MDT 2008 (Devices manufactured in clean rooms and associated controlled environments) • MDT 2010 (Devices manufactured using electronic components including communication devices) • MDT 2011 (Devices which require packaging, including labelling)
Class of device	Class III, Rule 6
Year of first certificate issued for the device	2017
Name and Single Identification Number of Notified Body	TÜV Sued Product Service GmbH Ridlerstrasse 65 80339 München SIN: 0123

3 DEVICE DESCRIPTION

The **EM Disposable Stylet** is a pre-calibrated electro-magnetically (EM) tracked guide wire for navigated placement of intracranial catheters or shunts in neurosurgery with the aid of the Brainlab Cranial EM navigation system. It is flexible and has one sensor coil placed at its distal end, ensuring accurate tracking of its tip position. Further the stylet can be used as an intracranial pointer device during craniotomy / cranieCtomy for navigation of anatomical landmarks.
The device consists of a guide wire, a seal (handle area), a cable and a connector. A shunt or catheter is not included. It is being delivered sterile (Ethylene oxide sterilization).

Compatible intracranial catheters from third-party manufacturers must fulfill the following criteria:

- Inner diameter (min. – max.): 1.3 mm - 1.9 mm
- Length: ≤ 250 mm

Compatible Brainlab Software:

- Cranial EM

3.1 INTENDED USE, INDICATIONS FOR USE, INTENDED PURPOSE

3.1.1 INTENDED PURPOSE

The device enables intracranial placement of catheters / shunts and stereotactic localization in neurosurgery.

3.1.2 INTENDED USE

The **EM Disposable Stylet** is intended for single use only. It is a pre-calibrated instrument, intended for electromagnetically tracked placement of intracranial catheters and for use as intracranial pointer in combination with the Brainlab **Cranial EM** navigation system only.

3.1.3 INDICATIONS FOR USE

The **EM Disposable Stylet** is an accessory of the **Cranial EM** system and is indicated for following procedures.

Intended surgical procedures are:

- Intracranial catheter placement
- Tumor resections
- Skull base surgery
- Craniotomies / craniectomies
- Transsphenoidal procedures

The surgical procedures for navigated intracranial catheter placement include clinical indications, where ventricular catheter for the EVD, shunt or Ommaya reservoir is applied. The clinical indications are:

- Therapy of hydrocephalus
- Therapy of increased ICP
- Cyst aspiration

The clinical indications for intracranial pointer device are:

- Resections of tumors located in different areas of the brain, whereby skull base tumors and tumors requiring transsphenoidal approaches are included;
- Localization of access point or trajectory during intracranial catheter placement, craniotomies or craniectomies.

3.2 CONTRAINDICATIONS

Contraindications, side effects, adverse events, warnings, cautions and risks (independent of their rate and probability of occurrence) associated with the **EM Disposable Stylet** are outlined in the current instruction for use.

The **EM Disposable Stylet** is not to be used for other purposes than indicated. It is the user's responsibility to adequately use the stylet in combination with **Cranial EM** system and to decide in each case whether it is reasonable to use the device as pointer or as guiding stylet for placing a catheter during intracranial procedures.

Contraindications and side effects depend on the compatible catheter to be used with the **EM Disposable Stylet**.

There are no known additional contraindications specifically for the **EM Disposable Stylet**. Generally, contraindications depend on the catheter to be used and are associated with the neurological procedures according to the intended use of the device under evaluation.

3.3 INTENDED PATIENT POPULATION

There are no gender or age limitations for intended patients. The **EM Disposable Stylet** is intended for use with adult or pediatric patients.

3.4 RISKS/WARNINGS/SIDE EFFECTS

For clinical use of the Cranial EM system following side effects may apply in general, however, they are not specifically related to the **EM Disposable Stylet**.

Side effects for clinical use of the Cranial EM system

- Extended intervention time in certain cases due to additional time for setup and patient registration.
- In certain cases additional incisions to the patients skin/bone are made for registration purposes and attachment of a skull fixated reference array.

Complications that may result from the use of **EM Disposable Stylet** include those associated with medications, materials and methods utilized in the surgical procedure, as well as the patient's degree of tolerance to any foreign object temporarily inserted in the brain. However, these complications may in general occur for any neurosurgical intervention and are independent from the device itself. The following complications have been reported:

- Failure in accuracy
- Mechanical failures
- Distortion in the magnetic field

Side effects associated with shunt catheter placement (independent from the **EM Disposable Stylet** itself)

- Minor bleeding
- Hematoma without neurological compromise
- Infection
- Overdraining
- Shunt migration

Side effects associated with tumor resection procedures (independent from the **EM Disposable Stylet** itself)

- Minor bleeding
- Hematoma without neurological compromise
- Infection

Potential adverse events associated with shunt catheter placement (independent from the **EM Disposable Stylet** itself)

- Device malfunction
- Subdural fluid collection
- Hemorrhage
- Hematoma with neurological compromise
- Development of abdominal pseudocyst (strictly associated with peritoneal catheter)

Potential adverse events associated with tumour resection procedures (independent from the **EM Disposable Stylet** itself)

- Haemorrhage
- Haematoma with neurological compromise
- Seizure
- Brain swelling
- Infarction
- Disturbance of consciousness
- Motor deterioration
- Hemiparesis
- Aphasia or other neurologic deficit

Cautions

- The **EM Disposable Stylet** is a highly sensitive and pre-calibrated medical device. Handle it with extreme care and verify its accuracy on known landmarks.
- While connecting to the adapter, ensure that the stylet cable is completely uncoiled and not knotted.

Warnings

- The stylet is delivered sterile. If it comes into contact with an unsterile environment during unpacking or clinical use, dispose of the device immediately.
- Verify that the expiration date has not lapsed prior to opening the sterile packaging. If the expiration date has lapsed, the product must be disposed of.
- Verify the sterile packaging prior to opening that it is not damaged. Visually inspect for breaches in the sterile barrier system integrity prior to use. Do not use if the sterile packaging is broken.
- The stylet must only be connected to and used in combination with the **EM Base Station**, using the Instrument Adapter EM for **EM Disposable Stylet**, and not connected to any other device.
- Do not bend the stylet out of shape and do not straighten a bent stylet. A permanently bent or damaged stylet can cause severe patient injury and must be disposed of, as electrical safety and tracking accuracy cannot be ensured.
- Do not modify the **EM Disposable Stylet**.
- The stylet should only be used with closed tip catheters no longer than 25 cm, with its lumen diameter greater or equal to 1.3 mm and not greater than 1.9 mm. For correct catheter placement follow the catheter's instructions for use.
- Verify prior to use that the stylet slides easily (without sticking) in and out of the catheter.

- Always secure the catheter by hand during insertion and ensure that the tip of the stylet touches the catheter's closed tip but without penetrating any catheter drainage holes.
- Only the distal metal guide wire of the stylet can be used invasively. No other part of the stylet is intended to come into direct patient contact.
- Always secure the catheter by hand during the removal of the stylet.
- Be aware that tracking accuracy may be affected if the tip of the stylet is positioned near or inside any other metal instrument. The EM system cannot detect or compensate for distortions of the stylet caused by other metals.
- The stylet is designed for single-use only and must be disposed of after use. Reprocessing damages the device and will lead to inaccurate navigation or other serious patient injury.
- Be aware that you are navigating the tip of the stylet and not the tip of the catheter.
- Use of this equipment adjacent to or stacked with other equipment should be avoided because it could result in improper operation. If such use is necessary, this equipment and the other equipment should be observed to verify that they are operating normally.
- Portable RF communications equipment (including peripherals like antenna cables and external antennas) should not be used closer than 30 cm from any part of the Brainlab Navigation Station including cables specified by Brainlab. Otherwise, degradation of the performance could result.
- Use of accessories, transducers and cables other than those specified or provided by the manufacturer of this equipment could result in increased electromagnetic emissions or decreased electromagnetic immunity of this equipment and result in improper operation.

Residual risks:

No other significant residual risks beside those listed in side effects, complications and adverse events exist.

The following table summarizes and quantifies all identified and mitigated risks related to the EM Disposable Stylet:

Table 2 - Summary of risks related to functional safety and effective performance

Risk (harm and hazardous situation)	Probability after measures
Hazard: Sharp edges Harm: Damage of critical structures. Hazardous situation: The EM Stylet is used as a pointing device and is being inserted in the patient´s brain.	<0.001%
Hazard: Sharp edges Harm: The user cuts itself or puncture its skin with sharp edges of the EM Stylet. Hazardous situation: The user holds the EM Stylet in hands during installation, clinical procedure and dismantling.	<0.001%
Hazard: Electricity Harm: Electric shock can lead to death of patient or user. Hazardous situation: The EM Stylet is plugged into the EM base station and used as intended. The EM Stylet tip or components are in direct contact with the patient and the user. High voltages lie at the instrument in single fault condition.	<0.001%

Risk (harm and hazardous situation)	Probability after measures
Hazard: Burn Harm: Damage of critical brain structures. Hazardous situation: The EM Stylet is inserted in the patient´s brain or held by the user. The temperature of EM Stylet tip and other components is too high.	<0.001%
Hazard: Wrong materials used Harm: Cytotoxic reaction, sensitization, irritation and intracutaneous reactivity, or systemic acute toxicity. Hazardous situation: Leachables or extractables from materials of components of EM Stylet with direct patient contact, are non-biocompatible for its intended use.	≥ 0,001% and < 0,1%
Hazard: Damaged product Harm: Patient injury due to device failures. Hazardous situation: The device is damaged or its intended performance is degraded due to sterilization process, transport or shelf life aging.	≥ 0,001% and < 0,1%
Hazard: Device contamination Harm: Patient infection or inflammation. Hazardous situation: The device is contaminated and not sterile.	≥ 0,001% and < 0,1%
Hazard: Ethylene oxide Harm: Cytotoxic reaction, sensitization, irritation and intracutaneous reactivity. Hazardous situation: Residues of ethylene oxide remain on device or within sterile packaging in toxic concentration after EO sterilization process.	<0.001%
Hazard: Endotoxins Harm: Pyrogenic reaction. Hazardous situation: Endotoxins on EM Stylet get in contact with patient brain during use.	≥ 0,001% and < 0,1%
Hazard: Prions Harm: Prion diseases. Hazardous situation: EM Stylet is contaminated with prions.	<0.001%
Hazard: Mechanical forces Harm: Infection of inflammation. Hazardous situation: The EM Stylet is inserted in the patient´s brain. Some components are loose and have to be removed separately. Some small elements stay in the patient´s brain.	≥ 0,001% and < 0,1%
Hazard: Wrongly placed catheter Harm: Damage of critical structures. Hazardous situation: The catheter is placed too shallow or too deep, because the tip of catheter is not aligned with the tip of the EM Stylet. The distal part of catheter doesn´t reach the intended position.	≥ 0,001% and < 0,1%
Hazard: Wrongly placed catheter Harm: Ineffective treatment. Hazardous situation: The catheter is placed outside of the ventricle (not in its intended position). The CSF cannot be drained.	≥ 0,1% and < 1%

Risk (harm and hazardous situation)	Probability after measures
Hazard: Inaccurate tracking Harm: Damage of critical structures. Hazardous situation: The tracking of the EM Stylet is not accurate. The EM Stylet is placed in positions different than intended.	≥ 0,001% and < 0,1%
Hazard: Foreseeable misuse Harm: Damage of critical structures. Hazardous situation: The EM Stylet is working not correctly due to being used in other way as intended. The tracking accuracy and mechanical stability get worsen.	<0.001%
Hazard: Foreseeable misuse Harm: Patient or user infection or patient injury due to device failure. Hazardous situation: - Packaging does not allow sterile handling of the device. - Device is reprocessed and reused, and as a consequence sterility or intended performance are no longer ensured. - Device is wrongly disposed of.	≥ 0,001% and < 0,1%

4 SUMMARY OF CLINICAL EVALUATION AND POST-MARKET CLINICAL FOLLOW-UP (PMCF)

At the time of the MDR release the EM Disposable Stylet has been successfully on the market for nearly 5 years. Besides pre-clinical data, the clinical evaluation of the EM Disposable Stylet is based on clinical data from a PMCF survey, post-market surveillance data including the evaluation of reported incidents and product complaints on product and on system level and data from a running PMCF study (started with the device being released under MDD).

4.1 DATA FROM CLINICAL INVESTIGATIONS

Post-Market Clinical Follow-up prospective study:

The patient population examined to date includes 9 patients; male and female adults of various ages. The medical indications for the intracranial catheter placements were hydrocephalus of any origin or ICP elevation. Silicone catheters with an inner diameter of between 1.3 and 1.5 mm which are suitable for the EM Disposable Stylet were used. MRI was used as additional imaging to verify proper placement of all catheters. Catheter placement accuracy was assessed using the system developed by Hayhurst et al., 2010. All 9 treatments were successful, 7 catheter placements were rated grade 1 and 2 rated as grade 2. According to the specification of at least 74% of catheter placements with "grade 1", until now the navigation accuracy of the EM Disposable Stylet can be rated as "successful" with 77,8%. 2 adverse events were recorded, but were not or unlikely related to the EM Disposable Stylet. The study is registered in the Netherlands at ccmo (“Central Committee on Research Involving Human Subjects”) with registration number NL76660.078.21.

4.2 OTHER CLINICAL DATA

Post-market surveillance data including the evaluation of reported incidents and product complaints on product and on system level

Summary Brainlab CID search: None of the complaints indicates a systematic error of the product or the biocompatibility or the use of the product, nor resulted in a risk for patient or user. All of them do not trigger an update on the existing risk analysis as suitable measures are already in place. No CAPA, field safety notification or corrective action were issued. All EM Disposable Stylet complaints have not a root cause related directly to the EM Disposable Stylet (but to the Software instrument App). So, they do not indicate a systematic error of the product or of the clinical use or the biocompatibility of the EM Disposable Stylet.

Summary Maude search: No incidents were found directly related with the use of the Brainlab EM Disposable Stylet. 19 records were found for similar device Medtronic AxiEM Stylet related to inaccuracy or non-functioning (lost tracking ability during procedure, or stylet was near wound retractor and distortions occurred, or stylet was not recognized by the Medtronic navigation system at all) of Medtronic AxiEM Stylet. In the reported incidents regarding inaccuracy the inaccuracy was detected by user and neither severe patient injuries nor death were reported that were directly related to use of electromagnetically tracked stylet. Non-functioning stylet did not lead to any patient harm. Procedure delay of less than one hour was reported in some cases. As the incidents occurring for the Medtronic AxiEM Stylet could also occur on the EM Disposable Stylet, they are considered in the risk analysis, but are not counted as clinical data applicable for the EM Disposable Stylet as to restrictions of MDR Article 61.

Summary BfArM search: No records were found describing incidents related to or applicable for the EM Disposable Stylet.

Incident searches on System level: Incident searches on system level for the use cases "Frameless Stereotaxy" and "Cranial Resection" did not identify any new risks or side effects and no systematic issues. No corrective actions were triggered.

Conclusion incident search: Evaluating the production and post-production information for the EM Disposable Stylet, there were no new risks identified related to the use of EM Disposable Stylet that are not considered yet in current risk analysis. Also there is no change necessary based on the review that results in a higher rating of existing risks making it unacceptable. Therefore, it can be concluded that the risk analysis is still valid and an update is not necessary. There is no indication that the mechanical or electrical properties of the EM Disposable Stylet were not appropriate for the intended clinical use. No field safety notice (FSN) or field safety corrective action (FSCA) were issued for the EM Disposable Stylet. No clinical negative effect was reported. The safety and effectiveness of the device are still assured.

Pre-Clinical data from fresh cadaver studies

- Validation test plan and report - transsphenoidal intervention (Internal Registration Nr.: 0000006295 and 0000008204)
- Validation test plan and report - catheter shunt placement (Internal Registration Nr.: 0000006294 and 0000008201)

In eight transsphenoidal procedures (The EM Disposable Stylet was used for the image guided control during the preparation of the entry point to the pituitary gland) and eight placements of ventricular

catheters the intended use of the EM Disposable Stylet was shown. In total 16 placements have been performed and all were rated as acceptable.

The systematic review with a qualitative synthesis of information from the included studies by Song and Jo (2021) systematically assesses the suitability of fresh frozen cadavers (FFCs) for use primarily for surgical training and education but also thoroughly investigates the reasons of FFCs being an appropriate and clinically transferable realistic patient model. The reasons for this high grade of transferability of data and skills collected using FFCs to real patients included realistic texture and tissue quality, capability of reenacting actual operations, and accuracy of anatomical locations.

Fresh frozen cadavers do not include an embalming process. Tissue colours are realistic and minimally altered from the original conditions (Hayashi et al. (2016). Professors reported that incision and drainage procedures were performed with similar resistance and texture to those in real surgical situations. In addition, FFCs are being and can be used for cadaveric research involving precise measurement of distances of structures within the tissues.

FFCs are currently utilized for several purposes, including clinical/medical/surgical training, anatomical studies and cadaveric research including evaluation of medical devices. Although tissue properties are in general very realistic in terms of haptic, colour and operability and superior to embalmed cadavers, the grade of transferability of study results on real patients in terms of performance or safety data needs to be determined on an individual basis.

For the purpose of the evaluation of the implantation accuracy of intraventricular catheters using the EM Disposable Stylet and the appropriateness of the EM Disposable Stylet as a pointing device whole body fresh non-preserved cadavers were used in order to avoid leakage of cerebrospinal fluid, brain shrinkage and consequent dural detachment and air in the subdural space. Skin and tissue elasticity of both cadavers were well preserved and comparable to living patients. Also, when looking at the preoperative MRI scans of the cadavers, specific anatomical areas in the brain can still be well identified and even more importantly, CSF was visible in all ventricles and extraventricular CSF spaces. Considering the data from the systematic review from Song and Jo (2021), it can be concluded that the anatomical proportions and distances, the tissue properties and the operability of the tissue is comparable to real patients. This is in concordance to the MRI imaging data of the fresh cadavers being used for the cadaver study investigating the EM Disposable Stylet. For this reason, these preclinically collected data of the exact position of the inserted catheter and the exact location of the stylet in the ventricles of the brain and in the pituitary gland, collected intrasellarly during the cadaver tests, can be regarded as clinical evidence of the performance parameters.

Post market survey:

The minimum number of procedures in which the EM Disposable Stylet was used can be easily determined from the responses received: there were at least 243 surgical procedures. However, the upper limit can only be estimated from the sales figures. A total of 1066 EM Disposable Stylets have been sold to participating sites up to the date of participation in the survey. The statements of the survey therefore very likely apply to about 400 EM Disposable Stylets that were used in surgical procedures. The customer group can be considered as representative as different levels of experience and frequency of device usage are covered. The survey addresses questions about the clinical use. The claims on clinical safety and performance are therefore supported. Following table shows the cumulative results:

Procedures done using the EM Disposable Stylet	
<10	24

Procedures done using the EM Disposable Stylet	
10…30	9
> 30	4
Type of Procedures	
Shunt / EVD / Ommaya reservoir placement	161
Tracking during tumor resection	12
Tracking during procedures requiring transsphenoidal approach	8
Other	(10)*
Experienced incidents, adverse events or complications (note: only review cycle 2018)	
None	11
Incident already reported	0
Incident not reported yet	0
Bleeding or injury or important anatomical structures	0
Other	0
Experienced device failures	
None, device always functioned as intended	28
Insufficient tracking accuracy	3
Magnetic disturbances	0
Broken guide wire, cable or other component of the EM Disposable Stylet	0
Broken sterile barrier, detected before opening sterile packaging	0
Guide wire not compatible to used catheter	3
Other	7**

Figure 1 Summary of post-market survey results (review cycles 2018 - 2021)

* 10 customers mentioned “other” procedures, where 8 of them were within the intended use. Two customer used the device inside an endoscope channel to track the endoscope, with no problem on tracking or accuracy. This usage represents an off-label use and hazards that could occur during this usage (“EM Disposable Stylet tracking is not accurate”) are already covered by current risk analysis. No new risks arise from this off-label use. Instructions for use contain already an entry regarding EM Disposable Stylet placed inside other metal instrument.

** Following device failures/incompatibilities were mentioned in the survey:

- Insufficient accuracy in one case during treatment of slit ventricle syndrome (shunt). Customer mentioned that accuracy was usually sufficient for ventricular drain placement. No detailed information could be retrieved from the customer, and no complaint regarding this case was found in Brainlab CID database.

- Angle of catheter was “off” (approximately 5%) according to one surgeon. Also here, no detailed information could be retrieved from the customer and no complaint was found in Brainlab CID database. Account owner was informed and a complaint was filed for further investigation.
- Magnetic interferences with stereotactic frame or metal retractors (foreseeable and known behaviour, described as a warning in instructions for use)
- Not working EM Disposable Stylet after placing this on a magnetic mat (known issue with EM instruments when they come in contact with magnetic material)
- Not working EM Disposable Stylet (known bug caused by the navigation software, not caused by EM Disposable Stylet)
- No compatibility with TEW cannula for trigeminal neuralgia (cannula diameter too big for the EM Disposable Stylet; compatible cannula diameters are stated in the instructions for use)
- No compatibility with the Codman catheter the customer uses (stylet too short)
- Not related to the EM Disposable Stylet but mentioned by the surgeon in the survey: Tracking volume of the field generator too small, problems to achieve a good acceptable patient registration

No complications, incidents or adverse events related to the EM Disposable Stylet were reported by the customers who replied.

4.3 SUMMARY ON SAFETY AND PERFORMANCE AND BENFIT/RISK CONCLUSION

4.3.1 REQUIREMENT ON PERFORMANCE

Object tracking is a key enabling technology in the context of computer-assisted medical interventions. Allowing the continuous localization of medical instruments and patient anatomy, it is a prerequisite for providing instrument guidance to subsurface anatomical structures. The only widely used technique that enables real-time tracking of small objects without line-of-sight restrictions is electromagnetic tracking (Franz et al., 2014).

The general benefits of EM tracking are applied in the Brainlab Cranial EM navigation system together with the *EM Disposable Stylet*. Since the *EM Disposable Stylet* enables extending the current scope of indications and enables the Brainlab Cranial EM system to be used for these additional indications at reduced time investments.

Specifically, *EM Disposable Stylet* enables surgeons to navigate the placement of intracranial catheters and identification of anatomical structures when used as a pointer device. The image guidance of the stylet allows the surgeon to work less invasively and to better control the actual position of the instrument tip.

In comparison to the optically navigated *Disposable Stylet,* the *EM Disposable Stylet* has the advantage, that the sensor is placed directly at the tip of the stylet, whereas for optically navigated stylets the tracking markers are located at the proximal handle part or dedicated array. Thus, the navigated *EM Disposable Stylet* is less susceptible for tracking inaccuracy related to bending of flexible guide wire and allows that even under bending the correct tip position is displayed.

Image guidance of the stylet can eliminate poor catheter placement, potentially leading to reduced catheter obstructions and catheter/shunt revision rate (Hayhurst et al., 2010; Jung & Kim, 2013), which

would require additional surgeries. In the case of Ommaya reservoir placement, the enhanced placement accuracy compared to freehand catheter placement, leads to reduced risks of chemo-therapy leakage into the tissue potentially causing toxicity.

The absence of rigid head fixation for electromagnetic tracking allows additional cohorts to benefit from neuronavigation (Azeem & Origitano, 2007). The frameless and pinless system makes the electromagnetic neuronavigation easy to apply and well suited for pediatric patients. The pediatric neurosurgical population presents certain problems not applicable to its adult counterpart. Children are less able to tolerate the rigid head fixation required for many guidance systems. The use of the Mayfield head clamp is inappropriate in children under 2 years of age, and even in those older than 2, rigid head fixation makes positioning and skin preparation awkward. The pain involved in using rigid head fixation and the increased use of anesthetic agents is also an issue that must be considered. Such factors cause increases in operative time and make surgery more difficult (Clark et al., 2008). Therefore, electromagnetic navigation for these pediatric indications additionally supports the clinical benefits in comparison to conventional non-navigated procedures.

The claims on clinical performance are additionally supported by preclinical compatibility tests of catheters, cadaveric validation tests, an in-vitro verification test, usability tests as well as PMS and PMCF survey and PMCF study data.

Within the pre-clinical cadaveric validation studies the intended use of the EM Disposable Stylet was confirmed by two representative procedures. Eight ventricular catheters were successfully placed using EM neuronavigation (75% grade 1 and 25 % grade 2 placements) and eight transsphenoidal procedures were successfully performed using the EM Disposable Stylet for the image guided control during the preparation of the entry point to the pituitary gland. Considering the data from the systematic review from Song and Jo (2021), it can be concluded that the anatomical proportions and distances, the tissue properties and the operability of the tissue is comparable to real patients. For this reason, these preclinically collected data of the exact position of the inserted catheter and the exact location of the stylet in the ventricles of the brain and in the pituitary gland, collected intrasellarly during the cadaver tests, can be regarded as clinical evidence of the performance parameters.

For demonstrating that the EM Disposable Stylet meets the specified accuracy requirements a comprehensive in-vitro verification test was performed using a measurement phantom. It was shown that the accuracy requirement in the recommended tracking volume is fulfilled.

On system level, an in-vitro tracking accuracy and distortion detection test of EM Disposable Stylet referring to Medtronic AxiEM Stylet was performed. These tests confirm the tracking accuracy and the distortion detection functionality for the EM Disposable Stylet and they are still valid for the present evaluation.

Using ground-truth measurement with a coordinate measuring machine on a phantom, accuracy validation tests have been performed for the registration methods provided by the Cranial EM software, as well as for the accuracy of the trajectory guidance. The results show a mean target error below 2.0 mm, and an angular error no greater than 2°. Thus, the system and the EM Disposable Stylet perform to the specified accuracy.

The PMCF Survey Report contains clinical data of representative customer groups from about 400 ventricular catheter placements and use as a pointer device at neuronavigation-assisted neurologic

procedures since product release. The survey confirms the clinical claims on clinical safety and performance.

For use as an EM pointing device, the level of evidence is considered sufficient as the pointing function is also used in locating the catheter entry point and the risk is very low (see data from PMS).

The performance of catheters with defined dimensions has been verified, particularly to avoid that the shunt / catheter tip is significantly displaced during removal of the *EM Disposable Stylet* which is also considered in the risk analysis and therefore to ensure a basic requirement of catheter placements. Dimensions of compatible catheters are indicated accordingly in the instructions for use of the *EM Disposable Stylet*.

Moreover, the clinical performance of the *EM Disposable Stylet* in terms of usability has been demonstrated by the summative usability evaluation of the complete Cranial EM navigation system including the stylet in addition to formative evaluation activities.

The fact that the electromagnetically tracked instruments can be affected by metal artefacts (like metal wound retractor or other metal parts near the tracking area. See one report in MAUDE describing this issue with Medtronic AxiEM Stylet near wound retractor) is meanwhile well known to the physicians and well described in the instructions for use of the EM Disposable Stylet. Also one Brainlab customer mentioned this in the survey response, as he was trying to see what happens when EM Disposable Stylet gets near a bullet that was located in the patient's brain. In the reviewed literature this effect is listed as a disadvantage of the electromagnetic tracking, which is being outweighed by the advantages of it.

One customer wrote in his post market survey reply that "*the EM Disposable Stylet is hard to fit in the ventricular catheter (adult GAV shunt) and especially difficult to push through the burr hole deflector. Once in, it works, but after reaching the target it is again quite difficult to pull the EM Disposable Stylet back while keeping the catheter in place.*" On the other hand he wrote that from a technological point of view, the EM Disposable Stylet works just fine. No case or complaint was found in CID database mentioning this reported issue. According to EM Disposable Stylet Instructions for Use (provided in the leaflet with every stylet) the compatibility of the EM Disposable Stylets with catheters is exactly specified for catheters with inner diameter 1.3mm to 1.9mm. The customer used a Miethke catheter with smaller inner diameter of 1.2mm, what explains the problems he encountered.

Overall, no new or unknown complications or risks associated with the use of the *EM Disposable Stylet* could be revealed in the course of present clinical evaluation. Hazards and their clinical consequences have been characterized according to their putative harm for patients and probability of occurrence. Risk-mitigating measures have been taken. From a technical, biological and clinical point of view, the residual risk for clinical use of the product under evaluation is tolerable after implementation of risk minimizing measures. For more detailed information, reference is made to the risk management file. Moreover, cautions and warnings are outlined in the instructions for use.

All indications derived from the data generated in PMS cycles 2018-2021 provide evidence that the clinical use of the EM Disposable Stylet is safe and effective and represents the state of the art.

A prospective PMCF study for the EM Disposable Stylet to investigate the clinical safety and performance aspects of intracranial catheter placements for the medical indications, hydrocephalus of any origin or ICP elevation was initiated in 2018. The first treatments in the ongoing PMCF study for the

EM Disposable Stylet were successful. These results confirm the safety and effectiveness of the EM Disposable Stylet within its intended use. However, a comparison to the objectives described in the CEP identified gaps and therefore the ongoing PMCF study is deemed very important to generate the missing clinical data. Comparing the results of the performance testing to the CEP objectives, following gaps have been identified. Table 3 lists the different combinations for patient population and surgical procedure and gives information on whether there is a gap to the MDR requirements.

Table 3: Different combinations for patient population and surgical procedure at clinical performance testing and gaps to the MDR requirements.

Clinical Data for Adults and Children	Clinical Evidence	Sufficient?	PMS/PMCF activities
Data for adults in intracranial catheter placement	4, 7, 8, 11	ok	However, the retrospective study is needed to have more evidence available for the next PMS evaluation as the patient enrolment in the Prospective PMCF study is slower than expected
Data for adults in tracking of anatomical structures (e.g. tumor resection, skull base surgery, transsphenoidal approach)	7, 8	Gap	PMS survey about performance of the device when used as a pointing device, incl. accuracy.
Data for children in Intracranial catheter placement	7, 8	Gap	Retrospective study is needed to gather more clinical relevant data.
Data for children in tracking of anatomical structures (e.g. tumor resection, skull base surgery, transsphenoidal approach)	-	Gap	PMS survey about performance of the device when used as a pointer device, incl. accuracy and quantitative information on performed paediatric cases

From the clinical perspective there are too little specific real world clinical data for use in pediatric patients and on using the device in the surgical procedures for approach to skull base tumors including transsphenoidal approach (in adult and pediatric patients).

Therefore, the ongoing/planned PMCF studies (prospective and retrospective) and a dedicated survey are supposed to focus on collecting the lacking data in order to appropriately close the data gaps.

4.3.2 REQUIREMENT ON SAFETY

Brainlab has established a risk management system reflecting the requirements from GSPR 2, 3, 4 and 5 (MDR Annex I, Chapt.1) meaning that during development and the entire life cycle of the device risk management activities are carried out and updated regularly. This includes the systematic identification of hazards, hazardous situations and corresponding risks including their severity and probability

assessment and regular update as well as the identification of risks which are residual risks, the overall residual risk and risks in the ALAP region.

A comprehensive risk analysis for the product under evaluation has been performed by Brainlab. Thereby potential risks have been addressed and assessed. In the risk analysis, hazards and their clinical consequences have been characterised according the alleged harm for patients and probability of occurrence. Risk mitigating measures have been taken. For more detailed information, reference is made to the risk management file, which is part of the technical documentation. From a technical, biological and clinical point of view, the residual risk for clinical use of the product under evaluation is acceptable after implementation of risk-mitigating measures. Moreover, warnings, cautions, side effects, adverse events and contraindications are outlined in the instructions for use in detail.

To validate the usability of the device under evaluation Brainlab AG performed formative tests for the *EM Disposable Stylet*, packaging and the summative usability evaluation for the complete Cranial EM navigation system including the stylet. Suitability of the device and its IFU were validated according to EN 62366. The *EM Disposable Stylet* was included also in formative and summative usability evaluation of the Cranial EM navigation system. The evaluation was done by experienced neurosurgeons. All tests demonstrated that the scenario can be carried out successfully. Neither the objective, nor the subjective rating including the interviews indicated any usability relevant issues.

For the EM Disposable Stylet an analysis of user related risks was done. The use related risks are linked to catheter insertion procedure itself. Independent from the stylet (navigated or standard stylet delivered with catheters) it is possible, that the stylet tip is not aligned with the tip of the catheter. The procedure to insert the catheter over the stylet only *in situ* and hold both, the catheter and the stylet, during insertion and exit is state of the art for all ventricular catheters. The handling and procedure with the *EM Disposable Stylet* is not new. Therefore, the risks are not introduced by the *EM Disposable Stylet*. Referring to the experience with the Brainlab optical stylet and competitors' products users are aware of these common risks.

To mitigate the user-related risk for contraindicated reuse of the *EM Disposable Stylet* the labelling and also the double peel pouch packaging (standard packaging for sterile delivered single use products) and the type of instrument indicate that the instrument must not be reused. Additionally the electronic counter integrated in the *EM Disposable Stylet* allows using the instrument only during one treatment. Navigation will not work if the user tries to reuse the instrument or to use it during another treatment. Another user-related risk is that the *EM Disposable Stylet* gets unsterile during unpacking. The packaging of the *EM Disposable Stylet* was evaluated by design reviews and meetings with OR nurses. Both packages (double peel pouch and single / dispenser box) are commonly used for sterile delivered medical products. The users are aware not to use sharp tools to open a box with sterile products and also how to open a double peel pouch packaging. In summary, all use related risks of the *EM Disposable Stylet* are state of the art for sterile single use products and other stylets commonly used with ventricular catheters. The *EM Disposable Stylet* does not have any use related risks that where not considered and risks are properly mitigated.

The safety characteristics and the intended use of the EM Disposable Stylet do not require specific training. Catheter / shunt placements using a stylet are well-known procedures as they are also part of the neurosurgical education. Each catheter is placed by means of a stylet. Therefore, there is no need for a specific training on catheter / shunt placements as such as the methodology of placing a ventricular catheter with a non-navigated versus the navigated disposable stylet is the same. The specific difference using the device under evaluation for the intended procedure is the aspect of using a navigation system

for the insertion of the catheter into the brain. Having said this, the understanding of using a navigation system with integrated instruments is the key factor for successfully using the device under evaluation. This training is provided within the training on the cranial EM navigation system including understanding the principle of navigation, registration and instrument integration. Additional information can be found in respective User Guides as well. Thus, no device-specific training for the EM Disposable Stylet is considered necessary for a safe use of the device.

No complications, incidents or adverse events related to the device were reported by the customers. No issues and/or safety critical incidents have been identified that were reported to external authorities. Moreover, available data on the state of the art, Brainlab CID and adverse events databases indicate no new or unknown complications or risks to question the safety and performance of the device under evaluation.

Clinical data on the device under evaluation clearly indicate an acceptable level of safety for ventricular catheter placement and use as a pointing device at neuronavigation-assisted neurologic procedures. EM navigated shunt catheter placement improves the quality of catheter position and eliminates incorrect placements reducing shunt failure rates (Hayhurst et al., 2010), not only in slit ventricles but also in regular ventricle size shunt surgeries as described by (Jung et al., 2013). Both, (Clark et al., 2008) and (Azeem & Origitano, 2007) observed one case of infection each in their studies. The respective infection rates of 4.4% and 3.2% are comparable to the rates reported in the state of the art.

The knowledge gained from the State of the Art regarding the usual complication rate serve as a benchmark for evaluating the complication rate in surgical interventions that require the EM Disposable Stylet. From SOTA there is an average complication rate of 11% for EM navigated operations, whereby these complications occurred in the course of the shunt placement and are not necessarily related to the EM Disposable Stylet as such. Therefore, the result of the PMCF survey and the ongoing PMCF study is within the expected range of no complications with the EM Disposable Stylet as root cause.

The PMCF Survey with feedback of about 400 clinical uses of the device and the ongoing PMCF study with 9 clinical uses by now appraised as successful, proves the successful clinical use of the device under evaluation in the last years. According to these data the use of EM Disposable Stylet is a safe medical application that offers high accuracy for ventricular catheter placement and neuronavigation.

After evaluation of production and post-production information for EM Disposable Stylet an indication for a systematic error of the product or the use of the product could not be identified. There are no unconsidered risks or the need of higher rating of existing risks that would require an update of the risk analysis or resulting in unacceptable risks. No information was found to suggest the need for corrective or preventive actions beyond what is covered by the Brainlab CAPA process. Safety of the clinical use of the device is still assured. Reported device failures during the post market survey are already addressed in the current risk analysis.

The product under evaluation has no special design feature that pose special safety concerns. The guide wire is the only part of the device that is used invasively in direct contact with the patient and consists of stainless steel (1.4301) which is known as biocompatible material. Besides, it has an atraumatic tip (no sharp edges) to minimize tissue damage. The performed biological evaluation covers

the requirements according to current applicable versions of ISO 10993-1 and ISO 14971 for a device with limited contact duration (≤ 24h). The clinical claims on safety can therefore be confirmed.

In the course of the present clinical evaluation, no new or unknown complications or risks associated with the use of the *EM Disposable Stylet* could be revealed.

4.3.3 REQUIREMENT ON ACCEPTABILITY OF SIDE EFFECTS

During clinical use, side effects that apply for the Cranial EM system in general are of moderate severity. These include extended intervention time in certain cases due to additional time for setup and patient registration. These potential side effects are not specifically related to *EM Disposable Stylet*. There are no known contraindications or side effects that occur when using the EM Disposable Stylet.

Methods for the minimization of the risk of distortions in the magnetic field of the highly sensitive and pre-calibrated *EM Disposable Stylet*, caused by metals or magnetic fields of other devices, are listed in the devices' manuals. Moreover, the instructions for use contain detailed orders for the physician to manage all mentioned warnings and to minimise the potential risks.

According to the performed incident search no other incidents concerning side-effects were found directly related with the EM Disposable Stylet. It can be stated that the remaining risks of side effects are still acceptable.

Additionally, no complications, incidents or adverse events were reported in the PMCF Survey with feedback of about 400 clinical uses of the device and the ongoing PMCF study with 9 clinical uses enrolled by now.

Therefore, it can be stated that the remaining side effects are acceptable.

4.3.4 REQUIREMENT ON ACCEPTABLE BENEFIT/RISK RATIO

The use of EM-tracked guide wires for ventricular catheter placement in the treatment of intracranial hypertension and for localisation of neurologic pathologies when used as a pointer combined with an EM neuronavigation system is documented in several clinical studies. EM-tracked guide wires are commonly used in adult and pediatric patients and represent the current state of the art.

Neuronavigation systems in general offer higher accuracy than freehand regarding catheter placement. EM tracked neuronavigation provide some additional benefits to the most common alternative neuronavigation system – the optical tracking system. These benefits include that there are no line-of-sight problems, that a non-invasive DRF is used, rigid head fixation is not required, accuracy is improved and specific probes are used with the EM system that are designed to fit ventricular catheters and thus the weight and feel of the catheter is essentially unchanged, in contrast to bulky adapted systems used with optical navigation (Clark et al., 2008). The tip-tracked navigation improves the accuracy and allows the stylet to be flexible, as the sensor is placed at the distal end of the tip. There is no need of tip calibration, as the instrument is pre-calibrated

Since initial market release of the EM Disposable Stylet in 2017 no severe adverse events have been reported for the *EM Disposable Stylet* and the remaining risks associated with the use of *EM Disposable Stylet* have to be considered as of minor clinical significance.

Moreover, the evidence obtained through cadaveric testing, the PMCF survey and the PMCF clinical investigation show that the *EM Disposable Stylet* as pre-calibrated and image-guided tool is successfully used for accurate placements of intracranial catheters and when used as a pointer device. With regard to the patient population, there is no evidence of differences in the safety profile for the intended age groups. No risks specific to a particular age group such as pediatric patients have been identified.

The benefit/risk ratio of using the EM Disposable Stylet can be regarded as positive when an at least moderate benefit for the patient has to be held out by the responsible physician. The latter can particularly be expected in patients with hydrocephalus, intracranial high pressure, patients that undergo cyst aspiration and with other neurologic pathologies that benefit from the accuracy of localisation by using the *EM Disposable Stylet*.

4.4 PLANNED OR ONGOING PMCF

Post-market surveillance activities and post-market clinical follow-up have been planned as documented in PMS Plan and PMCF plan.

PMS

The primary objectives of the annual systematic review PMS activities are to confirm the clinical performance and safety of the device when exposed to a larger population of patients and clinical users, to evaluate the significance and acceptability of any risks that remain after risk mitigation and to detect emerging risks i.e. remote risks on the basis of factual evidence. The claims on clinical performance and safety as stated and discussed in present clinical evaluation shall be supported by collection of PMS data.

PMCF

The PMCF study aims to assess ventricular catheter placement using the *EM Disposable Stylet* as guiding stylet in order to confirm the clinical performance and safety of the device being mainly evaluated based on data from an equivalent device, as it was defined for the MDD certified EM Disposable Stylet. For this reason intraoperative or postoperative image data sets will be analysed to assess ventricular catheter placement accuracy and in addition to investigate complication rates. The grading system from (Hayhurst et al., 2010) is used for the assessment of ventricular catheters placement accuracy.

The start of the PMCF study was initially planned for December 2018, one year after initial release of the *EM Disposable Stylet*. However, due to contractual difficulties Brainlab had to change the selected site. The study is running at Erasmus MC in Rotterdam/Netherlands. Due to long review cycles within the ethics committee and restrictions during worldwide COVID-19 pandemic outbreak the ethics committee approval delayed. The clinical study started beginning of 2022. The study is registered in the Netherlands at ccmo (“Central Committee on Research Involving Human Subjects”) with registration number NL76660.078.21.

The first treatments in the ongoing PMCF study for the EM Disposable Stylet were successful. These results confirm the safety and effectiveness of the EM Disposable Stylet within its intended use. However, as stated in chapter 4.3.1 there are too little specific real world clinical data for use in pediatric

patients and on using the device in the surgical procedures for approach to skull base tumors including transsphenoidal approach (in adult and pediatric patients). Therefore,

- the Post Market Survey will be supplemented with questions about the performance of the device when used as a pointing device, incl. accuracy and with questions about quantitative information on performed pediatric cases.
- the ongoing prospective PMCF study should focus on those data and provide more clinical evidence. According to the hospital performing the PMCF study there will be probably included 5-10 pediatric cases during the next year.
- based on the information above, more clinical real world evidence will be required for the catheter insertion indication. Consequently, an additional retrospective PMCF study “Catheter placement” retrospectively assessing intracranial catheter placement using the EM Disposable Stylet compared to the free-hand method in the adult and pediatric population will be performed. Because of the retrospective nature of the analysis the primary endpoint reflecting the catheter placement accuracy with the EM Disposable Stylet is the proximal revision rate within 7 days after surgery. This parameter when carefully evaluated for the causality of the revision (i.e. the cause must have been the insertion, not secondary catheter displacement or congestion etc.) is a valuable performance parameter for the device. The study protocol is in review phase by the Ethics Committee (EC) of the site Erasmus University Medical Center Rotterdam in Netherlands and will start as soon as the approval by the Ethics Committee is available.

5 POSSIBLE DIAGNOSTIC OR THERAPEUTIC ALTERNATIVES

Other available medical alternative for ventricular catheter placement are the freehand technique, ultrasound-guided placement, fluoroscopic-guided placement, endoscopic-assisted placement, smartphone-assisted placement, robotic guided placement and optically navigated placement.

The surgical procedures include clinical indications, where ventricular catheter for the EVD, ventriculoperitoneal (VP) / -atrial (VA) shunt or a ventricular access device (VAD, reservoir) is applied. The most common clinical indication is therapy of hydrocephalus and management of intracranial pressure (ICP). Furthermore ventricular catheters are indicated for cyst aspiration. In general, clinical symptoms and indications in the context of ventricular catheter placements are similar across the patient population, from neonates to adults. There are no specific requirements or risks for certain age groups.

It can be concluded that the suitability of certain medical option depends mostly on the target location of the catheter and respective requirement on accuracy. Other decisive factors are the necessity of a head fixation, direct feedback provision of correct trajectory / catheter tip, required size of burr hole, extension of the operating time due to additional set-up or registration time, the sensitivity of the system (e.g. magnetic field distortions).

The presence of small ventricles in neonates and young pediatric patients or patients with slit ventricles or any anatomical distortion make free-hand insertion of ventricular catheters a formidable challenge. Especially in these challenging, complex clinical conditions, the use of adjuncts or high-tech approaches, such as navigational systems are becoming increasingly widespread. Frameless neuronavigation has been used by several authors who report it to be a safe and beneficial option for achieving optimal positioned ventricular catheters (Kim et al. 2006; Gil et al. 2002), thus reducing the need of revision surgeries and postoperative complications.

Image guidance allows a three dimensional reconstruction of the ventricular system and real time visualization based on imaging using pre-operative CT or MRI images during catheter insertion in tri-planar views. During preoperative planning, the exact target points can be defined so that the ideal trajectory, entry point, and length of catheter can be selected and adjusted for each individual patient. The tip of the ventricular catheter can be accurately placed in free cerebrospinal fluid space away from the choroid plexus or too close to ependymal surfaces. Trajectory planning also ensures that the selected trajectory avoids any vascular structures during insertion, which can lead to unnecessary complications. Furthermore, the use of navigation also means that the entry point of insertion is flexible and is not reliant on the standard anatomical entry points. This may be useful in cases where the reuse of a previous scalp incision or milling hole must be avoided, and in the absence of the cranium after craniectomy. (Low et al. 2010)

The usage of EM-tracked stylets with neuronavigation system provides several advantages including high accuracy and obviation of rigid head fixation. The use of EM-tracked stylets as pointer device with neuronavigation systems is also beneficial compared to optical tracking, the most common alternative. EM neuronavigation systems overcome the disadvantages associated with optic tracking neuronavigation systems such as the line-of-sight problem and comprise a high level of safety. In summary, EM tracked stylets combined with EM neuronavigation systems represent the current state of the art for surgical procedures for navigated shunt catheter placement and the planning or localization of intracranial structures when used as a pointer device.

Image-guided insertion of intracranial catheters is considered a routine procedure. (Keric et al. 2013)

Required accuracy depends on respective use case and target location of the catheter / shunt which is why no concrete millimeter value can be given. In general, it can be concluded based on pertinent data that the accuracy of market-available stylets being in a range of 1 – 3 mm is sufficient for the intended use cases to achieve correct catheter positions within the ventricle. In summary, clinical effectiveness and benefits of electromagnetically tracked stylets are proven in comparison to their potential related complications or risks based on long established history of clinical use.

6 SUGGESTED PROFILE AND TRAINING FOR USERS

The **EM Disposable Stylet** is used by Neurosurgeons. No specific training is needed for users familiar with cranial EM navigation systems. For users non-familiar with cranial EM navigation systems a training on using Brainlab Cranial EM navigation systems is recommended.

7 REFERENCE TO ANY STANDARDS, HARMONIZED STANDARDS AND COMMON SPECIFICATIONS APPLIED

Standard	Title	Applied full or in part
EN ISO 13485:2016 + AC:2018*	Medical devices - Quality management systems - Requirements for regulatory purposes	Full
ISO 14971:2019	Medical devices - Application of risk management to medical devices	Full

Standard	Title	Applied full or in part
ISO 15223-1:2021*	Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements	Full
ISO 20417:2021	Medical devices — Information to be supplied by the manufacturer	Full
IEC 62366-1:2015	Medical devices – Application of usability engineering to medical devices	Full
MEDDEV 2.7-1 Rev.4:2016	Clinical evaluation: A guide for manufacturers and notified bodies	Full
EN 60601-1:2006 + Cor.:2010 + A1:2013	Medical electrical equipment - Part 1: General requirements for basic safety and essential performance	Full
ASTM F2503-13	Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment	Full
EN 60601-1-2:2015	Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests	Full
DIN EN 60529:2014	Degrees of Protection Provided by Enclosures (IP Code)	Full
ISO 10993-1:2018	Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process	Full
ISO 10993-4:2017	Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood	Full
ISO 10993-5:2009	Biological evaluation of medical devices – Part 5: Tests for in vitro cytotoxicity	Full
ISO 10993-7:2008/AMD 1:2019	Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals	Full
EN ISO 10993-17:2009	Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances.	Full
EN ISO 10993-18:2020	Biological evaluation of medical devices - Part 18: Chemical characterization of materials	Full
ISO 19227:2018	Implants for surgery - Cleanliness of orthopedic implants - General requirements.	Full
ASTM F3127:2016	Standard Guide for Validating Cleaning Processes Used During the Manufacture of Medical Devices	Full

Standard	Title	Applied full or in part
EN ISO 7153-1:2016	Surgical instruments – Materials – Part 1: Metals	Full
EN ISO 11135:2020	Sterilization of healthcare products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices	Full
ISO 11737-1:2018/Amd 1:2021*	Sterilization of medical devices - Microbiological methods – Part 1: Determination of a population of microorganisms on products	Full
ISO 11737-2:2019*	Sterilization of medical devices - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process	Full
EN ISO 11607-1:2020	Packaging design and validation for terminally sterilized medical devices - Part 1: Determination of a population of microorganisms on products	Full
EN ISO 11607-2:2020	Packaging design and validation for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes	Full
MDCG 2019-9	Summary of safety and clinical performance A guide for manufacturers and notified bodies	Full
AAMI TIR28:2016	Product adoption and process equivalence for ethylene oxide sterilization	Full
ASTM F1980-16	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices	Full
ASTM D4169-16	Standard Practice for Performance Testing of Shipping Containers and Systems	Full
ISO 9626:2016	Stainless steel needle tubing for manufacture of medical devices - Requirements and test methods	Full
ASTM F1929-15	Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration	Full

**Harmonized according to Summary of references of harmonized standards published in the Official Journal – Regulation (EU) 2017/745*

8 REVISION HISTORY

SSCP revision number	Date issued	Change description	Revision validated by NB
003	expected March 2023	First issue according MDR 2017/745	☒ yes Validation language: English ☐ no

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