Summary of Safety and Clinical Performance (SSCP)

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the Embosphere Microspheres.

The SSCP is not intended to replace the instructions for use as the main document to ensure the safe use of the Embosphere Microspheres, nor to provide diagnostic or therapeutic suggestions to intended users or patients.

The English version of this SSCP document (SSCP-0001-001) has been validated by the notified body. The following information is intended for users/healthcare professionals. A more general information summary is provided for patients and lay persons in SSCP-0001-002.

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1.0 Device identification and general information

1.1 Device trade name:

The device trade name is Embosphere® Microspheres, and the model numbers covered by this SSCP are presented in Table 1 and Table 2.

Table 1. Catalog numbers of Embosphere Microspheres in syringe

Nominal size	Colour code (labelling identifying line)	Reference code by volume	
		1 ml	2 ml
50-100 µm	Grey	S010GH	S020GH
40-120 µm	Orange	S110GH	S120GH
100-300 µm	Yellow	S210GH	S220GH
300-500 µm	Blue	S410GH	S420GH
500-700 µm	Red	S610GH	S620GH
700-900 µm	Green	S810GH	S820GH
900-1200 µm	Purple	S1010GH	S1020GH

Table 2. Catalog numbers of Embosphere Microspheres in vial

Nominal size	Colour code (labelling identifying line)	Reference code by volume of Embosphere	
		1 ml	2 ml
50-100 µm	Grey	V010GH	V020GH
40-120 µm	Orange	V110GH	V120GH
100-300 µm	Yellow	V210GH	V220GH
300-500 µm	Blue	V410GH	V420GH
500-700 µm	Red	V610GH	V620GH
700-900 µm	Green	V810GH	V820GH
900-1200 µm	Purple	V1010GH	V1020GH

1.2 Manufacturer Information

The name and address of the manufacturer of the Embosphere Microspheres are provided in Table 3.

Table 3. Manufacturer Information

Manufacturer Name	Address of Manufacturer
Biosphere Medical S.A.	Parc des Nations – Paris Nord II, 383 Rue de la Belle Etoile, 95700 Roissy en France, FRANCE

1.3 Manufacturer Single Registration Number (SRN)

The Single Registration Number for the manufacturer is included in Table 4 and Table 5.

1.4 Basic UDI-DI

The basic Unique Device Identifier (UDI) with Device Identification (DI) key is provided in Table 4 and Table 5.

1.5 Medical Device Nomenclature Description / Text

The "Classificazione Nazionale dei Dispositivi medici" (CND) code and descriptors for the subject device(s) are listed in Table 4 and Table 5.

1.6 Risk Class of Device

The EU device risk classification for the Embosphere Microspheres is listed in Table 4 and Table 5.

Table 4. Device Identification Information of Embosphere Microspheres in syringe

Device Name	EU Device Class	Product Number	Basic UDI-DI	Single Registration Number (SRN)	CND Code	CND Terms
Embosphere Microspheres in syringe 50-100 µm - 1 ml	III	S010GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in syringe 50-100 µm - 2 ml	III	S020GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in syringe 40-120 µm - 1 ml	III	S110GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in syringe 40-120 µm - 2 ml	III	S120GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in syringe 100-300 µm - 1 ml	III	S210GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in syringe 100-300 µm - 2 ml	III	S220GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in syringe 300-500 µm - 1 ml	III	S410GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION IMPLANTS AND SYSTEMS
Embosphere	III	S420GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION

Device Name	EU Device Class	Product Number	Basic UDI-DI	Single Registration Number (SRN)	CND Code	CND Terms
Microspheres in syringe 300-500 µm - 2 ml						IMPLANTS AND SYSTEMS
Embosphere Microspheres in syringe 500-700 µm - 1 ml	III	S610GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in syringe 500-700 µm - 2 ml	III	S620GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in syringe 700-900 µm - 1 ml	III	S810GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in syringe 700-900 µm - 2 ml	III	S820GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in syringe 900-1200 µm - 1 ml	III	S1010GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in syringe 900-1200 µm - 2 ml	III	S1020GH	088445048565E2	FR-MF-000005250	C0104020203	EMBOLIZATION IMPLANTS AND SYSTEMS

Table 5. Device Identification Information of Embosphere Microspheres in vial

Device Name	EU Device Class	Product Number	Basic UDI-DI	Single Registration Number (SRN)	CND Code	CND Terms
Embosphere Microspheres in vial 50-100 µm - 1 ml	III	V010GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in vial 50-100 µm - 2 ml	III	V020GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in vial 40-120 µm - 1 ml	III	V110GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION IMPLANTS AND SYSTEMS
Embosphere	III	V120GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION

Device Name	EU Device Class	Product Number	Basic UDI-DI	Single Registration Number (SRN)	CND Code	CND Terms
Microspheres in vial 40-120 µm - 2 ml						IMPLANTS AND SYSTEMS
Embosphere Microspheres in vial 100-300 µm - 1 ml	III	V210GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in vial 100-300 µm - 2 ml	III	V220GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in vial 300-500 µm - 1 ml	III	V410GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in vial 300-500 µm - 2 ml	III	V420GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in vial 500-700 µm - 1 ml	III	V610GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in vial 500-700 µm - 2 ml	III	V620GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in vial 700-900 µm - 1 ml	III	V810GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in vial 700-900 µm - 2 ml	III	V820GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in vial 900-1200 µm - 1 ml	III	V1010GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION IMPLANTS AND SYSTEMS
Embosphere Microspheres in vial 900-1200 µm - 2 ml	III	V1020GH	088445048794EK	FR-MF-000005250	C0104020203	EMBOLISATION IMPLANTS AND SYSTEMS

1.7 Year of EU Market Introduction

The year that the Embosphere Microspheres was first placed on the European Union market is presented in Table 6 and Table 7.

1.8 Authorised Representative (if applicable)

Not applicable.

1.9 Notified Body name and NB's Single Identification Number

The Notified Body involved in the conformity assessment of the Embosphere Microspheres in accordance with Annex IX of the Medical Device Regulation 2017/745 of the European Union and responsible for validating the SSCP is listed in Table 6 and Table 7.

The NB Single Identification Number is listed in Table 6 and Table 7.

Table 6. Legal manufacturer and Notified Body Information for Embosphere Microspheres in syringe

Device Name	Year Placed on EU Market	Legal Manufacturer		Notified Body	
		Name	SRN	Name	ID Number
Embosphere Microspheres 50-100 µm - 1 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 50-100 µm - 2 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 40-120 µm - 1 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 40-120 µm - 2 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 100-300 µm - 1 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 100-300 µm - 2 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 300-500 µm - 1 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 300-500 µm - 2 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 500-700 µm - 1 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 500-700 µm - 2 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 700-900 µm - 1 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797

Device Name	Year Placed on EU Market	Legal Manufacturer		Notified Body	
		Name	SRN	Name	ID Number
Embosphere Microspheres 700-900 µm - 2 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 900-1200 µm - 1 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 900-1200 µm - 2 ml	2003	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797

Table 7. Legal manufacturer and Notified Body Information for Embosphere Microspheres in vial

Device Name	Year Placed on EU Market	Legal Manufacturer		Notified Body (NB)	
		Name	SRN	Name	ID Number
Embosphere Microspheres 50-100 µm - 1 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 50-100 µm - 2 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 40-120 µm - 1 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 40-120 µm - 2 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 100-300 µm - 1 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 100-300 µm - 2 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 300-500 µm - 1 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 300-500 µm - 2 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 500-700 µm - 1 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797

Device Name	Year Placed on EU Market	Legal Manufacturer		Notified Body (NB)	
		Name	SRN	Name	ID Number
Embosphere Microspheres 500-700 µm - 2 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 700-900 µm - 1 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 700-900 µm - 2 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 900-1200 µm - 1 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797
Embosphere Microspheres 900-1200 µm - 2 ml	2000	Biosphere Medical S.A.	FR-MF-000005250	BSI	2797

2.0 Intended Use of the Device

2.1 Intended Purpose

Embosphere Microspheres are designed to occlude blood vessels, for therapeutic or preoperative purposes, in the following procedures:

- Embolisation of hypervascular tumours and processes, including uterine fibroids, meningiomas, liver tumour.
- Embolisation of the prostate arteries for relief of symptoms related to Benign Prostatic Hyperplasia.
- Embolisation of arteriovenous malformations.
- Haemostatic embolisation.

40-120 µm microspheres are more specifically designed for embolisation of meningiomas and liver tumours.

2.2 Indications and Intended Patient Groups

The device Embosphere Microspheres is intended for therapeutic or preoperative embolisation for:

- Patients with symptomatic uterine fibroids
- Patients with hypervascular tumours and processes, including liver tumours.
- Patients with meningioma for reduction of intraoperative blood loss during resection procedure.

- Patients with lower urinary tracts symptoms (LUTS) related to Benign Prostatic Hyperplasia.
- Patients with arteriovenous malformations.
- Patients with conditions requiring haemostatic embolisation.

2.3 Contraindications:

All indications

- Patients unable to tolerate vascular occlusion procedures.
- Vascular anatomy or blood flow precluding correct catheter placement or embolic agent injection.
- Presence of arteries supplying the lesion not large enough to accept Embosphere Microspheres
- Presence of collateral vessel pathways potentially endangering normal territories during embolisation
- Presence or likely onset of vasospasm.
- Vascular resistance peripheral to the feeding arteries precluding passage of Embosphere Microspheres into the lesion
- In large diameter arteriovenous shunts (i.e., where the blood does not pass through an arterial/capillary/venous transition but directly from an artery to a vein)
- High-flow arteriovenous shunts or with a diameter greater than the selected microspheres
- Presence of severe atheromatous disease
- Patients with known allergy to gelatin.

50-100 µm, 40-120 µm and 100-300 µm microspheres are not recommended for use in the bronchial circulation.

UFE Specific Contraindications

- Pregnant women
- Suspected pelvic inflammatory disease or any other active pelvic infection
- Any malignancy of the pelvic region
- Endometrial neoplasia or hyperplasia
- Presence of one or more submucosal fibroids with more than 50% growth into the uterine cavity
- Presence of pedunculated serosal fibroid as the dominant fibroids
- Fibroids with significant collateral feeding by vessels other than the uterine arteries

PAE Specific Contraindications

- Active urinary tract infection or prostatitis
- Prostate cancer

- Bladder cancer
- Chronic renal failure
- Bladder atonia, neurogenic bladder disorder, or other neurological disorder impacting bladder function
- Bladder stones
- Urinary obstruction due to causes other than BPH, including urethral stricture
- Excessive vessel tortuosity or severe atherosclerosis

Neurological Specific Contraindications

- Presence of patent extra-to-intracranial anastomoses or shunts
- Presence of end arteries leading directly to cranial nerves
- In any vasculature where Embosphere Microspheres could pass directly into the internal carotid artery, vertebral artery, intracranial vasculature, or the above listed vessels

3.0 Device Description

Embosphere Microspheres are biocompatible, hydrophilic, non-resorbable, microspheres produced from an acrylic polymer and impregnated with porcine gelatin. The microspheres are provided in a 20-mL prefilled syringe with a standard Luer-lock tip. Contents: 1 mL or 2 mL of microspheres in sterile, pyrogen-free 0.9% NaCl solution. Embosphere Microspheres is packaged as sterile, single-use devices. Syringes are individually packaged in blister tray sealed by a Tyvek® peel-away lid. One (1) or five (5) sealed unit(s) packed is(are) placed inside a carton box with one (1) IFU. Additionally, Embosphere Microspheres are supplied in an 8-mL glass vial, individually packaged in a blister tray sealed by a peel-away Tyvek lid and placed in a 1-up or 5-up cardboard box.

Figure 1. Pictures of Embosphere Microspheres in syringe and Embosphere Microspheres in vial

3.1 Materials/Substances in Contact with Patient Tissues

Only the trisacryl copolymer microspheres impregnated with porcine gelatin will be in contact with patients' vessels.

The use of gelatin in Embosphere Microspheres is justified by both the clinical benefits of these devices compared to the alternative solutions which do not use material from animal origin, and the acceptable risks related to the use of gelatin for the manufacturing of the devices.

3.2 Operating principles

The procedure of arterial embolisation is similar for all arteries. Appropriately sized microspheres for target vessel occlusion are chosen by the trained specialist physician. The delivery procedure involves arterial access through an artery, using a guidewire and microcatheter under fluoroscopic guidance. Once the catheter tip is placed in the artery(ies) supplying the targeted tissue, Embosphere Microspheres mixed with a non-ionic contrast agent are delivered through an injection syringe in a controlled manner under visualization and mechanically occlude the feeding vessel(s) to interrupt artery blood flow to the targeted area.

Embosphere Microspheres have properties of compressibility and elasticity. Elastic properties allow temporary compression by 20 to 30%, facilitating smooth passage through microcatheters. The resilient material returns to its stated diameter immediately after delivery, thus allowing precise targeting and predictable results at the intended level of vessels occlusion. Embosphere Microspheres mechanically occlude blood flow to the target tissue.

Embosphere Microspheres are intended for embolisation only. It means that they are not intended to be loaded with therapeutic agents to achieve their clinical purpose, by occluding vessels. In addition, due to its composition, they cannot bound to drugs and as such do not have drug eluting properties.

3.3 Previous Generations or Variants (if applicable)

An equivalence assessment was performed for the following:

- Embosphere Microspheres in syringe
- Embosphere Microspheres in vial
- EmboGold Microspheres

EmboGold Microspheres are a coloured variant of Embosphere Microspheres. The only difference is the presence of colloidal gold to give a red colour and facilitate visualisation during handling.

Any identified differences between Embosphere and EmboGold Microspheres with regard to the clinical, technical, and biological characteristics were analysed and none are anticipated to significantly affect clinical safety or performance. In accordance with MEDDEV 2.7/1 Rev 4, the clinical, technical, and biological equivalence of the Embosphere and EmboGold Microspheres has been established through this analysis.

The clinical data collected pertaining to the equivalent devices may be used to support the safety and performance of both Embosphere and EmboGold Microspheres.

3.4 Accessories, devices and product to be used in combination with Embosphere Microspheres

Embosphere Microspheres are not provided with accessories.

The following accessories, not included with the devices and necessary for use, are summarised in the following table:

Table 8. Accessories not included with the devices and necessary for use

Component	Instructions for use
Saline solution	The microspheres are prepared with a mixture of non-ionic 50% contrast agent and 50% saline solution. For Embosphere Microspheres in syringe, this preparation is done in the syringe.
Contrast medium	
Sterile cup or large mixing syringe	For Embosphere Microspheres in vial, this preparation can be done in a sterile cup or in a large mixing syringe
Injection syringe	The microspheres are transferred into a 1mL or 3mL injection syringe. For the microspheres in syringe, the transfer from the syringe to the injection syringe is done through a three-way stopcock.
Three-way stopcock	
(Micro-)Catheter	The microspheres are injected into the patient through a (micro-)catheter.

Embosphere Microspheres are compatible with the following sizes of (micro-)catheters:

Table 9. Catheter compatibility with Embosphere Microspheres size range

Size Range (µm)	Color Code	1 mL	2 mL	Minimum Catheter ID
50-100	Grey	S010GH	S020GH	0.016" (0.41 mm)
40-120	Orange	S110GH	S120GH	0.016" (0.41 mm)
100-300	Yellow	S210GH	S220GH	0.017" (0.43 mm)
300-500	Blue	S410GH	S420GH	0.018" (0.46 mm)
500-700	Red	S610GH	S620GH	0.020" (0.51 mm)
700-900	Green	S810GH	S820GH	0.027" (0.69 mm)
900-1200	Purple	S1010GH	S1020GH	0.038" (0.97 mm)

4.0 Risks and Warnings

4.1 Residual Risks and Undesirable Effects

The potential complications/ undesirable effects related to the Embosphere Microspheres device as identified in the Instructions For Use are summarized in Table 10.

Table 10. Embosphere Microspheres: Potential Hazards/Risks

Subject Devices indication	Potential Adverse Events
All indications	• Post-embolisation syndrome, such as transient pain, nausea, vomiting, fever, possibly delayed from the time of embolisation • Transient hypertensive episode Complications related to catheterization procedure: • Complications related to catheterization (e.g. haematoma at the site of entry, clot formation at the tip of the catheter and subsequent dislodgement, nerve and/or circulatory injuries which may result in leg injury, infection) • Vessel or lesion rupture and haemorrhage • Vasospasm Complications related to mistargeted embolisation: • Occlusion of vessels in healthy territories • Paralysis resulting from untargeted embolisation or ischemic injury from adjacent tissue oedema • Stroke or cerebral infarction • Ischaemia at an undesirable location, including ischaemic stroke, ischaemic infarction (including myocardial infarction), and tissue necrosis • Blindness, hearing loss, loss of smell, and/or paralysis • Capillary bed occlusion and tissue damage • Undesirable reflux or passage of Embosphere Microspheres into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds, such as the internal carotid artery, pulmonary, or coronary circulations • Pulmonary embolism due to arterial venous shunting • Recanalisation • Death
UFE Specific Potential Complications	• The most frequently anticipated post procedure complications are abdominal pain, discomfort, fever and/or nausea, collectively known as “Post-embolisation Syndrome.” Some patients may also experience constipation. This is generally managed with prescription or over-the-counter medications. • Amenorrhea • Premature ovarian failure (i.e., menopause) • Uterine/ovarian necrosis • Phlebitis • Deep vein thrombosis with or without pulmonary embolism • Vaginal discharge • Tissue passage, fibroid sloughing, or fibroid expulsion post Uterine fibroids embolisation

Subject Devices indication	Potential Adverse Events
	• Post- Uterine fibroids embolisation intervention to remove necrotic fibroid tissue • Vagal reaction • Hysterectomy
PAE Specific Potential Complications	• The most frequent post-procedure complication includes "Post-PAE Syndrome", which includes nausea, vomiting, fever, pelvic pain, burning sensation, dysuria, and frequent or urgent urination • Non-targeted embolisation of the rectum, bladder, scrotum, penis, or other areas • Skin burn (radiation exposure) from prolonged fluoroscopy time • Blood in urine, • Blood in semen • Blood in stool • Bladder spasm • Urinary tract infection • Urinary retention • Constipation • • Urethral obstruction
Neurological Specific Potential Complications	• Ischemic stroke or ischemic infarction • Neurological deficits, including cranial nerve palsies

4.2 Warnings and Precautions

PRECAUTION

<u>All indications</u>

- DO NOT USE THIS PREFILLED SYRINGE TO DIRECTLY INJECT EMBOSPHERE MICROSPHERES. THIS IS A "RESERVOIR" SYRINGE. PLEASE REFER TO INSTRUCTIONS PARAGRAPH.
- Embosphere Microspheres must only be used by specialist physicians trained in vascular embolisation procedures. The size and quantity of microspheres must be carefully selected according to the lesion to be treated, entirely under the physician's responsibility. Only the physician can decide the most appropriate time to stop the injection of microspheres.
- Patients with known allergy to contrast medium may require corticosteroids prior to embolisation.
- Additional evaluations or precautions may be necessary in managing periprocedural care for patients with the following conditions:
  - Bleeding diathesis or hypercoagulative state
  - Immunocompromise
- Do not use if blister tray, peel-away film, screw cap or syringe are damaged.
- This is a disposable product. Discard opened syringes after use. All procedures must be performed

according to an aseptic technique.

- For single patient use only - Contents supplied sterile

Never reuse, reprocess, or resterilise. Reusing, reprocessing or resterilising may compromise the structural integrity of the device and or lead to device failure, which in turn may result in patient injury, illness, or death. Reusing, reprocessing or resterilising may also create a risk of contamination of the device and or cause patient infection or cross infection including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness, or death of the patient. All procedures must be performed according to accepted aseptic technique.

- The syringe is intended for embolic use only. Do not use for any other application.

UFE Specific Precautions

- There is an increased chance of retro-migration of Embosphere Microspheres into unintended blood vessels as uterine artery flow diminishes. Embolisation should be stopped when the vasculature surrounding the fibroid can no longer be visualized but before complete stasis in the uterine artery.
- UFE should only be performed by Interventional Radiologists who have received appropriate training for treatment of uterine leiomyomata (fibroids).

Liver tumour Specific Precautions

There is no known incompatibility between Embosphere Microspheres and chemotherapeutics used for the treatment of liver tumours.

PAE Specific Precautions

- The PAE procedure should only be performed by interventional radiologists who have received appropriate training.
- Collateral circulation may be present and can dilate and supply adjacent arteries as resistance within the prostatic bed increases. Therefore, there is potential for severe complications with nontargeted embolisation.
- There is an increased chance of retro-migration of Embosphere Microspheres into unintended blood vessels as prostatic artery flow diminishes. Embolisation should be stopped when the vasculature surrounding the prostate can no longer be visualized but before complete stasis in the prostatic artery.

Haemostatic indication Specific Precautions

- Embolisation of the splenic artery may be associated with inferior vena cava thrombus.

WARNINGS

All indications

- Embosphere Microspheres contain gelatin of porcine origin, and therefore, could cause an immune reaction in patients who are hypersensitive to collagen or gelatin. Careful consideration should be given

prior to using this product in patients who are suspected to be allergic to injections containing gelatin stabilizers.

- Studies have shown that Embosphere Microspheres do not form aggregates, and, as a result, penetrate deeper into the vasculature as compared to similarly sized PVA particles. Care must be taken to choose larger sized Embosphere Microspheres when embolising arteriovenous malformations with large shunts to avoid passage of the spheres into the pulmonary or coronary circulation.
- Some of the Embosphere Microspheres may be slightly outside of the range, so the physician should be sure to carefully select the size of Embosphere Microspheres according to the size of the target vessels at the desired level of occlusion in the vasculature and after consideration of the arteriovenous angiographic appearance. Embosphere Microspheres size should be selected to prevent passage from artery to vein.
- Because of the significant complications of misembolisation, extreme caution should be used for any procedures involving the extracranial circulation encompassing the head and neck, and the physician should carefully weigh the potential benefits of using embolisation against the risks and potential complications of the procedure. These complications can include blindness, hearing loss, loss of smell, paralysis, and death.
- Serious radiation induced skin injury may occur to the patient due to long periods of fluoroscopic exposure, large patient diameter, angled x-ray projections, and multiple image recording runs or radiographs. Refer to your facility's clinical protocol to ensure the proper radiation dose is applied for each specific type of procedure performed. Physicians should monitor patients that may be at risk.
- Onset of radiation-induced injury to the patient may be delayed. Patients should be counselled on potential radiation side effects and whom they should contact if they show symptoms.
- Pay careful attention for signs of mistargeted embolisation. During injection carefully monitor patient vital signs to include SaO2 (e.g. hypoxia, CNS changes). Consider terminating the procedure, investigating for possible shunting, or increasing microsphere size if any signs of mistargeting occur or patient symptoms develop.
- Consider upsizing the microspheres if angiographic evidence of embolisation does not quickly appear evident during injection of the microspheres.

<u>UFE Specific Warnings</u>

<u>Warnings About UFE and Pregnancy</u>

- The effects of UFE on the ability to become pregnant and carry a foetus to term, and on the development of the foetus, have not been determined. Therefore, this procedure should only be performed on women who do not intend future pregnancy.
- Women who become pregnant following UFE may be at increased risk for postpartum haemorrhage, preterm delivery, caesarean delivery, and malpresentation.
- Devascularization of the uterine myometrium resulting from UFE may theoretically put women who become pregnant following UFE at increased risk of uterine rupture.

<u>Other UFE Warnings</u>

- When using Embosphere Microspheres for uterine fibroid embolisation, do not use microspheres smaller

than 500 microns.

- An appropriate gynecologic work-up should be performed on all patients presenting for embolisation of uterine fibroids (e.g., gynecologic history, fibroid imaging, endometrial sampling to rule out carcinoma in patients with abnormal menstrual bleeding).

- The diagnosis of uterine sarcoma could be delayed by taking a nonsurgical approach (such as UFE) to treating fibroids. It is important to pay close attention to warning signs for sarcoma (e.g., rapid tumour growth, postmenopausal with new uterine enlargement, MRI findings) and to conduct a more thorough work-up of such patients prior to recommending UFE. Recurrent or continued tumour growth following UFE should be considered a potential warning sign for sarcoma and surgery should be considered.

PAE Specific Warnings

- A thorough clinical evaluation should be performed on all patients presenting for embolisation for BPH (e.g., urinalysis, digital rectal exam, symptom scores, prostate imaging, prostate-specific antigen test, transrectal ultrasound) to rule out prostate cancer.

- Because of the tortuous vessels and duplicative feeding arteries in the pelvic area, extreme caution should be used when performing prostatic artery embolisation (PAE). Complications of mistargeted embolisation include ischemia of the rectum, bladder, scrotum, penis, or other areas.

- When using Embosphere Microspheres for prostatic artery embolisation, do not use microspheres smaller than 100 microns. It is recommended to use 300-500 microns.

Warnings About PAE and Fertility

- The effects of PAE on fertility have not been determined. Therefore, this procedure should not be performed on men wanting to father a child.

Haemostatic Specific Warnings

- Since Embosphere Microspheres have not been evaluated to control bleeding or haemorrhaging for neurovascular indications they should not be used for this purpose in the neurovasculature.

Warnings about use of small microspheres

- Careful consideration should be given whenever use is contemplated of embolic agents that are smaller in diameter than the resolution capability of your imaging equipment. The presence of arteriovenous anastomoses, branch vessels leading away from the target area or emergent vessels not evident prior to embolisation can lead to mistargeted embolisation and severe complications.

- Microspheres smaller than 100 microns will generally migrate distal to anastomotic feeders and therefore are more likely to terminate circulation to distal tissue. Greater potential of ischaemic injury results from use of smaller sized microspheres and consideration must be given to the consequence of this injury prior to embolisation. The potential consequences include, swelling, necrosis, paralysis, abscess, and/or stronger post embolisation syndrome.

- Post embolisation swelling may result in ischaemia to tissue adjacent to target area. Care must be given to avoid ischaemia intolerant, nontargeted tissue such as nervous tissue.

4.3 Other Relevant Safety Aspects

Not applicable.

5.0 Summary of Clinical Evaluation and Postmarket Clinical Follow-up

5.1 Summary of Clinical Data for the Equivalent Device

An equivalence assessment was performed for the following:

- Embosphere microspheres and EmboGold microspheres

EmboGold Microspheres are a variant of Embosphere Microspheres, coloured in red with colloidal gold to facilitate visualisation during handling.

As addressed in the clinical evaluation report, any identified differences with regard to clinical, technical, and biological characteristics were analysed and none are anticipated to significantly affect clinical safety or performance. In accordance with MEDDEV 2.7/1 Rev 4, the clinical, technical, and biological equivalence of the above-listed subject devices has been established through this analysis. Therefore, clinical data collected in this evaluation pertaining to the EmboGold Microspheres were also used to support the safety and performance of the Embo Microspheres.

Clinical data from 3 articles with EmboGold Microspheres (Worthington-Krisch 2005, Lohle 2005, Loffroy 2011) were included in the clinical evaluation of Embosphere Microspheres. The following tables summarize the clinical data for the equivalent device EmboGold.

Table 11. Summary of the publication of Worthington-Krisch 2005

Reference	Worthington-Kirsch R, et al. The Fibroid Registry for Outcomes Data (FIBROID) for Uterine Embolization: Short-Term Outcomes. Obstet Gynecol. 2005;106 (1):52-59.
Design of the study	Multicenter registry
Objectives	To investigate the short-term safety of uterine embolization for leiomyomata in a large cohort of patients treated in a variety of clinical settings.
METHOD	
Inclusion Criteria	Patients undergoing uterine embolization for leiomyomata
Exclusion Criteria	Non-described
Product	Embosphere and EmboGold Microspheres (73%) and PVA particles (31%)
Method	Examining the FIBROID Registry, a multicenter prospective voluntary registry of patients undergoing uterine embolization for leiomyomata, we studied the frequency of adverse events and predictors of adverse events within 30 days of the procedure. For the Registry, an adverse event was defined as any event that was unexpected and resulted in unanticipated physician office or emergency room visits, or unanticipated therapy (medical or surgical). Adverse events were scored according to the Society of Interventional Radiology scale for severity.
Randomization method	Summary statistics were used to describe the data set, and univariate and multivariate analyses

Reference	Worthington-Kirsch R, et al. The Fibroid Registry for Outcomes Data (FIBROID) for Uterine Embolization: Short-Term Outcomes. Obstet Gynecol. 2005;106 (1):52-59.
	were used to determine which factors might influence the incidence of adverse events.
Statistical method	The Wilcoxon rank-sum test for continuous variables and the X^2 test for categorical variables were used to test for differences. To determine factors that predict "any (one or more) adverse event at 30 days" a stepwise Generalized Estimating Equations (GEE) method was used. Nonsignificant variables were eliminated sequentially, resulting in a predictive model for any adverse event at 30 days, containing significant variables only.
RESULTS	
Sample size	3,160 patients enrolled
Follow Up	within the first 30 days the procedure of uterine embolization for leiomyomata
Patients criteria	Non-described
Performance result	Non-described
Safety results	major in-hospital complications occurred in 0.66%, and post discharge major events occurred in 4.8% within the first 30 days. The most common adverse event after discharge was inadequate pain relief requiring additional hospital treatment (2.4%). Thirty-one patients required additional surgical intervention within 30 days after treatment, 3 of whom required hysterectomy (0.1%). There were no deaths. Multivariate analysis showed modest increased odds for an adverse event for African Americans, smokers, and those with prior leiomyoma procedures. There were no differences in outcome based on the practice site experience, practice type, or any procedure- related factors.
CONCLUSION	
Claims that are supported within this publication	Uterine leiomyomas (uterine fibroids)
Conclusion and comments	Uterine embolization for leiomyomata is a low risk procedure with little variability in short-term outcome based on either patient demographics or practice setting.

Table 12. Summary of the publication of Lohle 2006

Reference	Lohle P, et al. Limited Uterine Artery Embolization for Leiomyomas with Tris-Acryl Gelatin Microspheres: One-Year Follow-Up. J Vasc Interv Radiol 2006 Feb;17 (2).
Design of the study	Prospective cohort study
Objectives	To assess the safety and efficacy of uterine artery embolization (UAE) using large calibrated tris-acryl gelatin microspheres (Embosphere and EmboGold).
METHOD	
Inclusion Criteria	women with a uterine fibroid, reporting heavy menstrual bleeding, pain, and/or bulk-related symptoms in whom insufficient clinical results were obtained with previous medical therapy or myomectomy.
Exclusion Criteria	Women with postmenopausal status, malignancy, pedunculated fibroids, and pregnancy.
Product	Embosphere Microspheres
Method	At 12 months, relief of symptoms and patient satisfaction were assessed and volume reductions of the uterus and dominant fibroid were calculated and compared to baseline values. Major and minor complications were assessed. Major complications, defined as events requiring immediate additional therapy (including emergency hysterectomy), permanent adverse sequelae (including permanent amenorrhea), or death were recorded.
Randomization method	No randomization. The choice of embolic agent used was influenced by factors such as operator preference and availability in stock and was independent of patient or fibroid characteristics.
Statistical method	Statistical analysis was performed with the t-test for continuous data and comparison of proportions with the X^2 test. *P* values less than 0.05 were considered statistically significant.

Reference	Lohle P, et al. Limited Uterine Artery Embolization for Leiomyomas with Tris-Acryl Gelatin Microspheres: One-Year Follow-Up. J Vasc Interv Radiol 2006 Feb;17 (2).
RESULTS	
Sample size	158 women.
Follow Up	At 12 months, relief of symptoms and patient satisfaction were assessed and volume reductions of the uterus and dominant fibroid were calculated
Patients criteria	Median age of the subjects was 43 years (mean, 42.3 y; range, 23–53 y).
Performance result	Preprocedural symptoms were heavy menstrual bleeding in 89%, pain in 64%, and bulk related symptoms in 57%. At 12 months follow-up, the proportion of women with heavy menstrual bleeding, pain, and bulk-related symptoms had decreased to 9%, 8%, and 8%, respectively. Patient satisfaction was grouped as follows: very satisfied 57%, satisfied 36%, and not satisfied 7%. Mean uterine and dominant fibroid volumes before UAE were 532 cm^3 and 201 cm^3, respectively. At 12-month follow-up MR imaging, mean uterine volume decreased to 260 cm^3 and mean dominant fibroid volume to 78 cm^3. These differences were statistically significant ($P < .0001$).
Safety results	Major complications: There were no procedure-related deaths. No emergency hysterectomy was needed. Permanent amenorrhea occurred in 11% of women. Minor complications: • Transient amenorrhea (13%) • fibroid expulsion (10%) Twelve women (7.6%) had additional therapy: nine underwent additional embolization and three had hysterectomy.
CONCLUSION	
Claims that are supported within this publication	Uterine leiomyomas (uterine fibroids)
Conclusion and comments	Targeted UAE using large calibrated microspheres is safe and effective in the relief of symptoms in the majority of patients. At 12 months, a marked fibroid and uterine volume reduction is obtained.

Table 13. Summary of the publication of Loffroy 2011

Reference	Loffroy R, et al. A comparison of the results of arterial embolization for bleeding and non-bleeding gastroduodenal ulcers. Acta Radiol 2011 Dec 1;52(1):1076-82.
Design of the study	Retrospective comparative study
Objectives	To compare the results of arterial embolization for bleeding (BU) and non-bleeding (NBU) gastroduodenal ulcers.
METHOD	
Inclusion Criteria	• patients admitted from January 2000 to February 2008 for transcatheter arterial embolization to treat massive bleeding (defined as a need for more than 4 U of blood/ 24 h) from gastroduodenal ulcers
Exclusion Criteria	• Non-described
Product	EmboGold Microspheres and various embolics
Method	Transcatheter embolization was performed in 57 patients (39 men, 18 women, mean age 69.8 years) who experienced acute bleeding from gastroduodenal ulcers. At the time of embolization

Reference	Loffroy R, et al. A comparison of the results of arterial embolization for bleeding and non-bleeding gastroduodenal ulcers. Acta Radiol 2011 Dec 1;52(1):1076-82.
	active contrast extravasation was seen in 36 of 57 patients, while in the remaining 21 patients' embolization was based on endoscopic findings. Patient demographics, clinical success, need for re-intervention secondary to re-bleeding, and 30-day complication and mortality rates were reviewed and compared between the two groups by using statistical analyses. the clinical success was defined as the absence of re-bleeding that required further intervention in the form of second embolization, re-endoscopic treatment, or surgery.
Randomization method	Non-randomized
Statistical method	Univariate analyses were performed, first to compare the NBU and BU groups, and second to investigate whether clinical failure was associated with blind embolization. Categorical variables were compared between groups using the Chi-square test; count and continuous variables were compared using the non-parametric Wilcoxon rank-sum test. Logistic regression analyses between clinical success and non-outcome variables were performed with and without the blind embolization variable and were then compared using a likelihood-ratio test to evaluate whether blind embolization affects the relationship. A stepwise multivariate logistic regression analysis was performed, with a P value of 0.10 for removal, to determine the variables for which blind embolization was independently associated with clinical failure. A P value ≤ 0.05 was considered statistically significant.
RESULTS	
Sample size	57 patients Bleeding ulcer group n=36 Non-bleeding ulcer group n=21
Follow Up	30-day follow-up
Patients criteria	39 men, 18 women, mean age 69.8 years
Performance result	Between the two groups (NBU vs BU), clinical success (61.9 vs. 75.0%, P = 0.30), need for re-intervention (38.1 vs. 27.8%, P = 0.42), and 30-day complication (9.5 vs. 5.6%, P = 0.57), and mortality (28.6 vs. 25%, P = 0.77) rates were not statistically different. Embolization in patients in NBU group did not have impact on clinical success (OR, 0.54; 95%CI, 0.17 -1. 72; P = 0.30).
Safety results	Minor complications reported: • Transient increase in liver enzyme activities • Transient increase in serum amylase levels without symptoms • Hematoma in the groin area • false aneurysm of the femoral artery treated medically by compression No major or ischemic gastrointestinal complications were identified by clinical examination.
CONCLUSION	
Claims that are supported within this publication	Hemostatic indications: Bleeding gastroduodenal ulcers
Conclusion and comments	In conclusion, this study showed no difference of outcome between patients who underwent embolization for NBU and those who underwent embolization for BU after failed attempts at endoscopic hemostasis. Therefore, in situations where no extravasation is seen angiographically, Autor's advocate the practice of embolization of the most likely offending vessel based on endoscopic guidance. Arterial embolization in patients with angiographically NBU is as safe and effective as embolization in patients with BU.

5.2 Summary of Clinical Investigations of the Subject Device

The following tables summarize the Merit sponsored clinical investigations.

Table 14. Summary of the study Beaujeux et al, 1996

Reference	**Beaujeux et al, 1996**
Objective	To evaluate an embolic agent that is precisely calibrated, perfectly spherical in shape, and soft but non-resorbable for use in the embolization of tumors and arteriovenous malformations (AVM)
Study design	Authors used ES in 200 to 600 µm in diameter for tumors and for facial AVMs, ES 400 to 600 µm diameter for spinal cord AVMs, and ES over 1000 µm in diameter for cerebral AVMs. Authors assessed devascularization of the catheterized pedicle. Clinical follow up was performed to monitor any onset of pain, fever, deficit, or change in clinical state. Histologic verification was performed for 22 patients (16 tumors and 6 facial AVMs) after surgery.
Summary of performance results	Clinical improvement occurred in 52% of cases (n = 11), even in those instances in which embolization had not led to modification of the angiographic aspect of the AVM. Beneficial clinical results lasted on average 6 months (range, 24 hours to 3 years).
Summary of Safety results	Of a total of 128 procedures, no proximal vascular occlusion or any backward surge of microspheres causing the involuntary occlusion of healthy branches was noted. Spinal cord AVMs: no clinical complication Cerebral AVMs: no complication Facial AVMs: no complication Hypervascularized tumors: Embolization was tolerated without immediate complication; however, two cases of massive meningioma were extensively embolized (subtotal devascularization) in one session, producing tumoral necrosis leading to cerebral oedema and aggravation of preexisting neurologic symptoms. These two cases and the patients were able to undergo surgery satisfactorily after a suitable interval.

Reference	Beaujeux et al, 1996
Conclusion	The microspheres are easy to use and allow precise control of the embolization procedure. Their physical characteristics make them a safe embolic agent.

Table 15. Summary of the study IDE G990250

Reference	IDE G990250
Objective	The overall objective of this study was to generate clinical data to support a 5 IO(k) Premarket Notification to add the indication of uterine artery embolization to the labelling for Embosphere® Microspheres.
Study design	113 UFE patients and 50 hysterectomy patients were included. 132 women were included and up to three investigational sites. All women were required to be between the ages of 30 and 50 years, inclusive, have one or more uterine fibroid(s) and a uterine volume of 250 cc or greater as determined by ultrasound imaging, and present with a history of symptoms due to their uterine fibroids. Presenting symptoms could include abnormal pelvic bleeding, pelvic pain, or 'bulk-related symptoms. All subjects were to be treated with bilateral uterine artery embolization using Embospheres. The primary efficacy endpoint of the Phase II study was to determine whether UFE using Embosphere® Microspheres reduced symptoms associated with the presence of uterine fibroids, specifically abnormal bleeding, pain, and/or bulk effects. Secondary efficacy endpoints included evaluations of the treatment on uterine and fibroid volumes and quality of life for the study population. Determining the types arid rates of adverse events associated with Embosphere® Microspheres was also a primary objective, and this safety data was to be compared to adverse events associated with a prospectively treated population of patients undergoing hysterectomy for their uterine fibroids. All subjects were to be evaluated for adverse events at the time of treatment, prior to hospital discharge, within 3 weeks of discharge, and at 3, 6, and 12 months after discharge. All subjects were also to be evaluated for effectiveness of the treatment at 3, 6, and 12 months following the embolization procedure.
Summary of performance results	UFE with Embosphere® Microspheres also had a significant positive

Reference	IDE G990250
	impact on bulk-related symptoms. 78 percent of the UFE patients achieved success on pelvic pain, 75 percent on pelvic discomfort and 62 percent on urinary dysfunction. These results were very similar to those of the patients in the hysterectomy group, who achieved success rates of 80 percent on pelvic pain, 73 percent on pelvic discomfort and 67 percent on urinary dysfunction. The UFE patients also had significant improvements in quality of life as shown by both the SF-12 scores and the study specific patient questionnaires. Although the UFE patients began the study with mean SF-12 scores at approximately the 25th percentile for women of that age group, these scores had risen to the 50th percentile by 3 months following UFE and were maintained throughout the long-term follow-up. No significant differences were observed between the UFE and hysterectomy patients on any quality-of-life measures.
Summary of Safety results	Twenty-six percent of patients in the UFE study experienced adverse events associated with the procedure as compared to 48% of the patients undergoing hysterectomy, which has long been considered the "gold standard" for treating uterine fibroids. This difference was statistically significant ($p<0.01$). In addition, fewer UFE patients experienced adverse events that required more than nominal therapy as compared to hysterectomy patients (3.8% versus 12%, respectively, $p=0.07$).
Conclusion	UFE with Embosphere Microspheres provides a significant reduction of bulk-related symptoms and improvement of quality of life. The Embosphere Microspheres clinical performance is associated with fewer adverse events that required more than nominal therapy as compared to the reference therapy, hysterectomy.

Table 16. Summary of the study IDE G120141

Reference	IDE G120141
Objective	To expand the indication for Embosphere Microspheres to include prostatic artery embolization (PAE) for symptomatic benign prostate hyperplasia (BPH).
Study design	Prospective, open label premarket study 59 patients were enrolled, and 58 patients were treated.

Reference	IDE G120141
Summary of performance results	The cohort was typical of the patient population treated for symptomatic benign prostatic hyperplasia. Mean age at baseline was 67.7 ± 9.7, lower urinary tract symptoms were severe as reflected in a mean International Prostate Symptom Score (IPSS) of 21.5 ± 6.8, and mean quality of life (QOL) score from the IPSS questionnaire was 4.8 ± 0.9 ("mostly dissatisfied" to "unhappy"). Mean IPSS scores improved from 21.5 ± 6.8 at baseline to 6.3 ± 5.8 (<0.0001) and 6.2 ± 5.8 (<0.0001) at 1-3 month and 9-16-month follow-up respectively. A reduction of IPSS score by at least 3 points was achieved at 9-16 months in 97% of patients, and 90% dropped by at least 1 symptom category. The reduction of LUTS reflected in the IPSS changes affected mean quality of life. Mean QOL scores improved significantly from 4.8 ± 0.9 ("mostly dissatisfied" to "unhappy") pre-embolization to 1.4 ± 1.2 (<0.0001) and 1.4 ± 1.1 (<0.0001; "pleased" / "mostly satisfied") at 1-3 month and 9-16-month follow-up respectively.
Summary of Safety results	There have been no unanticipated adverse device effects (UADEs). <u>Adverse Events</u>: • 45/58 (77.6%) treated patients reported a total of 192 AEs • 41/58 (70.7%) treated patients reported a total of 124 AEs considered related to the treatment by the investigator. This includes AEs with a reported relationship to study treatment as "possible, probable or definite". • 7 / 58 (12.1%) treated patients reported a total of 9 AEs with a grade of 3 or higher A total of 7 SAEs have been reported for 7. Six of these events were described in previous annual reports. • Grade 3 impacted stool • Grade 3 fever • Grade 1 chest pain • Grade 3 sepsis

Reference	IDE G120141
	• Grade 3 dysuria. • Grade 3 abdominal pain • Grade 1 duodenal ulcer
Conclusion	Consistent with the literature, this study showed clinical benefits of PAE with Embosphere Microspheres for the treatment of lower urinary tract symptoms. The Symptoms and quality of life improvement after PAE with Embosphere Microspheres is associated with low incidence and severity of the adverse events.

Table 17. Summary of the study PAE-P4-17-01

Reference	**PAE-P4-17-01: A Prospective Post Market Study of Patients with Symptomatic Benign Prostatic Hyperplasia treated by Prostatic Artery Embolization with Embosphere® Microspheres**
Objective	Prostatic artery embolization with Embosphere Microspheres is a relatively new procedure. The goal of this post market study is to evaluate long-term safety and effectiveness in a 'real world' setting
Study design	Prospective, open label post market study. Up to 500 patients with LUTS due to BPH will be enrolled in this single arm post market study
Primary criteria	Evaluate the long-term effectiveness of prostatic artery embolization (PAE) with Embosphere Microspheres as assessed by the International Prostate Symptom Score (IPSS) for those subjects who are eligible to complete a baseline IPSS for comparative purposes
Secondary Criteria	▪ Evaluate IPSS and QoL after discontinuation of indwelling bladder catheter (IBC) post PAE ▪ Evaluation of treatment-related adverse events ▪ Evaluate frequency of indwelling bladder catheter (IBC) removal post PAE ▪ Technical Success o Successful embolization of treated prostate gland ▪ Evaluation of additional treatments for refractory or recurrent LUTS due to BPH post PAE

	Evaluation of change from baseline in erectile function at 12 months post PAE using the Sexual Health Inventory for Men (SHIM
Summary of performance results	Study ongoing
Summary of Safety results	Study ongoing

5.3 Summary of Clinical Data from Other Sources

A comprehensive literature review was performed to gather clinical data in support of continued CE-marking and to assist in documenting conformity with the relevant European MDR concerning device safety and performance. Literature search strategies were designed to identify articles relevant to the Embosphere Microspheres. The results of the literature review also provide verification that all clinical hazards have been addressed in the subject device risk analyses. Both favourable and unfavourable references have been identified and summarized.

5.4 Overall Summary of Clinical Performance and Safety

The devices Embosphere Microspheres have been used effectively for:

- Embolisation of hypervascular tumours and processes, including uterine fibroids, meningiomas and liver tumours.
- Embolisation of the prostate arteries for relief of symptoms related to Benign Prostatic Hyperplasia.
- Embolisation of arteriovenous malformations.
- Haemostatic embolisation.

Clinical Benefits/Performance Analysis

Performance data from the Embosphere Microspheres (ES) clinical literature data and State-Of-the-Art and Safety and Performance literature of Comparable devices (CD) are summarized in Table 18.

Comparable medical devices identified in the state-of-the-art literature used for embolotherapy, and quite like Embosphere Microspheres are:

- Non spherical Polyvinyl Alcohol particles: Contour™ (Boston Scientific), PVA Particles (Cook)
- Spherical PVA particles: BeadBlock™ (Boston Scientific)
- Microspheres made of hydrogel coated with hydrophobic polymers: Embozene™ (Boston Scientific)
- Microspheres made of PolyEthylene Glycol (PEG): Hydropearl® (Terumo)

Contour SE™ (Boston scientific), another spherical PVA-based particle was identified in the literature but are off the market.

Table 18. Comparative Cumulative Success Rates from literature: Embosphere Microspheres

Performance metric	Success Rate: Embosphere	Success Rate: Comparable devices	P-value
Technical success			
Overall embolisation procedure success rate	98% (7%) (n = 1586)	95% (4%) (n = 1166)	p < 0.001
Clinical success of uterine fibroids embolisation			
Rate of fibroids volume reduction (from baseline) at ≥6 months	63% (11%)	74% (17%)	p ≥ 0.05
Rate of patients with complete infarction at ≥6 months	94% (9%) (n=258)	81% (14%) (n=279)	p < 0.001
Rate of patients with tumours growth control at ≥6 months	90% (9%) (n=64)	69% (13%) (n=124)	p = 0.004
Rate of patients with symptoms improvement at ≥12 months	87% (6%) (n=943)	83% (13%) (n=189)	p ≥ 0.05
Symptoms score reduction at 6 months (from baseline)	59% (9%)	62% (11%)	p ≥ 0.05
Rate of patients with QoL improvement at ≥12 months	91% (6%) (n=238)	72% (n=121)	p < 0.001
QoL score improvement at 6 months (from baseline)	54% (36%)	75% (38%)	p ≥ 0.05
Clinical success of HVT embolisation			
Rate of patients with disease control at ≥6 months	53% (24%) (n=114)	43% (22%) (n=196)	p < 0.001
Rate of patients with symptoms improvement at ≥12 months	44% (2%) (n=76)	-	-
Progression free survival	11 (11) mo	14 (9) mo	p ≥ 0.05
Rate of survival at 12 months	100% (n=25)	62% (n=24)	p = 0.001
Mean overall survival	18 (7) mo	14 (8) mo	p ≥ 0.05
Clinical success of Meningioma preoperative embolisation			
Resection success rate	99%	99%	p ≥ 0.05

Performance metric	Success Rate: Embosphere	Success Rate: Comparable devices	P-value
	(n=66)	(n=196)	
Intraoperative blood loss	412 mL (194 mL)	503 mL (330 mL)	p = 0.04
Clinical success of BPH embolisation			
Rate of patients with symptoms improvement (after removing the indwelling bladder catheter) at ≥12 months	89% (9%) (n=630)	86% (5%) (n=151)	p ≥ 0.05
IPSS reduction rate at ≥12 months (from baseline)	64% (15%)	62% (11%)	p ≥ 0.05
Quality of life score improvement rate at ≥12 months (from baseline)	63% (17%)	65% (11%)	p ≥ 0.05
Qmax improvement rate at ≥12 months (from baseline)	106% (55%)	93% (43%)	p ≥ 0.05
Change in IIEF-5 score at ≥12 months (from baseline)	p ≥ 0.05 (n = 546)	p ≥ 0.05 (n = 120)	-
Clinical success of AVM embolisation			
Rate of patients with complete infarction at ≥6 months	64% (5%) (n=121)	44% (27%) (n=89)	p = 0.005
Rate of patients with symptoms improvement at ≥6 months	64% (15%) (n=166)	77% (19%) (n=71)	p ≥ 0.05
Clinical success of Heamostatic embolisation			
Rate of patients with immediate bleeding control rate	90% (10%) (n=326)	90% (7%) (n=500)	p ≥ 0.05
Rate of patients with long-term bleeding control rate (≥6 months)	83% (17%) (n=170)	62% (19%) (n=246)	p < 0.001

The clinical benefits for the subject devices have been substantiated via objective evidence from the clinical data from literature. The ability of the subject devices to achieve the intended performances was assessed and documented. The results of the performance analysis demonstrate that the subject devices perform as intended and are State-Of-the-Art.Clinical Risks/Safety Analysis

Safety data for the Embosphere Microspheres have been analysed through a review of the peer-reviewed

literature and post market data. As illustrated by the data in Table 19 and Table 20, Embosphere Microspheres exhibit very low major and minor adverse event rates, and these rates compare favourably with those reported for other embolics in the clinical literature data and state-of-the-art literature. No new safety concerns specific to the subject device were identified in this evaluation, and the rates reported in the literature are consistent with available data for state-of-the-art comparable devices.

Table 19. Embosphere Microspheres: Potential Complications

Potential complications	Rate in literature
All indications	
- Post-embolisation syndrome, such as transient pain, nausea, vomiting, fever, possibly delayed from the time of embolization	13.2% (780/5924)
- Transient hypertensive episode	0.1% (8/5924)
Complications related to catheterization procedure: - Complications related to catheterization (e.g. haematoma at the site of entry, clot formation at the tip of the catheter and subsequent dislodgement, nerve and/or circulatory injuries which may result in leg injury, infection) - Vessel or lesion rupture and haemorrhage - Vasospasm	0.1% (9/5924)
Complications related to mistargeted embolisation: - Occlusion of vessels in healthy territories - Paralysis resulting from untargeted embolization or ischemic injury from adjacent tissue oedema - Stroke or cerebral infarction - Ischaemia at an undesirable location, including ischaemic stroke, ischaemic infarction (including myocardial infarction), and tissue necrosis - Blindness, hearing loss, loss of smell, and/or paralysis - Capillary bed occlusion and tissue damage - Undesirable reflux or passage of Embosphere Microspheres into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds, such as the internal carotid artery, pulmonary, or coronary circulations - Pulmonary embolism due to arterial venous shunting	1.0% (61/5924)
- Recanalisation	No case reported with Embosphere Microspheres

- Death	0.4% (25/5924)
Complications related to allergy: - Allergic reaction to medications (e.g. analgesics) - Allergic reaction due to contrast media or embolic material - Cutaneous irritations (e.g. rash), possibly delayed from the time of embolization	0.3% (18/5924)
- Foreign body reaction necessitating medical intervention	No case reported with Embosphere Microspheres
UFE Specific Potential Complications	
- The most frequently anticipated post procedure complications are abdominal pain, discomfort, fever and/or nausea, collectively known as "Post-embolization Syndrome." Some patients may also experience constipation. This is generally managed with prescription or over-the-counter medications.	11.79% (379/3213)
- Amenorrhea	1.31% (42/3213)
- Premature ovarian failure (i.e., menopause)	2.40% (77/3213)
- Uterine/ovarian necrosis	0.06% (2/3213)
- Phlebitis	No case reported with Embosphere Microspheres
- Deep vein thrombosis with or without pulmonary embolism	0.12% (4/3213)
- Vaginal discharge	No case reported with Embosphere Microspheres
- Tissue passage, fibroid sloughing, or fibroid expulsion post Uterine fibroids embolisation - Post- Uterine fibroids embolisation intervention to remove necrotic fibroid tissue	4.36% (140/3213)
- Vagal reaction	0.03% (1/3213)
- Hysterectomy	0.06% (2/3213)
PAE Specific Potential Complications	
- The most frequent post-procedure complication includes "Post-PAE Syndrome", which includes nausea, vomiting, fever, pelvic pain, burning sensation, dysuria, and frequent or urgent urination	17.5% (176/1008)

- Non-targeted embolization of the rectum, bladder, scrotum, penis, or other areas	0.2% (2/1008)
- Skin burn (radiation exposure) from prolonged fluoroscopy time	0.8% (8/1008)
- Blood in urine,	3.5% (35/1008)
- Blood in semen	3.5% (31/1008)
- Blood in stool	2.1% (21/1008)
- Bladder spasm	0.4% (4/1008)
- Urinary tract infection	0.5% (5/1008)
- Urinary retention	1.3% (12/1008)
- Constipation	No case reported with Embosphere Microspheres
- Urethral obstruction	0.1% (1/1008)
Neurological Specific Potential Complications	
- Ischemic stroke or ischemic infarction	0.1% (1/907)
- Neurological deficits, including cranial nerve palsies	No case reported with Embosphere Microspheres

Table 20. Embosphere Microspheres Overall Side Effects Assessment

Safety metric	Overall rates	Comparable devices Overall rates	P value
Overall rate of post embolisation syndrome with Embosphere Microspheres compared to the state-of-the-art benchmark devices	13.2% (780/5924)	14.8% (667/4477)	p = 0.01
Overall rate of infection events with Embosphere Microspheres compared to the state-of-the-art benchmark devices	1.8% (109/5924)	1.2% (53/4477)	p = 0.01
Overall rate of mistargeted embolisation events with Embosphere Microspheres compared to the state-of-the-art benchmark devices	1.0% (61/5924)	2.9% (133/4477)	p < 0.001

Overall rate of death events with Embosphere Microspheres compared to the state-of-the-art benchmark devices	0.4% (25/5924)	0.4% (20/4477)	p > 0.05

As illustrated by the above data, the Embosphere Microspheres exhibit low major and minor adverse event rates, which compare favourably with those reported for comparable embolisation devices and alternative therapies in the clinical literature data and state-of-the-art literature.

5.5 Postmarket Clinical Follow-up

Clinical Evaluation Report of Embosphere Microspheres has concluded that for the indications stated in the IFU, the evidence presented is adequate to support the long-term safety and performance of subject device. A Post Market Clinical Follow-up study is ongoing to gather additional information to evaluate long-term (3 year) effectiveness of Embosphere Microspheres for the BPH indication which is a more recent indication.

Summary of the PMCF Plan of Embosphere Microspheres:

- Proactive PMCF data will be collected and assessed for a 3-years duration (end of enrollment: early 2020 / estimated completion date: early 2023) on 500 patients among 15 sites (France, Italy, United Kingdom, United States).
- Long term effectiveness of PAE on LUTS will be evaluated by IPSS at baseline, 3 months, 12 months, 24 months and 36 months. Safety will be assessed by evaluating treatment related adverse events at the same time points, plus at 4 weeks following embolisation. Technical success (successful embolisation of treated prostate gland) will be evaluated. Erectile function will be assessed at baseline and 12 months by SHIM score. Frequency of indwelling bladder catheter (IBC) removal post PAE will be evaluated. Additional treatments for refractory or recurrent LUTS due to BPH post prostatic artery embolisation will also be recorded.
- The assessment will be documented in the PMCF Evaluation Report.
- The assessment will evaluate if and what are the continuing PMCF requirements.

6.0 Therapeutic Alternatives

The therapeutic alternatives for each indication are summarized from Table 21 to Table 23.

Table 21. Treatment options of Uterine Fibroids

Treatment options of Uterine Fibroids		Reference
Available treatments	There is no curative medical treatment of uterine fibroids. Effective medical treatments on the symptoms are transient and partial. The management of symptomatic fibroids is therefore mainly surgical (hysterectomy or myomectomy) or minimally invasive (See Figure 2 below). The embolisation technique is a possible conservative treatment mode. Embolisation consists of the injection of particles until the interruption of blood flow. It is contraindicated in the case of submucosal or pedicled submucosal myoma.	NICE 2010 HAS 2011

Treatment options of Uterine Fibroids		Reference
	Drug treatments by GnRH agonists. are used preoperatively and result in decreased uterine size and fibroid volume, increased preoperative haemoglobin levels, and decreased intraoperative blood loss; There are non-drug treatments like thermoablation.	
Gonadotropin-releasing hormone (GnRH) agonist (Medical therapy)		
Description	By inducing a state of hypoestrogenism and temporary menopause with amenorrhea, GnRH agonists have been used to shrink fibroids and restore haemoglobin levels in symptomatic women. Preoperative treatment for 3–4 months, of GnRH agonist appears to be relevant and beneficial in patients with submucous fibroids to reduce fibroid-related bleeding and anaemia, uterine volume, and fibroid size, to facilitate or enable endoscopic or transvaginal surgery.	Perez-Lopez *et al.* 2014 Donnez *et al*. 2016
Summary of clinical benefit	Benefits include a resolution of preoperative anaemia; a decrease in fibroid size; a reduction of endometrial thickness and vascularization with subsequently improved visibility and reduced fluid absorption and the possibility of surgical scheduling.	Perez-Lopez *et al.* 2014 Donnez *et al*. 2016
Summary of clinical risk	They cannot be used for long periods of time because of their side effects, such as hot flushes, sleep disturbances, vaginal dryness, depression, and bone loss. This preoperative treatment is associated with post-injection endometrial bleeding due to the flare-up effect.	Perez-Lopez *et al.* 2014 Donnez *et al*. 2016
Target population	Patients with symptomatic intramural and/or subserosal uterine fibroids.	Perez-Lopez *et al.* 2014
Hysterectomy		
Description	Hysterectomy is the surgical removal of the uterus. This surgical procedure has long been considered standard surgical treatment for symptomatic intramural and submucous fibroids, particularly for women not wishing to conceive or those of premenopausal age (40–50 years).	Donnez *et al*. 2016
Summary of clinical benefit	It eliminates the symptoms and removes the lesions.	Perez-Lopez *et al.* 2014
Summary of clinical risk/Limits	• Surgical procedure requiring general anaesthesia • No possibility to conceive Adverse events: • Infection (8%) • Transfusion (7%)	Perez-Lopez *et al.* 2014

Treatment options of Uterine Fibroids		Reference
	• Bleeding/Haemorrhage (6%) • Anaesthetic complication (4%) • Urinary retention (2%) • Haematoma (2%) • Urinary retention (2%) • Dyspareunia (2%) • Pelvic pain (2%) • Endometritis (2%) • Metrorrhagia (2%) • Pulmonary embolus (1%) • Sepsis (0.4%) • Thrombosis (0.4%) • Ovarian failure (0.2%) • Permanent amenorrhea (0.2%)	
Target population	Hysterectomy should be considered when other therapeutic options have failed, and the patient does not want to retain her uterus and accepts the risks of surgery.	Perez-Lopez *et al.* 2014
Myomectomy		
Description	Myomectomy is the surgical removal of uterine fibroids. In contrast to hysterectomy, the uterus remains preserved. The procedure can be performed by hysteroscopic or laparoscopy.	Donnez *et al.* 2016
Summary of clinical benefit/advantages	• Conservative treatment • Removal of the uterine fibroids	Donnez *et al.* 2016
Summary of clinical risk/limits	• Invasive surgical procedure requiring general anaesthesia • Risk of morcellation of uterine fibroids • Risk of potential for dissemination of an unsuspected uterine sarcoma • Risk of fibroids recurrence • myomectomy of very large fibroids may be associated with significant perioperative complications such as bleeding requiring transfusion and bowel or bladder injury. • Hysteroscopy-related complications include uterine perforation, haemorrhage, cervical laceration, and fluid overload while long term sequelae include adhesions. • laparoscopic myomectomy should be considered with caution for women with fibroids of more than 5 cm in diameter, those with several fibroids and those with deep intramural myomas Adverse events in literature: • Infection (8%)	Donnez *et al.* 2016 Kröncke 2017

Treatment options of Uterine Fibroids		Reference
	• Transfusion (7%) • Bleeding/Haemorrhage (6%) • Unexpected intrauterine penetrations (5%) • Anaesthetic complication (4%) • Non-elective laparoconversions (3%) • Urinary retention (2%) • Haematoma (2%) • Urinary retention (2%) • Urinary tract infection (2%) • Surgical evacuation of subfascial haematoma (2%) • Dyspareunia (2%) • Pelvic pain (2%) • Endometritis (2%) • Metrorrhagia (2%) • Thrombosis (0.4%) • Ovarian failure (0.2%) • Permanent amenorrhea (0.2%)	
Target population	Hysteroscopic myomectomy for submucosal fibroids greater than 2 cm and for intramural fibroids distorting the endometrial cavity may be considered in subfertile women.	Perez-Lopez *et al.* 2014
Uterine Arteries Embolisation (UAE)		
Description	UAE is defined as the delivery of an embolic agent via a catheter or microcatheter placed in both uterine arteries. The goal of the treatment is definitive embolisation of the uterine arteries inducing a prolonged vascular occlusion and then ischemia of myomatous tissue while avoiding permanent damage to the uterus. .	SIR 2014
Summary of clinical benefit	Clinical performance of UAE in SOA literature: • Symptoms relief (UFS score) at 3 months: 93% of patients (NICE 2010) • Symptoms relief at 6 months: 84% of patients (NICE 2010) • Symptoms relief at 12 months: 95% of patients (Katsumori 2018) • Symptoms relief at 24 months: 83% to 88% of patients (NICE 2010) • Symptoms relief at 5 years: 73% of patients (NICE 2010) • Quality of life improvement (UFS-QOL) at 4 months: 94 % of patients (Katsumori 2018) • Quality of life improvement (UFS-QOL) at 6 months: from 44 to 79 ($p<0.05$) NICE 2010 • Quality of life improvement (UFS-QOL) at 12 months: 96% of patients (Katsumori 2018) • Quality of life improvement (UFS-QOL) at 3 years: from 46 to 89 ($p<0.05$) NICE 2010	NICE 2010 Perez-Lopez *et al.* 2014 Katsumori 2018

Treatment options of Uterine Fibroids		Reference
Summary of clinical risk	Adverse events of UAE in SOA literature (max rate): • Post embolisation syndrome (72%) • Ovarian dysfunction/failure (61%) • Transient Amenorrhea (41%) • Vaginal discharge (25%) • Sepsis (16%) • Embolisation procedure failure with further interventions (12%) • Fibroids expulsion (8%) • Infection (6%) • Death (5%) • Uterine artery spasm (5%) • Urinary tract infection (2%) • Artery dissection/perforation (2%) • Groin bleeding/Pseudoaneurysm (2%) • Allergic reaction/ Rash (2%) • Bleeding/Haemorrhage (2%) • Permanent Amenorrhea (2%) • Urinary retention (2%) • Sever pain (1%) • Severe vasovagal event (1%) • Hematometra (1%) • Pelvic abscess (1%) • Structural damage (1%) • Pulmonary embolus (1%) • Hematoma (0.6%) • Contrast reaction (0.1%) • Hypertension (0.1%) • Deep vein thrombosis (0.1%) • Septic uterus (2 cases) • Uretic obstruction requiring nephrectomy (1 case) Post-embolisation syndrome is thought to be caused by an inflammatory response to targeted tissue necrosis. It is characterized by leucocytosis, fever, nausea/vomiting and prolonged pain lasting up to seven days and is a common reason for re-hospitalization and possible re-intervention. For patients with a symptomatic uterine fibroid and a desire for children, the role of UAE as a treatment option is still not sufficiently defined in the current literature. Pregnancy after UAE is possible. The risk of miscarriage may be increased. A minimum wait time of approximately 6 months between fibroid treatment with UAE and conception is recommended. (Kröncke 2017)	Bruno 2004 Worthington-Kirsch 2005 Smeets 2006 NICE 2010 Perez-Lopez *et al.* 2014 Barnard 2017 Basile 2018 Freire 2016 Katsumori 2018 Katsumori 2019 Torre 2017 Kröncke 2017

Treatment options of Uterine Fibroids		Reference
Target population	• UAE is an option for women with symptomatic fibroids, who no longer desire fertility but who wish to avoid surgery or are poor surgical or anaesthetic risks.	NICE 2010 HAS 2011 Perez-Lopez et al. 2014
Thermoablation: High-intensity focused ultrasound (HIFU)		
Description	Ablation with high-intensity focused ultrasound (HIFU) is a non-invasive treatment which is performed under the guidance of either MR or ultrasound. HIFU has been used to treat a variety of solid benign and malignant lesions. It produces focal fibroid coagulation and necrosis without alteration of surrounding normal myometrium. It is non-invasive, requires no general anaesthetic or hospitalization, and uses high-intensity ultrasound waves to destroy fibroids, by heating, without damaging adjacent normal structures.	Perez-Lopez *et al.* 2014
Summary of clinical benefit	• It is an ambulatory procedure without incisions, allowing women to return to work after one or two days. • Non-invasive procedure • Better results are achieved for intramural fibroids • The reported experience shows that HIFU is associated with 70% symptoms score improvement at 13 months. (Froeling 2013)	Perez-Lopez *et al.* 2014
Summary of clinical risk	• MR-guided HIFU is not recommended for pedunculated subserosal fibroids. • The presence of bowel loops or abdominal wall scars in the projected pathway of the ultrasound beam may preclude use of the technique. • Common symptoms during the procedure are short-term lower abdominal pain, leg pain and buttock pain.	Perez-Lopez *et al.* 2014
Target population	Patients with symptomatic uterine intramural fibroids without presence of interposed bowel loops or abdominal wall scars.	Perez-Lopez *et al.* 2014

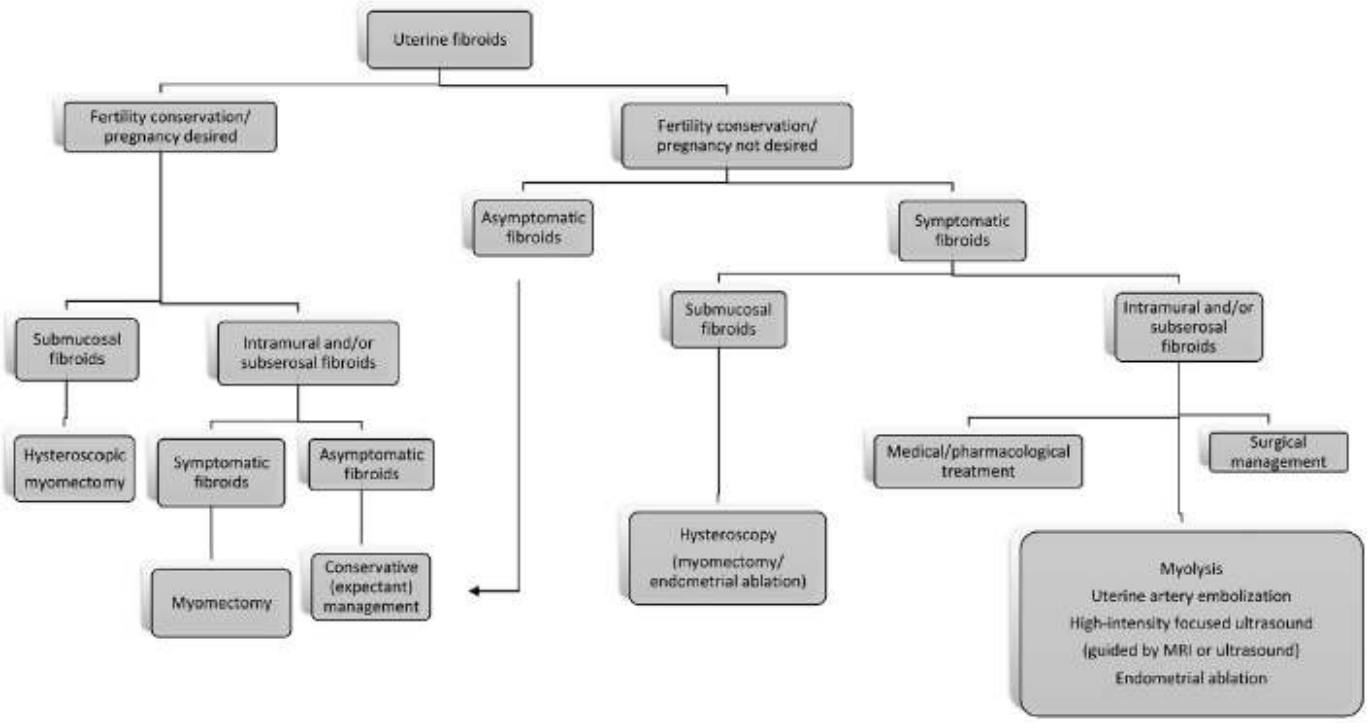

Figure 2. Suggested flowchart for the management of uterine fibroids. (Source Perez-Lopez 2014)

Table 22. Treatment options of Hypervascular Tumours (including liver tumours)

Treatment options of Hypervascular Tumours (Hepatocellular Carcinoma)		Reference
Available treatments	Available therapeutic options can be divided into curative and noncurative interventions. Curative therapies include surgical resection, transplantation, and ablative techniques such as thermal ablation. Each of these approaches offers the chance of long-term response and improved survival. Noncurative therapies, which attempt to prolong survival by slowing tumour progression, include transarterial chemoembolisation (TACE), transarterial radioembolisation (TARE), and systemic chemotherapy (See Figure 3 below).	NICE 2010 HAS 2011
Surgical resection		
Description	Surgical resection of the tumours by laparoscopy or open surgery	Marrero et al. 2018 (ASSLD guideline)
Summary of clinical benefit	• For patients with single tumours, well-preserved organ function, and no evidence of portal hypertension. Surgical resection offers a low perioperative mortality and is associated with survival rates of nearly 70% at 5 years. • There is technically no size cut-off for tumour diameter, and large tumours can be safely resected if there is sufficient functional remnant tissue.	Marrero et al. 2018 (ASSLD guideline)
Summary of clinical risk	• The risk of recurrence following resection is up to 70% at 5 years, with the most important predictors being tumour differentiation, micro- and macrovascular invasion, and the presence of satellite nodules.	Marrero et al. 2018 (ASSLD guideline)
Target population	Surgical resection is the treatment of choice for resectable HVT and HCC occurring in patients without cirrhosis, which accounts for 5%-10% of HCC in Western countries.	Marrero et al. 2018 (ASSLD guideline)
Transplantation		
Description	Transplantation of the target organ (e.g. liver) to the patient.	Marrero et al. 2018 (ASSLD guideline)
Summary of clinical benefit	• Transplantation is a highly effective, efficient therapy for early-stage HCC because it offers optimal treatment of both the underlying liver disease and the tumour, and is associated with excellent long-term survival rates for HCC within Milan criteria occurring in the setting of decompensated liver disease.	Marrero et al. 2018 (ASSLD guideline)
Summary of clinical risk	• Transplantation is limited by the extreme shortage of available organ allografts and the need for lifelong immunosuppression.	Marrero et al. 2018 (ASSLD guideline)
Target population	Patients with early stage liver tumours.	Marrero et al. 2018 (ASSLD

Treatment options of Hypervascular Tumours (Hepatocellular Carcinoma)		Reference
		guideline)
Thermal ablation		
Description	Destruction or ablation of tumour cells can be achieved by the injection of chemical substances (ethanol, acetic acid, and boiling saline) or by modifying local tumour temperature (radiofrequency [RFA], microwave, laser, cryotherapy). The procedure can be done percutaneously with minimal invasiveness or during laparoscopy and is currently considered the best option for patients with BCLC stage A who are not candidates for surgical intervention.	Marrero et al. 2018 (ASSLD guideline)
Summary of clinical benefit	Several randomized controlled trials (RCTs) have confirmed the superiority of RFA over ethanol injection in terms of survival, particularly in BCLC stage A with nodules between 2 and 4 cm. Thermal ablative techniques have the best efficacy in tumours with maximum diameter less than 3 cm, although microwave ablation potentially provides better tumoral response than RFA.	Marrero et al. 2018 (ASSLD guideline
Summary of clinical risk/Limits	• The recurrence rate after thermal ablation is similar to that observed after surgical resection, • It has been shown that local recurrence is related to size and higher with tumours that are >3 cm • HCC recurrence can occur at new sites in the liver in around 40% of individuals.	Marrero et al. 2018 (ASSLD guideline
Target population	Patients with BCLC stage A who are not candidates for surgical intervention.	Marrero et al. 2018 (ASSLD guideline
Transarterial embolization		
Description	Transarterial embolisation is locoregional therapy which consists in superselective bland embolisation of a targeted hypervascular tumors. Some hypervascular tumours like liver tumors being drug resistant and life-threatening disease, specialist physicians may adopt multiple therapeutic approach. Locoregional chemoinfusion procedure into the tumors may usually be followed by embolisation procedure. The successive use of locoregional chemoinfusion and transarterial embolisation is named conventional transarterial chemo embolisation (cTACE). The rationale for cTACE is that intraarterial chemotherapy with lipiodol and chemotherapeutic agents, followed by transarterial embolisation, will result in a strong cytotoxic effect combined with ischemia. The goal of cTACE is to cause tumour necrosis and tumour growth control; however, the goal of therapy is to prolong patient survival. Note: It should be distinguished to the drug eluting TACE which combine cytotoxic drug and drug eluting microspheres before embolisation procedure. The drug eluting microspheres	Marrero et al. 2018 (ASSLD guideline) HAS 2011

Treatment options of Hypervascular Tumours (Hepatocellular Carcinoma)		Reference
	are intended to be used in this procedure with specific chemotherapeutic drugs to ensure a progressive release over the time from the embolization site. Embosphere Microspheres cannot bound to drug and act as drug eluting microspheres. Embosphere Microspheres are not drug eluting microspheres. Embolisation can be used: • preoperatively hypervascular lesions, to reduce intraoperative bleeding. • preoperatively, to promote hypertrophy of a healthy segment of the liver before palliative hepatectomy, • palliative, in order to treat complications related to cancer: pain, bleeding.	
Summary of clinical benefit/advantages	• Median OS in BCLC B patients treated with TACE in RCTs has increased from 20 to 26 months because of improved patient selection with acknowledgement that Child-Pugh may not be sufficient to determine patients with expected survival benefit associated with chemoembolisation. (Marrero et al. 2018) • TACE is associate with lower systemic administration of chemotherapy and related side effects. • 47% and 23% local control for TACE (hazard ratio 66.5, P<.001) at 1 and 2 years, respectively. (Sapir 2017) • Patients with HCC and the largest tumour greater than 30 mm treated with LRT prior to liver transplantation have improved survival compared to patients not receiving LRT with respectively 29.5 ± 8.4 months (95% CI 13.0–46.0 months) versus 11 ± 5.1 months (95% CI 1.1–20.9 months). (Habibollahi 2017) • TAE of is associated with 80% survival at 6 months, 62% to 70% survival at 1 years and 41% to 47% survival at 2 years, and 29% survival at 3 years in the treatment of liver tumours (Rand 2005; Maluccio 2006).	Rand 2005 Maluccio 2006 Sapir 2017 Habibollahi 2017 Gaba 2017 Marrero et al. 2018 (ASSLD guideline)
Summary of clinical risk/limits	• Contraindicated for larger tumours with portal vein invasion (Marrero et al. 2018) Adverse events of TAE in SOA literature (max rate): • Post embolisation syndrome (5%) • Biliary or liver abscess (4%) • Severe liver failure (2%) • Biliary stricture (4%) Post-embolisation syndrome is thought to be caused by an inflammatory response to targeted tissue necrosis. It is characterized by leucocytosis, fever, nausea/vomiting and prolonged pain lasting up to seven days and is a common reason for re-hospitalization and possible re-intervention. Adverse events of TACE in SOA literature (max rate): • Nausea (40%) • Pain (37%) • Biliary stricture (4%) • Biliary or liver abscess (4%) • Cholecystitis (2%)	Sapir 2017 Gaba 2017 Marrero et al. 2018 (ASSLD guideline Abajian 2018 Wang 2018

Treatment options of Hypervascular Tumours (Hepatocellular Carcinoma)		Reference
	• Severe liver failure (2%) • Renal failure (2%) • Gastric ulcer (1%) • Myocadiac infarction (1%) Adverse events of TACE and TAE in SOA literature (max rate): Technical adverse events • Iatrogenic vessel dissection precluding treatment (< 1%) Hepatic adverse events • Liver failure (5%) • Liver infarction (< 1%) • Abscess, functional sphincter of Oddi (2%) • Abscess, biliary-enteric anastomosis, biliary stent, or sphincterotomy with premedication (15%) • Biloma requiring percutaneous drainage (<1%) Extrahepatic adverse events • Surgical cholecystitis (< 1%) • Hematologic suppression (e.g., anaemia, thrombocytopenia, leukopenia) (23%) • Pulmonary arterial oil embolus (< 1%) • Gastrointestinal ulceration/haemorrhage (< 1%) • Contrast induced nephropathy or acute renal failure (10%) • Death within 30 days (4%) Procedure side effects • PES requiring extended hospital stay or readmission (31%) • Hepatic artery occlusion (owing to chemotherapy damage) (63%) Radiation related adverse events • Skin injury (<1%)	
Target population	Patients with intermediate stage HCC who are not eligible for curative treatments.	Marrero et al. 2018 (ASSLD guideline
Transarterial radioembolisation (TARE)		
Description	TARE has emerged as an alternative therapy to TACE. In contrast to TACE, the therapeutic action of TARE is predominately radiation with yttrium 90 as opposed to embolisation.	Marrero et al. 2018 (ASSLD guideline
Summary of clinical benefit/advantages	• The reported experience with TARE in large, prospective, nonrandomized trials has shown consistent results, particularly among those with BCLC B with OS of 16.4-18.0 months.	Marrero et al. 2018 (ASSLD guideline
Summary of clinical	• Specific risks related to radiation which is carcinogenic itself. (Marrero et al. 2018)	Marrero et al.

Treatment options of Hypervascular Tumours (Hepatocellular Carcinoma)		Reference
risk/limits	• Biliary stricture (4%) • Gastric Ulcer (3%) • Hypervolemia (1%) • Oesophageal varices (1%)	2018 (ASSLD guideline) Sapir 2017
Target population	Patients with intermediate stage HCC who are not eligible for curative treatments.	Marrero et al. 2018 (ASSLD guideline
Systemic chemotherapy		
Description	It consists in a systemic delivery of chemotherapeutic drug. Sorafenib is the most used oral multikinase inhibitor that initially demonstrated a survival advantage in the front-line setting in a phase 3 double-blind, placebo-controlled trial.	SIR 2014
Summary of clinical benefit	• Median absolute survival benefit of approximately 3 months.	Perez-Lopez *et al.* 2014
Summary of clinical risk	• side-effect profile characterized most by hand-foot skin reaction, diarrhea, weight loss, and hypertension.	Perez-Lopez *et al.* 2014
Target population	Patients with unresectable HCC who are ineligible for or progress after TACE should be considered for systemic therapy.	NICE 2010 HAS 2011 Perez-Lopez et al. 2014

Table 23. Treatment options of Hypervascularized Tumours (Meningioma)

Treatment options of Hypervascularized Tumours (Meningioma)		Reference
Available treatments	Surgical excision and embolisation are the main therapeutic options proposed, together or independently.	HAS 2011
Surgical excision		
Description	Surgical excision of the tumours.	Marrero et al. 2018 (ASSLD guideline)
Summary of clinical benefit	• For patients with single tumours, well-preserved organ function, and no evidence of portal hypertension. Surgical resection offers a low perioperative mortality and is associated with survival rates of nearly 70% at 5 years. • There is technically no size cut-off for tumour diameter, and large	Marrero et al. 2018 (ASSLD guideline)

Treatment options of Hypervascularized Tumours (Meningioma)		Reference
	tumours can be safely resected if there is sufficient functional remnant tissue.	
Summary of clinical risk	• The target tumours should be surgically accessible.	Marrero et al. 2018 (ASSLD guideline)
Target population	Surgical resection is the treatment of choice for resectable HVT and HCC occurring in patients without cirrhosis, which accounts for 5%-10% of HCC in Western countries.	Marrero et al. 2018 (ASSLD guideline)
Embolisation		
Description	Tumour embolisation is defined as the blocking of the vascularization of the tumour, either endovascular or by direct percutaneous injection of embolic agents, permanent or temporary, into the tumour.	HAS 2011
Summary of clinical benefit/advantages	• Embolisation can be preoperative to reduce intraoperative blood loss by avoiding transfusion and thus reducing the time and complications of surgery. • Embolisation can also be palliative to improve the quality of life of patients by partial resolution, symptoms by reducing the volume of the lesion. • Meningiomas are the most common tumours to be embolized.	HAS 2011 Suzuki 2017
Summary of clinical risk/limits	• hypervascularized tumours are generally amenable to an endovascular approach. • Major complications are rare. However, stroke and intracerebral haemorrhage have been reported in up to 3–6%. Post-embolisation syndrome is thought to be caused by an inflammatory response to targeted tissue necrosis. It is characterized by leucocytosis, fever, nausea/vomiting and prolonged pain lasting up to seven days and is a common reason for re-hospitalization and possible re-intervention.	HAS 2011 Duffis 2012 Suzuki 2017 Tanaka 2018
Target population	Patients with hypervascularized tumours accessible by an endovascular approach.	HAS 2011

Table 24. Treatment options of Benin Prostatic Hyperplasia

Treatment options of Benin Prostatic Hyperplasia		Reference
Available treatments	Patients with mild LUTS are generally treated with watchful waiting or lifestyle modification prior to undergoing medical treatment. Medical treatment is usually the first-line treatment option (See Figure 3 below) and is indicated for patients with moderate LUTS. The two main categories of medications for management of BPH are a-blockers and 5a-reductase inhibitors. Patients who cannot tolerate these drugs, whose disease is refractory to treatment, or who develop complications of BPH while receiving medical therapy are considered for surgical therapy such as Transurethral resection of the prostate (TURP), thermotherapies like laser or less invasive therapies such as Prostate artery embolisation (PAE).	SIR position statement 2014
Drug treatment		
Description	Alpha blocker works by relaxing the muscle in the prostate gland and at the base of the bladder, making it easier to pass urine. 5-alpha reductase inhibitor works by reducing testosterone, which shrinks the prostate gland if it is enlarged.	NICE 2010
Summary of clinical benefit	• Alpha-blockers do not alter the natural progression of the disease (little impact on prostate growth, the risk of urinary retention or the need for BPH-related surgery). • Several studies have demonstrated that 5ARI therapy, in addition to improving symptoms and causing a modest (25–30%) shrinkage of the prostate, can alter the natural history of BPH through a reduction in the risk of acute urinary retention (AUR) and the need for surgical intervention.	Nickel et al. 2018
Summary of clinical risk	• Alpha-blocker and 5ARI treatments are associated with erectile dysfunction, decreased libido, ejaculation disorders, and rarely, gynecomastia.	NICE 2010 SIR position statement 2014
Target population	Patients with mild to moderate LUTS secondary to BPH.	NICE 2010
Transurethral resection of the prostate (TURP)		
Description	Transurethral resection of the prostate (TURP) consists in removing part of the prostate gland, generally using an instrument that passes through the urethra. Note: Open prostatectomy is an alternative to TURP to men with prostates estimated to be larger than 80 cm^3, but it is an invasive surgical procedure with concomitant morbidity and extended hospitalization.	NICE 2010
Summary of clinical	• TURP is effective on reducing IPSS, QOL, Qmax on average by 78%, 80%	SIR position

Treatment options of Benin Prostatic Hyperplasia		Reference
benefit	and 179%respectively.	statement 2014 Carnevale 2016
Summary of clinical risk	• 20% of patients have significant complications, including bleeding, sexual dysfunction, incontinence, and dilutional hyponatremia. Contemporary series have reported the following complications: • retrograde ejaculation (65%), • Haematuria (46%) • Fever (29%) • Bleeding (2–9%), • Erectile dysfunction (6.5%), • Urinary retention (4.5–13%), • Infection (3–4%; sepsis 1.5%), • Bladder neck contracture (3–5%), • Prostatic capsule perforation with significant extravasation (2-6%), • TUR syndrome (0.8%), • Incontinence (<1%), • Surgical retreatment (2%/year)	Carnevale 2016 Nickel 2018 Zumstein 2018
Target population	Patients with mild to moderate to severe LUTS secondary to BPH.	NICE 2010
Prostate artery embolisation (PAE)		
Description	Prostatic artery embolisation for benign prostate hyperplasia is usually done using local anaesthesia. Under X-ray guidance, the prostate is approached through the left or right femoral artery. Super-selective catheterisation of the small prostatic arteries is done using fine microcatheters through the pelvic arteries. Embolisation involves the introduction of microparticles to completely block the prostatic vessels.	NICE 2018
Summary of clinical benefit/advantages	• Technical success, when defined as embolisation of at least one prostatic side, is achieved in greater than 95% of patients • Prolonged Foley catheterization is not necessary, and is sometimes avoided completely • Relief begins to occur within days in most cases, and side effects are generally mild	SIR position statement 2014 Isaacson

	Treatment options of Benin Prostatic Hyperplasia	Reference
	• The effect of the treatment is significant, with marked reduction in IPSS (50% - 71%) and improvement in urinary flow rates (69% - 133%), and these results seem durable over at least I year of follow-up (Wang 2018). • Quality of life scores improvement (45% - 80%) suggest that patients are quite satisfied with their urinary symptoms following the treatment.	2017 Golovko 2018 Wang 2018 de Assis 2019 Moschouris 2019
Summary of clinical risk/limits	• Occasionally, PAE cannot be technically achieved on at least one side, usually as a result of atherosclerosis, small artery size, tortuosity, or inability to achieve safe position for embolisation. • The prostatic arterial supply is intimately related to that of the other pelvic organs, especially the bladder and rectum, and there is potential for severe complications with nontarget embolisation. • Minor side effects are common following PAE, including urinary frequency, dysuria, pelvic pain, haematuria, blood in the stool, hematospermia, and diarrhea. These are almost always self-limited but underscore the possibility that nontarget embolisation may occur even if not detected during the procedure. • Post-embolisation syndrome is thought to be caused by an inflammatory response to targeted tissue necrosis. It is characterized by leucocytosis, fever, nausea/vomiting and prolonged pain lasting up to seven days and is a common reason for re-hospitalization and possible re-intervention. • Ionizing radiation and iodinated contrast material are required for procedural guidance. Although older men are less sensitive to stochastic effects of radiation exposure than younger patients, prolonged fluoroscopy times are not uncommon during a PAE procedure, and deterministic effects such as skin burn could potentially occur. The risk of these deterministic effects is greater in older individuals, and therefore radiation exposure must be carefully monitored. Contrast material can cause allergic reaction or nephropathy. Adverse events of PAE in SOA literature: • Burning and pain (24%) • Haematuria (11%) • Irritative voiding urethral burning (10%) • Fever (10%) • Retropubic pain (9%) • Hematospermia (8%) • Haematuria (8%) • Acute urinary retention (6%) • Hyperaemia (5%) • Rectal bleeding (4%)	SIR position statement 2014 Wang 2018 Golovko 2018 Zumstein 2018 Moschouris 2019

Treatment options of Benin Prostatic Hyperplasia		Reference
	• Urinary tract infection (3%) • Bladder ischemia (3%) • Rectal ischemia (3%) • Inguinal hematoma (3%) • Urinary incontinence (1%)	
Target population	Patients with mild to moderate to severe LUTS secondary to BPH with prostate volume of 30–80 cc.	SIR position statement 2014

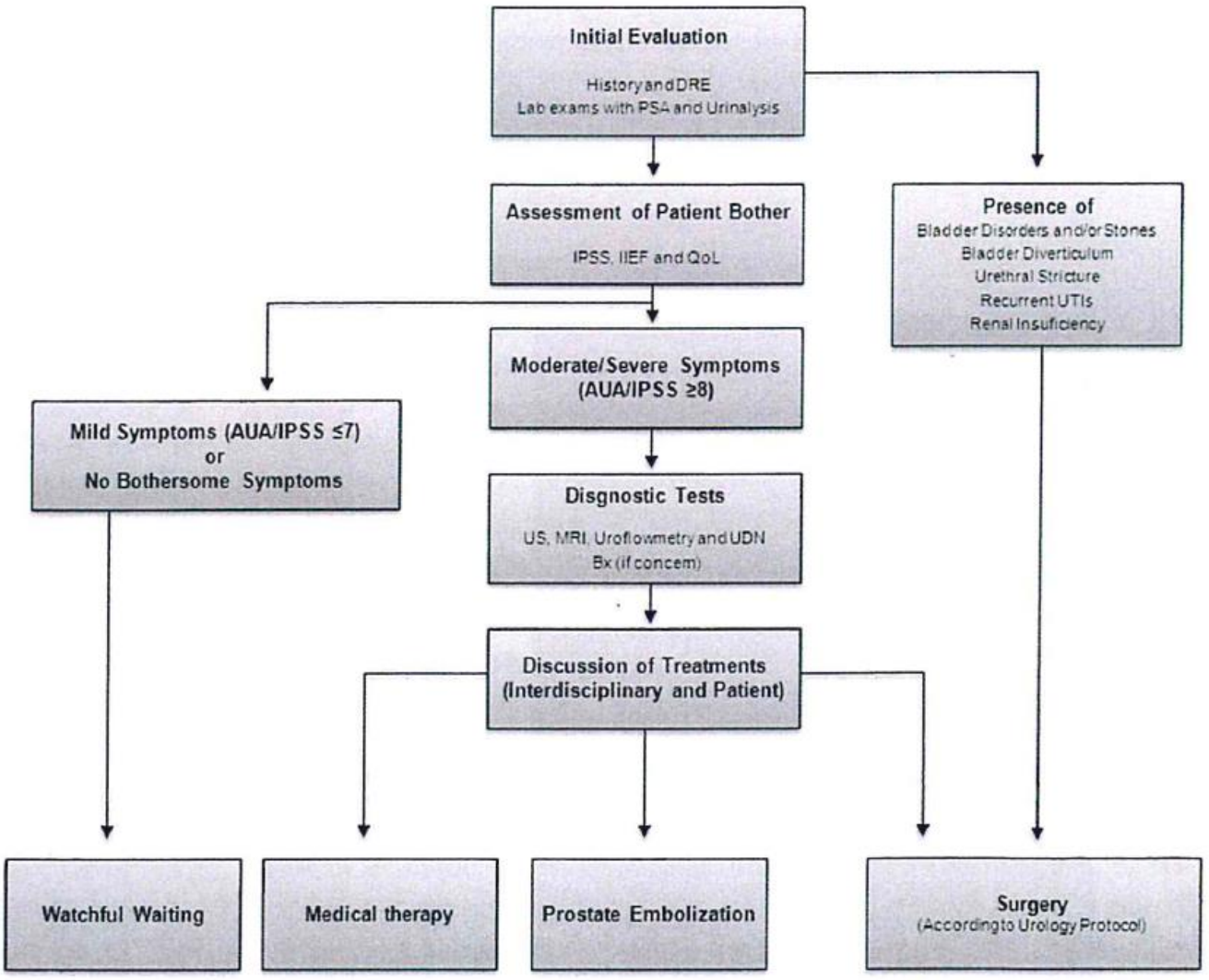

Figure 3. Diagram of BPH diagnosis and treatment (Carnevale CIRSE 2013)

Table 25. Treatment options of AVM

Treatment options of AVM		Reference
Available treatments	The aim of AVM treatment is to prevent or avoid the bleeding risk and symptoms associated with AVM (epilepsy, headache, functional impairment), in order to allow the patient to lead a normal life. To reduce the risk of haemorrhage, it is necessary to exclude the AVM from the general circulation. Four therapeutic options are available for the treatment of arteriovenous malformations: • targeted treatment by microsurgery, • endovascular, • radiotherapy or • therapeutic abstention and medical surveillance. These treatments are used alone or in combination according to their risks. Therapeutic abstention may be justified especially if there has never been a clinical episode of haemorrhage or disabling symptomatology.	HAS 2011
Microsurgery		
Description	It consists of the immediate excision of the complete or partial lesion, ensuring the treatment of the intracranial hypertension and cancelling any risk of bleeding if it is complete. Surgery is the oldest therapeutic method. It is essential in case of compressive hematoma	HAS 2011
Summary of clinical benefit	• Microsurgery provides treatment for AVM symptoms and eliminates bleeding if it is complete. • Multimodality treatment (including endovascular embolisation) is considered for patients with significant risk of surgically induced neuro deficit (Narayanan 2017). • AVM complete occlusion rate is about 92%. (Stapleton 2018)	HAS 2011 Narayanan 2017 Stapleton 2018
Summary of clinical risk	• The neurological and haemorrhagic surgical risk is based on 3 parameters: the size, the functional location, and the existence of deep venous drainage.	HAS 2011
Target population	Patient with bleeding risk AVM eligible for surgery.	HAS 2011
Radio therapy		
Description	Stereotactic radiosurgery is an irradiation administered in a single session. The rays are focused precisely on the AVM. It is proposed for AVM less than 3.5 cm in diameter and most often located deep in the brain. The result is only 2 to 3	Narayanan 2017

Treatment options of AVM		Reference
	years later, because the treatment causes a delayed reaction in the abnormal vessels that are gradually closing. Arteriography is necessary to affirm that the AVM has disappeared. The risk of haemorrhage persists if the AVM has not disappeared.	
Summary of clinical benefit	• Radiosurgery can eradicate AVM in 60 to 90% of cases depending on its size (Narayanan 2017).	Narayanan 2017
Summary of clinical risk	• Radiosurgery cannot be an emergency treatment since the desired vascular obliteration is delayed for several weeks or months. • Complications directly related to radiosurgery are rare: mortality directly related to treatment is zero, there is no immediate morbidity. • Delayed morbidity is attributable to the formation of radiation injury or rebleeding. The rate of rebleeding before the occlusion does not seem to be different from that related to the natural evolution of the AVM. It is estimated at a little over 3% in the 2 years following treatment. • The risk of haemorrhage persists if the AVM has not disappeared.	HAS 2011 Narayanan 2017
Target population	Patient without immediate bleeding risk AVM ineligible to surgery.	HAS 2011
AVM Embolisation		
Description	This is an endovascular technique for occlusion of the nidus endovascular. The goal of endovascular treatment is to reduce the size of the AVM and the risks associated with this malformation as well as non-targeted embolisation. It may or may not be associated with radiation therapy and surgery. The most used embolics in the studies are the platinum microspires or coils. Embolisation of AVMs is principally an adjunctive treatment modality in the management of AVMs, with a 2-fold purpose well expressed by Kerber: "If the lesion is not curable by embolic blockade, the embolic device render the lesion into a surgically resectable or radiation treatable one '' (Mackay and McDougall 2001). The purpose of preoperative embolisation is to facilitate surgical resection by obliterating surgically difficult- to-access feeding pedicles, decreasing the size of the nidus, and decreasing the potential for intraoperative blood loss.	Mackay and McDougall 2001 HAS 2011 Lam 2017
Summary of clinical benefit/advantages	• Appropriately administered embolisation may reduce the size of the nidus without abrupt changes in intraluminal pressure and minimize the risk of future arterial recruitment to the nidus. (HAS 2011) • Pre-surgical embolisation of large or giant AVMs minimizes blood loss, reduces intra-nidal flow and shortens operating time. The other objectives are to reduce the size of the nidus and promote its progressive thrombosis, to occlude deep vessels inaccessible to surgery, to obliterate the associated aneurysms and the fistulas with high flow. (HAS 2011) • AVM complete occlusion rate varies from 14% to 61% depending on location	Soromachi 1999 HAS 2011 Stapleton 2018 Sugiu 2019

Treatment options of AVM		Reference
	(Soromachi 1999; Sugiu 2019).	
Summary of clinical risk/limits	• Complete obliteration of AVMs has been difficult to achieve using embolisation alone, with angiographic cure ranging from 13% to 96% and being highly dependent on good selection of patients and lesions. Certain lesions, such as small and medium-sized superficial AVMs, are amenable to embolisation as monotherapy, especially in the acute phase of haemorrhagic stroke. (HAS 2011; Narayanan 2017) • The risks of the embolisation of AVM are essentially ischemic. They are related to thromboembolic complications or occlusion of parenchymal arteries by the embolic agent. (HAS 2011; Narayanan 2017) • Minor complications, such as post embolisation syndrome, are common after transarterial embolisation for AVM. Major complications, such as pulmonary embolism, renal vein thrombosis, and a large area of non-target embolisation, are rare. (Sheng 2017) • Haemorrhagic complications are rare but serious. • The vital risk of this type of treatment is estimated at 1% and functional at 2-4%. Adverse events of AVM embolisation in SOA literature (Max rate): • Ischemia (19%) • Persistent neurologic deficits (14%) • Haemorrhage (8%) • Skin necrosis/Ulceration (8%) • Death (3%)	Soromachi 1999 HAS 2011 Dabus 2016 Narayanan 2017 Sheng 2017 Donzelli 2019 Sugiu 2019
Target population	Palliative embolisation is intended for large and complex AVMs, not viable for surgery or radiotherapy, with the aim of reducing blood flow and thus minimizing or stopping the progression of neurological symptoms related to venous hypertension and / or an arterial deviation.	HAS 2011

Table 26. Treatment options of hypervascular processes for Haemostatic Embolisation

Treatment options of hypervascular processes for Haemostatic Embolisation		Reference
Available treatments	The choice of emergency treatment is made according to the location and the hemodynamic state of the patient. The goal of management is to stop the bleeding, restore a correct hemodynamic state if necessary and determine the cause of the bleeding in order to treat it. Surgery and embolisation are the two therapeutic options depending on the severity of the lesions treated. In the context of haemorrhaging of the spleen, liver and kidney, care should also be taken to be as conservative as possible. Embolisation is for patients with hemodynamically stable or compensated shock. In the opposite case, the surgical option is most often accepted.	HAS 2011
Haemostatic Surgery		
Description	Haemostatic surgery includes: • Vascular ligations; • Uterine plicatures or compression; • Exeresis of a uterine segment; • Radical treatments such as haemostasis hysterectomy	HAS 2011
Summary of clinical benefit	• Haemostatic surgery is recommended in case the patient is not hemodynamically stable or not in controlled haemorrhagic shock. • Haemostatic surgery is used when the risk of haemorrhage is not immediate. • Long term rebleeding control at 3 years is 45%. (Huang 2017)	HAS 2011 Huang 2017
Summary of clinical risk/limits	• No specific risk identified in the literature.	HAS 2011
Target population	Patients with vascular and post-partum haemorrhage	HAS 2011
Haemostatic Embolisation		
Description	The particles used for the embolisation of haemorrhage of vascular origin are resorbable or non-absorbable particles. There is no reference embolisation implant in the arterial embolisation of haemorrhages.	HAS 2011
Summary of clinical benefit/advantages	• Arterial embolisation is recommended in case of uterine atony, especially after vaginal delivery, cervico-uterine haemorrhage (placenta covering), cervico-vaginal tear (sutured or not accessible to surgery) and thrombi vaginal,	HAS 2011 Huang 2017

Treatment options of hypervascular processes for Haemostatic Embolisation		Reference
	including in case of coagulopathy. In these clinical indications, the efficiency is of the order of 85%. • The results of the studies highlight clinical success rate, defined as bleeding control, between 67.5% and 97.5% depending on the location. • Long term rebleeding control at 3 to 5 years varies from 42% to 65%. (Huang 2017; Huyett 2019; Ittrich 2017)	Ittrich 2017 Huyett 2019
Summary of clinical risk/limits	• the indication of embolisation may be retained when the patient is hemodynamically stable or in controlled haemorrhagic shock. Otherwise, the surgical option is commonly accepted. • Embolisation techniques are associated with risk of artery dissection and mistargeted embolisation.	HAS 2011
Target population	Patients with vascular and post-partum haemorrhage.	HAS 2011

7.0 Suggested profile and training for users

Embosphere Microspheres must only be used by specialist physicians trained in vascular embolisation procedures.

8.0 Applicable Standards and Common Specifications

The list of all applied common specifications (CS), international standards harmonized under the medical device directives and/or the MDR, and relevant adopted monographs of the European pharmacopoeia is provided in Table 27.

Table 27. Applicable Standards and Common Specifications

Document	Date/Version	Title
General Standards		
Regulation (EU) 2017/745	05 April 2017	Medical Device Regulation (MDR) of the European Union (Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices)
ISO 13485 EN ISO 13485	2016	Quality Systems – Medical Devices – Quality Management Systems. Requirements for Regulatory Purposes
NF EN ISO 14971	2019	Medical Devices – Application of Risk Management to Medical Devices
IEC 62366-1	2015/Amd 2020	Medical devices – Application of usability engineering to medical devices
NF EN ISO 14630	2013	Non-active surgical implants – General requirements
NF EN 1041+A1	2013	Terminology, Symbols and Information Provided with Medical Devices; Information Supplied by the Manufacturer with Medical Devices
NF EN ISO 15223-1	2017	Medical Devices – Symbols to be used with medical device labels, labelling, and information to be supplied
NF EN 556-1	2002	Sterilization of medical devices – Requirements for medical devices to be labelled “sterile”
NF EN ISO 11737-1	2018	Sterilization of medical devices – Microbiological methods – Part 1: Determination of a population of microorganisms on products development, validation and routine control of a sterilization process for medical devices
NF EN ISO 17665-1	2006	Sterilization of health care products – Moist heat – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices
NF EN ISO 11138-1	2017	Sterilization of health care products – Biological indicators – Part 1: General requirements
NF EN ISO 11138-3	2017	Sterilization of health care products – Biological indicators – Part 3: Biological indicators for moist heat sterilization processes
NF EN ISO 10993-1	2018	Biological Evaluation of Medical Devices – Part 1: Evaluation and testing
NF EN ISO 10993-3	2014	Biological Evaluation of Medical Devices – Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
NF EN ISO 10993-4	2018	Biological Evaluation of Medical Devices – Part 4: Selection of Tests for Interactions with Blood
NF EN ISO 10993-5	2010	Biological Evaluation of Medical Devices – Part 5: Tests for cytotoxicity: In Vitro methods
NF EN ISO 10993-6	2017	Biological Evaluation of Medical Devices – Part 6: Tests for local effects after implantation
NF EN ISO 10993-10	2013	Biological Evaluation of Medical Devices – Part 10: Tests for Irritation and sensitization
NF EN ISO 10993-11	2018	Biological Evaluation of Medical Devices – Part 11: Tests for system toxicity
NF EN ISO 10993-12	2012	Biological Evaluation of Medical Devices – Part 12: Sample preparation and reference materials

Document	Date/Version	Title
NF EN ISO 10993-17	2009	Biological Evaluation of Medical Devices – Part 17: Methods for the Establishment of Allowable Limits for Leachable Substances
NF EN ISO 10993-18	2020	Biological evaluation of medical devices – Part 18: Chemical characterization of materials
NF EN ISO 11607-1	2018	Packaging for Terminally Sterilized Medical Devices. Part 1: Requirements for materials, sterile barrier systems, and packaging systems.
NF EN ISO 11607-2	2018	Packaging for Terminally Sterilized Medical Devices. Part 2: Validation requirements for forming, sealing and assembly processes
NF EN ISO 14155	2020	Clinical investigation of medical devices for human subjects – Good clinical practice
NF EN ISO 22442-1	2016	Medical devices utilizing animal tissues and their derivatives – Part 1: Application of risk management
NF EN ISO 22442-2	2016	Medical devices utilizing animal tissues and their derivatives – Part 2: Controls on sourcing, collection and handling
NF EN ISO 22442-3	2008	Medical devices utilizing animal tissues and their derivatives – Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents
USP <151>	Last revision	Pyrogen testing
USP <87>	Last revision	Biological reactivity tests (in vitro)
EP 2.6.14 USP <85>	Last revision	Bacterial Endotoxins Assay
USP <161>	Last revision	Transfusion and infusion assemblies and similar medical devices
EP 2.9.19	Last revision	Particulate Contamination – Sub-visible particles
USP <660> / EP 3.2.1	Last revision	Glass containers for pharmaceutical use
USP <661>	Last revision	Containers
ASTM F981-04	2016	Standard Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Bone
ASTM F88/F88M-15	2015	Standard Test Method for Seal Strength of Flexible Barrier Materials
ASTM F1140-13	2013	Standard Test Methods for Internal Pressurization Failure Resistance of Unrestrained Packages for Medical Applications
ASTM F1608-16	2016	Standard Test Methods for Microbial Ranking of Porous Packaging Material (Exposure Chamber Method)
ASTM F1929-15	2015	Standard Test Method for Detecting Seal Leaks in porous Medical Packaging by Dye Penetration
ASTM D4169-16	2016	Standard Practice for Performance Testing of Shipping Containers and Systems
ASTM F2096-11	2019	Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization (Bubble Test)
ASTM F1980-16	2016	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
NF EN ISO 14644-1	2016	Classification of Air Cleanliness, Clean rooms & Associated Controlled

Document	Date/Version	Title
		Environments. Part 1: Classification of air cleanliness
NF EN ISO 14698-1	2004	Cleanrooms and associated controlled environments — Biocontamination control
MEDDEV 2.7.1	Rev. 4	Guidelines on Medical Devices – Clinical Evaluation – A Guide for Manufacturers and Notified Bodies under Directives 93/42/EEC
MDCG 2019-8 v2	2020	Guidance document Implant Card relating to the application of Article 18 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices
MDCG 2019-9	2019	Summary of safety and clinical performance A guide for manufacturers and notified bodies
MDCG 2020-5	2020	Clinical Evaluation – Equivalence. A guide for manufacturers and notified bodies
MDCG 2020-6	2020	Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies
Product Specific Standards		
ISO 594-1	1986	Conical Fittings with 6% (Luer) Taper for Syringes, Needles and Certain Other Medical Equipment – Part 1: General Requirements
ISO 594-2	1998	Conical Fittings with 6% (Luer) Taper for Syringes, Needles and Certain Other Medical Equipment – Part 2: Lock Fittings
NF EN ISO 7886-1	2018	Sterile hypodermic syringes for single use – Part 1: Syringes for manual use

9.0 Revision History

SSCP revision	ECN Number	Date Issued	Change description	Author/PRRC	Revision validated by the Notified Body	Date of Notified Body approval
001	PAR4029	12-Jan-2022	Initial release	Author: **Lionel Ekedi Ngando** Person Responsible for Regulatory Compliance: **Rosène Amossé**	☒ Yes Validation language: English ☐ No	21-Feb-2022

10.0 List of abbreviations

Term	Definition
ASSLD	American Association for the Study of Liver Diseases
AVM	Arteriovenous Malformations
BPH	Benign Prostatic Hyperplasia
CD	Comparable Devices
CE-mark	Conformité Européenne mark
CI	Complete Infarction
CIRSE	Cardiovascular and Interventional Radiological Society of Europe
DCR	Disease Control Rate
DEB	Drug Eluting Beads
ES	Embosphere Microspheres
EU	European union
FVR	Fibroids Volume Reduction
GnRH	Gonadotropin-Releasing Hormone
GS	Gelatin Sponge
HAS	Haute Autorité de Santé
HCC	Hepatocellular Carcinoma
HIFU	High Intensity Focused Ultrasound
HR-QOL	Health-Related Quality of Life
HVT	Hypervascular Tumors
IFU	Instructions for Use
IIEF	International Index of Erectile Function

Term	Definition
IPSS	International Prostate Symptom Score
LUTS	Lower Urinary Tract Symptoms
MDR	Medical Device Regulation
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
ND	Not Described
NICE	National Institute for Health and Care Excellence
OP	Open prostatectomy
PAE	Prostatic Artery Embolisation
PES	Post Embolisation syndrome
PFS	Progression Free Survival
PQI	Patients with Quality Of Life Improvement
PSI	Patients with Symptoms Improvement
PVA	Polyvinyl Alcohol
Qmax	peak flow rate
QOL	Quality of Life
QSI	Quality of Life Score Improvement
RCT	Randomized Controlled Trial
RFA	Radiofrequency
SIR	Society for Interventional Radiology
SOA	State of the Art
SSCP	Summary of Safety and Clinical Performance
SSR	Symptoms Score Reduction
TACE	Transarterial Chemoembolisation
TAE	Transarterial Embolisation
TARE	Transarterial Radioembolisation
TC	Tumour growth control
TSR	Technical success rate
TURP	Transurethral Resection of the Prostate
UAE	Uterine artery embolisation
UFE	Uterine Fibroids Embolisation
UFS-QOL	Uterine Fibroid Symptom Quality of Life
USP	United States Pharmacopeia