Non interventional post-authorisation safety study (PASS) to define the incidence of and potential risk factors for procedure-related neurological adverse events (AE) in patients undergoing ultrasound guided foam sclerotherapy (UGFS) for the treatment of lower limb varicose veins (VV) using Fibrovein 3% and 1% (sodium tetradecyl sulphate, STS, injection) incorporating a drug utilisation study

1. PROTOCOL INFORMATION

Version: 1.0

Date: 13 December 2014

EU PAS Register: not yet registered

2. MARKETING AUTHORISATION HOLDER AND FINANCIAL SPONSOR

STD Pharmaceutical Products Ltd., Plough Lane, Hereford, HR4 0EL, UK

Tel: +44 (0) 1432 373555

E-mail: enquiries@stdpharm.co.uk

3. RESPONSIBLE PARTIES

Chief Clinical Investigator (UK)

Professor Andrew W. Bradbury

BSc MB ChB (Hons) MD MBA FEBVS FRCSEd FRCSEng

Sampson Gamgee Professor of Vascular Surgery, University of Birmingham, UK

And

Consultant Vascular and Endovascular Surgeon, Heart of England NHS Foundation Trust, Birmingham, UK.

Address for correspondence: University Department of Vascular Surgery, Netherwood House, Solihull Hospital, Lode Lane, Solihull, B91 2JL, UK

PA: Mrs Tracy Ellis

Tel: +44 (0) 121 424 5570

Fax: +44 (0) 121 424 5086

E-mail: tracy.ellis@heartofengland.nhs.uk

Chief Scientific Investigators

Mr Bruce Gardiner BSc, Managing Director

Dr Mike Watkins BSc PhD, Qualified Person Pharmacovigilance (QPPV)

Address for correspondence: STD Pharmaceutical Products Ltd., Plough Lane, Hereford, HR4 0EL, UK

Tel: +44 (0) 1432 373555

E-mail: bgardiner@stdpharm.co.uk

E-mail: mikewatkins@stdpharm.co.uk

Co-ordinating Clinical Investigators

Mr Huw Davies

BSc (Hons) MB BS MRCS

Research Registrar, University Department of Vascular Surgery and Heart of England NHS Foundation Trust, Birmingham, B91 2JL, UK

Tel: +44 (0) 121 424 5570

E-mail: huw.davies@heartofengland.nhs.uk

Mr Matthew Popplewell

MB BS MRCS

Research Registrar, University Department of Vascular Surgery and Heart of England NHS Foundation Trust, Birmingham, B91 2JL, UK

Tel: +44 (0) 121 424 5570

E-mail: matthew.popplewell@heartofengland.nhs.uk

Departmental fax: +44 (0) 121 424 5086

Clinical Co-investigators

United Kingdom (*full list yet to be confirmed*)

Professor Julie Brittenden, Aberdeen (j.brittenden@abdn.ac.uk)

Mr Kaiwan Bhamgara, Elgin (kaiwan.bhamgara@nhs.net)

Mr Wesley Stuart, Glasgow (Wesley.Stuart@ggc.scot.nhs.uk)

Mr Stephen Kettlewell, Lanarkshire (stephenkettlewell@mac.com)

Prof Gerry Stansby, Newcastle (gerard.stansby@nuth.nhs.uk)

Mr Tim Lees, Newcastle (tim.lees@nuth.nhs.uk)

Mr Ben Banjeree, City Hospitals Sunderland (ben.banerjee@nhs.net)

Mr James Scurr, Liverpool (Scurr@rlbuht.nhs.uk)

Professor Charles McCollum, Manchester (cnmcc@manchester.ac.uk)

Professor Ian Chetter (Hull) (ian.chetter@hey.nhs.uk)

Mr Dan Carradice (Hull) (Daniel.Carradice@hey.nhs.uk)

Mr David Berridge, Leeds (David.Berridge@leedsth.nhs.uk)

Mr Jonathan Beard, Sheffield (jonathan.d.beard@sth.nhs.uk)

Professor Bruce Braithwaite, Nottingham (bruce.braithwaite@nhs.net)

Mr Martin Claridge, Birmingham (martin.claridge@heartofengland.nhs.uk)

Mr Harmeet Khaira, Birmingham (harmeet.khaira@heartofengland.nhs.uk)

Mr Mark Gannon, Birmingham (mark. gannon@heartofengland.nhs.uk)

Mr Mark Scriven, Birmingham (mark.scriven@heartofengland.nhs.uk)

Mr Donald Adam, Birmingham (donald.adam@heartofengland.nhs.uk

Mr Manjit Gohel, Cambridge (manjit.gohel@addenbrookes.nhs.uk)

Mr Philip Coleridge-Smith, London (p.coleridgesmith@adsum-healthcare.co.uk)

Professor Alun Davies, Imperial College, London (a.h.davies@imperial.ac.uk)

Mr Toby Richards, UCL and Royal Free Hospital, London (toby.richards@ucl.ac.uk)

Mr Stephen Black, Guys and St Thomas, London (stephen.black@gstt.nhs.uk)

Mr Robert Hinchliffe, St Georges, London (robhinchliffe@gmail.com)

Dr Katy Darvall (Taunton) (katydarvall@btinternet.com)

Mr Isaac Nyamekye, Worcester (isaac.nyamekye@worcsacute.nhs.uk)

Mr Haroun Gajraj, Vein Care Centre (Haroun.Gajraj@gmail.com)

Mr Marcus Brookes, Bristol (Marcus.Brooks@nbt.nhs.uk)

Professor Frank Smith, Bristol (Frank.C.T.Smith@bristol.ac.uk)

Mr Simon Payne, Portsmouth (simon.payne07@btinternet.com)

Professor Bruce Campbell, Exeter (bruce.campbell@nice.org.uk)

Mr Simon Ashley, Plymouth (simonashley@nhs.net)

Mr Robert Insall, Kent and Canterbury Hospital (robert.insall@nhs.net)

Mr Ken Woodburn, Royal Cornwall (ken.woodburn@rcht.cornwall.nhs)

Mr Keith Poskitt, Cheltenham and Gloucester (Keith.Poskitt@glos.nhs.uk)

France

Dr Jean-Marc Chardonneau, Nantes (jeanmarcchardonneau@yahoo.fr)

Dr Pierre Ouvry, Dieppe (ouvryp@wanadoo.fr)

Dr Pierre-Marie Noël de la Paquerie, Béziers (paquerie@wanadoo.fr)

Other Eligible European Countries

Centres from other European countries covered by decentralised procedure (DCP) UK/H/2775/001-4/DC will be added in due course as interest in the study dictates.

4. ABSTRACT

Title

Non-interventional post-authorisation safety study (PASS) [as defined by Directive 2001/83/EC (DIR) Art 1(15)] to define the incidence of and potential risk factors for procedure-related neurological adverse events (AE) in patients undergoing ultrasound guided foam sclerotherapy (UGFS) for the treatment of lower limb varicose veins (VV) using Fibrovein 3% and 1% (sodium tetradecyl sulphate, STS, injection) incorporating a drug utilisation study.

Rationale and Background

Across Europe, patients with lower limb varicose veins (VV) are increasingly treated without surgery.

In the UK, the National Institute of Clinical and Health Excellence (NICE) have recommended endothermal ablation (ETA) and ultrasound-guided foam sclerotherapy (UGFS) in preference to surgery for the treatment of VV.

(http://www.nice.org.uk/Guidance/QS67)

(http://www.nice.org.uk/guidance/CG168)

Randomised controlled trials and observational studies have indicated that the incidence of procedure-related neurological AE (including visual disturbance, migraine, and transient ischaemic attack, TIA) during and following UGFS is very low.

However, their exact incidence and cause have not yet been defined.

Fibrovein 3% and 1% were granted a UK license for the treatment of VV by means of UGFS in 2012 as part of a DCP (UK/H/2775/001-4/DC).

One of the post approval commitments is to perform a non-interventional PASS to assess the incidence and potential risk factors for procedure-related neurological AE.

Nested within this study we also wish to perform a drug utilisation study to examine the "real world" use of Fibrovein for UGFS.

Research questions and objectives

Research Questions:

1. What are the incidence, type, severity, duration, treatment (where required), and clinical outcome of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam?
2. To what extent, if any, are these procedure-related neurological AE associated with identifiable patient and treatment characteristics?
3. Post-marketing authorisation (PMA), how is UGFS with Fibrovein 3% and 1% being used in the "real world" to treat lower limb VVs (nested drug utilisation study)?

Objectives

To:

1. Define the incidence of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam
2. Further characterise these AE in terms of type, severity, duration, treatment (where required), and clinical outcome
3. To describe the relationship, if any, between procedure-related neurological AE and identifiable patient and treatment characteristics
4. Describe the PMA "real world" use of Fibrovein 3% and 1% foam for the treatment of lower limb VVs (nested drug utilisation study)

Study Design

This will be a non-interventional prospective, multicentre, PASS of patients undergoing UGFS for lower limb VV incorporating a nested drug utilisation study.

The study is purely observational will have no impact on the:

1. Decision to treat with UGFS
2. Nature of any aspect of the UGFS treatment provided
3. Management of any procedure-related neurological AE should they occur

Furthermore:

1. The results of the PASS will not be generalisable to patients having UGFS using other sclerosants or to other types of VV treatment
2. No access to medical records is required and no patient identifiable data will be recorded outside the direct clinical care team

For these reasons, the NHS Health Research Authority (HRA) does not consider this type observational non-interventional PASS study to:

1. Be "research"

   (http://www.hra-decisiontools.org.uk/research/)

2. Require NHS Research Ethical Committee (REC) approval

   (http://www.hra-decisiontools.org.uk/ethics/)

3. Require NHS R&D Management permission

   (http://www.hra.nhs.uk/documents/2013/09/approval-of-medical-devices-research-version-2-april-2008.pdf)

Please see HRA decision tools (**Appendix 1**)

Population

Adult (18 years and over) non-pregnant, non-breast-feeding, patients who are undergoing UGFS with Fibrovein for lower limb VV.

Variables

The following patient and treatment variables will be collected on Fibrovein PASS Proforma 1 (**Appendix 2**).

Patient:

1. Age
2. Gender
3. Height, weight and body mass index (BMI)
4. Primary versus recurrent VV
5. Co-existing deep venous disease and/or history of deep vein thrombosis (DVT)
6. CEAP clinical grade

   (http://www.veinforum.org/uploadDocs/1/Revised-CEAP-Classification---May-2004.pdf)

7. Type of VV: great saphenous vein (GSV), small saphenous vein (SSV), anterior accessory saphenous vein (AASV), and tributary veins

8. History of migraine / transient ischaemic attack (TIA) / stroke / diabetes mellitus (DM) / hypertension (high blood pressure, BP)
9. Smoking status
10. Known patent foramen ovale (PFO) (symptomatic or asymptomatic)
11. History of previous Fibrovein UGFS

Treatment:

1. Unilateral vs. bilateral (each treatment leg will generate a separate Fibrovein PASS Proforma 1 (**Appendix 2**)
2. Method of preparation of Fibrovein foam
3. Concentration of Fibrovein used
4. Fibrovein to gas ratio
5. Gas used: air vs physiological gases (O_2/CO_2) vs other
6. Volume of each concentration of Fibrovein used
7. Number of injection sites
8. Aliquot size (volume of foam injected at each injection site)
9. Concomitant surgical and non-surgical treatments for VV
10. Compression regime and duration following UGFS

Data Sources

The presence (and if present the type, severity, duration, treatment, and clinical outcome) or absence of procedure-related neurological AE associated with Fibrovein UGFS for lower limb VV, together with patient and treatment characteristics, will be collected Fibrovein PASS Proforma 1 (**Appendix 2**) at the end of each UGFS treatment session.

Each separate UGFS treatment session will generate a separate proforma.

In patients undergoing bilateral treatment a Fibrovein PASS Proforma 1 will be completed for each leg.

UGFS may be used either as the sole treatment for the patient's VV or in combination with another treatment modality.

In keeping with post-marketing pharmacovigilance (PV) requirements, in addition to completing Fibrovein PASS Proforma 1, co-investigators will be asked to contact the UK Co-ordinating Centre should a serious adverse event (SAE) occur at the time of the UGFS or if they become aware that a SAE has occurred subsequently. SAE details will be recorded on Fibrovein PASS Proforma 2 (**Appendix 3**).

SAE are defined by the UK Medicines and Healthcare Products Regulatory Agency (MRHA) (www.mhra.gov.uk) as those which:

1. Result in death
2. Are immediately life threatening
3. Require in-patient hospitalisation or prolongation of existing hospitalisation
4. Result in persistent or significant disability / incapacity, or substantial disruption of the ability to conduct normal life functions
5. Result in a congenital abnormality or birth defect
6. Represent an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

Co-investigators will be provided with instructions on how to complete the Fibrovein PASS Proformas 1 and 2 and telephone help will be available during normal office hours from the UK Co-ordinating Centre (contact details as given above).

Study size

The above data will be recorded in relation to 10,000 Fibrovein UGFS treatments.

Data analysis

Each completed Fibrovein PASS Proforma 1 will be transmitted to the UK Co-ordinating Centre where non-patient identifiable data will be held confidentially and entered into a password-protected computerised database for later analysis.

The Fibrovein PASS SAE Proforma 2 will be forwarded to STD Pharmaceuticals Ltd. in keeping with post-marketing PV requirements.

Recruitment Milestones

Data collection at the UK Co-ordinating Centre will start on 1 January 2015.

Between 15 and 25 further high-volume UGFS centres from the UK and France will be recruited to the study by 1 April 2015.

Centres from other European countries covered by decentralised procedure DCP (UK/H/2775/001-4/DC) will be added as interest in the study dictates.

Data collection in relation to 10,000 Fibrovein UGFS treatment sessions will take place over 3 years (approximately 3,500 treatment sessions per year) and be completed by 1 January 2018.

The final study report will be available by 1 April 2018.

5. AMENDMENTS

None at present

6. MILESTONES

Start of data collection: 1 January 2015

End of data collection: 1 January 2018

Duration of data collection: 3 years

Annual progress reports (defined by Article 107m(5) of Directive 2001/83/EC): 1 January 2016 and 2017

Six monthly Interim reports: 1 June 2015, 1 June 2016, and 1 June 2017

Final report of study results: 1 April 2018

7. RATIONALE AND BACKGROUND

Across Europe, patients with lower limb VV are increasingly treated without surgery.

In the UK, NICE have recommended thermal ablation and UGFS in preference to surgery for the treatment of VV.

(http://www.nice.org.uk/Guidance/QS67)

(http://www.nice.org.uk/guidance/CG168).

Randomised controlled trials and observational studies have indicated that the incidence of procedure-related neurological AEs (including visual disturbance, migraine, and TIA) following UGFS is low [Beckitt et al 2011, Bradbury et al 2010, Coleridge-Smith 2006, Guex 2005, Jia et al 2007].

However, their exact incidence and cause (please see below) has not yet been defined [Parsi 2012, Adatia et al 2013, Asbjornsan et al 2012, Willenburg 2013].

Fibrovein 3% and 1% were granted a UK license for the treatment of VV by means of UGFS in 2012 as part of DCP (UK/H/2775/001-4/DC).

One of the post approval commitments is to perform a non-interventional PASS to assess the frequency and nature of procedure-related neurological AE.

Nested within this study is a drug utilisation study to examine the "real world" use of Fibrovein for UGFS.

Data on SAE will also be collected in accordance with post-marketing PV requirements.

8. RESEARCH QUESTION AND OBJECTIVES

Research Questions

1. What are the incidence, type, severity, duration, treatment (where required), and clinical outcome of procedure-related neurological AE in patients undergoing UGFS for lower limb varicose veins (VV) using Fibrovein 3% and 1% foam?
2. To what extent, if any, are these procedure-related neurological AE associated with identifiable patient and treatment characteristics?
3. Post-marketing authorisation (PMA) how is UGFS with Fibrovein 3% and 1% being used in the "real world" to treat lower limb VVs (nested drug utilisation study)?

Objectives

To:

1. Define the incidence of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam
2. Further characterise these AE in terms of type, severity, duration, treatment (where required), and clinical outcome
3. To describe the relationship, if any, between procedure-related neurological AE and identifiable patient and treatment characteristics
4. Describe the PMA "real world" use of Fibrovein 3% and 1% foam for the treatment of lower limb VVs (nested drug utilisation study).

9. RESEARCH METHODS

9.1 Study Design

This will be non-interventional, observational, prospective, multicentre, PASS [as defined by Directive 2001/83/EC (DIR) Art 1(15)] of patients undergoing Fibrovein UGFS for lower limb VV with a nested drug utilisation study.

9.2 Setting and study population

Persons: non-pregnant, non-breast-feeding, patients aged 18 years or over, undergoing Fibrovein UGFS for lower limb VV

Place: public and private hospitals in the UK, France and other eligible (DCP) countries performing UGFS for VV

Data collection period: 1 January 2015 to 1 January 2018

Inclusion criteria: all non-pregnant, non-breast-feeding patients aged 18 years or over, undergoing Fibrovein UGFS (either alone or in combination with another modality such as endothermal ablation) for VV

Exclusion criteria: patient under 18 years of age; not undergoing Fibrovein UGFS as part of the their VV treatment; pregnancy, breast-feeding

Sampling: none, all suitable patients to be included

9.3 Variables

The following will be collected on Fibrovein PASS Proforma 1

Outcome of interest: procedure-related neurological AE

Exposures: 1% and/or 3% Fibrovein foam

Patient variables:

1. Age
2. Gender
3. Height, weight, and body mass index (BMI)
4. Primary versus recurrent VV
5. Co-existing deep venous disease / history of deep vein thrombosis (DVT)
6. CEAP clinical grade (C1-C6)

7. Type of VV: great saphenous vein (GSV), small saphenous vein (SSV), anterior accessory saphenous vein (AASV), and tributary veins
8. History of migraine / transient ischaemic attack (TIA) / stroke / diabetes mellitus (DM) / hypertension (high blood pressure, BP)
9. Smoking status
10. Known patent foramen ovale (PFO) (symptomatic or asymptomatic)
11. History of previous Fibrovein UGFS

Treatment variables:

1. Unilateral vs. bilateral
2. Method of preparation of Fibrovein foam
3. Concentration of Fibrovein used
4. Fibrovein to gas ratio
5. Gas used: air vs. physiological gases (O_2/CO_2) vs other
6. Volume of each concentration of Fibrovein used
7. Number of injection sites
8. Aliquot size (volume of foam injected at each injection site)
9. Concomitant surgical and non-surgical treatments for VV
10. Compression regime and duration following UGFS

9.4 Data Sources

Pilot study:

Heart of England NHS Foundation Trust, Birmingham, UK, commencing 1 January 2015

Full study

UK and French centres as listed above; centres from other eligible (DCP) countries to be added as interest in the study dictates

9.5 Study Size

A review of the literature (please see above) indicates that procedure-related neurological AE in patients undergoing Fibrovein UGFS for lower limb VV are either rare (< 1:1,000) or very rare (1:1,000-10,000).

Statistical advice has, therefore, been sought regarding the sample size required to define, within reasonable confidence intervals, the incidence of such AE.

A procedure-related neurological AE event rate of 0.3% equates to the observation of 30 such AE in association with 10,000 UGFS treatment sessions.

However, there is a 50% chance of observing > 30 such AE, and binomial theorem indicates that there is a 20% chance of observing > 35 such AE, in association with 10,000 UGFS treatments.

There is, therefore, an 80% chance (similar to 80% power) of observing < 35 such AE in association with 10,000 UGFS treatments.

If 35 such AEs were observed in association with 10,000 UGFS treatments, the 95% confidence intervals would range from 0.24% to 0.49%.

This would provide significant (P<0.05) evidence that the rate is less than 0.5%.

In other words, if the incidence of procedure-related neurological AE in association with UGFS is 0.35%, a sample size of 10,000 treatment sessions would provide the study with an 80% chance (power) of showing that the rate was significantly below 0.5% at the 5% significance level.

9.6 Data management

Data collection:

The presence (and if present the type, severity, duration, treatment, and clinical outcome) or absence of procedure-related neurological AE following Fibrovein UGFS for lower limb VV, together with patient and treatment characteristics, will be collected using the Fibrovein PASS Proforma 1 (**Appendix 2**) at the end of each UGFS treatment session.

Each separate Fibrovein UGFS treatment session will generate a separate Fibrovein PASS Proforma 1.

In patients undergoing bilateral treatment a separate Fibrovein PASS Proforma 1 will be completed for each leg.

Fibrovein UGFS may be used either as the sole treatment for the patient's VV or in combination with another treatment modality.

In keeping with standard post-marketing pharmacovigilance (PV) requirements, in addition to completing Fibrovein PASS Proforma 1, co-investigators will be asked to contact the UK Co-ordinating Centre should a serious adverse event (SAE) occur at the time of the UGFS, or if they become aware that a SAE has occurred subsequently.

SAE details will be recorded on Fibrovein PASS Proforma 2 (**Appendix 3**).

Co-investigators will be provided with instructions on how to complete Fibrovein PASS Proformas 1 and 2 (**Appendix 4**)

SAE are defined by the UK Medicines and Healthcare Products Regulatory Agency (MRHA) (www.mhra.gov.uk) as those which:

1. Result in death
2. Are immediately life threatening
3. Require in-patient hospitalisation or prolongation of existing hospitalisation
4. Result in persistent or significant disability / incapacity or substantial disruption of the ability to conduct normal life functions
5. Result in a congenital abnormality or birth defect
6. Represent an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

Data retrieval and preparation:

Each completed Fibrovein PASS Proforma 1 will be transmitted to the UK Co-ordinating Centre where non-patient identifiable data will be held confidentially and entered into an password-protected computerised database for later analysis.

Each Fibrovein PASS SAE Proforma 2 will be forwarded to STD Pharmaceuticals Ltd. in accordance with post-marketing PV requirements.

Statistical programme:

SPSS

9.7 Data analysis

Descriptive and summary statistics will be used to address the study objectives

1. Define the incidence of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein (3% and 1%) foam
2. Further characterise these AEs in terms of type, severity, duration, treatment (where required), and clinical outcome
3. To describe the relationship, if any, between procedure-related neurological AE and identifiable patient and treatment characteristics
4. Describe the PMA "real world" use of Fibrovein (3% and 1%) foam for the treatment of lower limb VVs (nested drug utilisation study)

9.8 Quality control

Data will be collected on standardised proformas.

Participating centres will be provided with instructions and training to ensure uniformity of data entry to the questionnaire.

Telephone support will be provided during normal office hours.

Questionnaires will be verified for completeness.

The entry of non-patient-identifiable data to a password-protected computerised database and analysis of collated data will be performed by suitably qualified individuals to ensure validity of results and reporting of trial findings.

9.9 Limitations of research methods

The main potential limitations of the study are:

1. Failure of collaborating centres to:
    i. Complete forms accurately
    ii. Transmit forms to the UK Co-ordinating Centre
2. Inability to verify the accuracy or completeness of data collection at the collaborating centres
3. Delayed (occurring after the end of the treatment) and non-neurological AE will not be captured (however, these are not the subject of this PASS)

10. PROTECTION OF HUMAN SUBJECTS

This will be a non-interventional, observational, prospective, multicentre, PASS of patients undergoing Fibrovein UGFS for lower limb VV with a nested drug utilisation study.

The study is purely observational will have no impact on the:

1. Decision to treat with UGFS
2. Nature of any aspect of the UGFS treatment provided
3. Management of any procedure-related neurological AE should they occur

Furthermore:

1. The results of the PASS will not be generalisable to patients having UGFS using other sclerosants or to other types of VV treatment
2. No access to medical records is required patient identifiable data will be recorded outside the clinical care team

For these reasons, the NHS Health Research Authority (HRA) does not consider this type non-interventional PASS study to:

1. Be “research”

   (http://www.hra-decisiontools.org.uk/research/)
2. Require NHS Research Ethical Committee (REC) approval

   (http://www.hra-decisiontools.org.uk/ethics/)
3. Require NHS R&D Management permission

   (http://www.hra.nhs.uk/documents/2013/09/approval-of-medical-devices-research-version-2-april-2008.pdf)

Please see HRA decision tools (**Appendix 1**).

Patients will be treated in accordance with the contemporary “standards of care” existing in each participating centre.

Co-investigators will be asked to complete a Fibrovein PASS (SAE) Proforma 2 and contact the UK Co-ordinating Centre should they become aware of any SAE.

11. MANAGEMENT AND REPORTING OF NEUROLOGICAL AE & SAE

Procedure-related neurological AE and SAEs will be reported immediately to the UK Co-ordinating Clinical Investigator:

- Mr Huw Davies, MB BS BSc (Hons) MRCS, Research Registrar, University Department of Vascular Surgery and Heart of England NHS Foundation Trust, Birmingham, UK

who will forward them within one working day to:

- Dr Mike Watkins BSc., PhD. Qualified Person Pharmacovigilance (QPPV), STD Pharmaceutical Products Ltd., Plough Lane, Hereford, HR4 0EL, UK

The QPPV will enter the AE into the pharmacovigilance system which involves a set of procedures based on current legislation.

Using the relevant procedures the QPPV will decide on the appropriate course of action.

The pharmacovigilance procedures are listed below:

- MAH4001 - Data collection and initial recording of adverse drug reactions
- MAH4002 - Assessment, Reporting, Recording and Follow-up of ADRs
- MAH4004 - Periodic Safety Update Report
- MAH4005 - Changing the Safety Information
- MAH4007 - Screening of the Scientific Literature
- MAH4008 - Pharmacovigilance Requirements of Distributors
- MAH4009 - Medical Information Enquiries
- MAH4010 - Signal Detection & Risk/Benefit Analysis
- MAH4011 - Processing of Adverse Drug Events to Third Party Products
- MAH4012 - QPPV contact out of working hours and back-up arrangements

New information regarding signals or information that might influence the benefit-risk balance will be picked up by SOP MAH4010.

A change in frequency of known AE will be assessed in the interim reports and if necessary changes to the company safety information will be made.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Annual progress reports will be available for the relevant competent authorities to review.

Six monthly interim reports will be assessed by the responsible parties to review recruitment rates and potential new safety information.

Study progress will also be reported in any PSURs (due April 2017) and risk management plan updates if applicable.

The results of the study will be presented at relevant learned societies and published in appropriate peer-reviewed journals.

13. REFERENCES

Adatia S et al. Acute ischemic stroke caused by paradoxical air embolism following injection sclerotherapy for VVs. Neurology India 2013; 61(4): 431-433.

Asbjornsen et al. Middle cerebral air embolism after foam sclerotherapy. Phlebology 2012; 27: 430–433.

Beckitt T, Elstone A, Ashley S. Air versus Physiological Gas for Ultrasound Guided Foam Sclerotherapy Treatment of Varicose Veins. Eur J Vasc Endovasc Surg; 2011; 42: 115-119.

Bradbury A et al. Ultrasound-guided foam sclerotherapy is a safe and clinically effective treatment for superficial venous reflux. J Vasc Surg 2010; 52(4): 939-945.

Coleridge Smith P. Chronic Venous Disease Treated by Ultrasound Guided Foam Sclerotherapy. Eur J Vasc Endovasc Surg 2006; 32(5): 577-583.

Guex JJ. Immediate & Midterm complications of sclerotherapy: report of prospective multicenter registry of 12,173 sessions. Dermatol Surg 2005; 31:123-128

Jia X et al. Systematic review of foam sclerotherapy for varicose veins. Br. J Surg. 2007; 94: 925-936.

Parsi K. Paradoxical embolism, stroke and sclerotherapy. Phlebology. 2012 Jun;27(4):147-67.

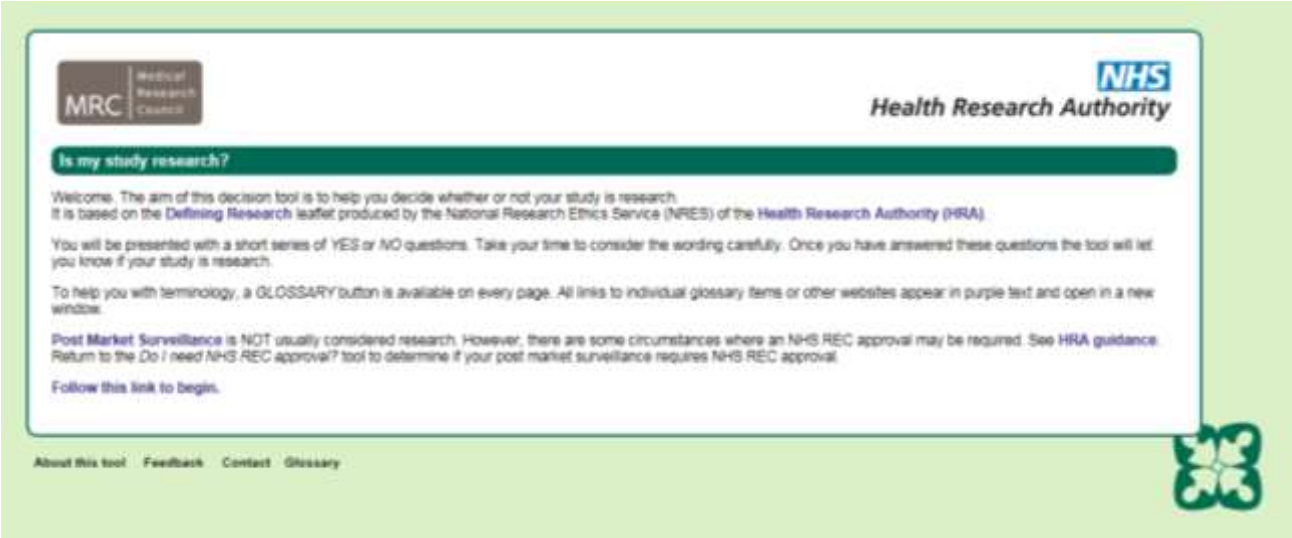
Willenberg T et al. Visual disturbance following sclerotherapy for varicose veins, reticular veins and telangiectasias: a systematic literature review. Phlebology 2013; 28: 195–200.

14. SIGNATURE OF CHIEF CLINICAL INVESTIGATOR (UK)

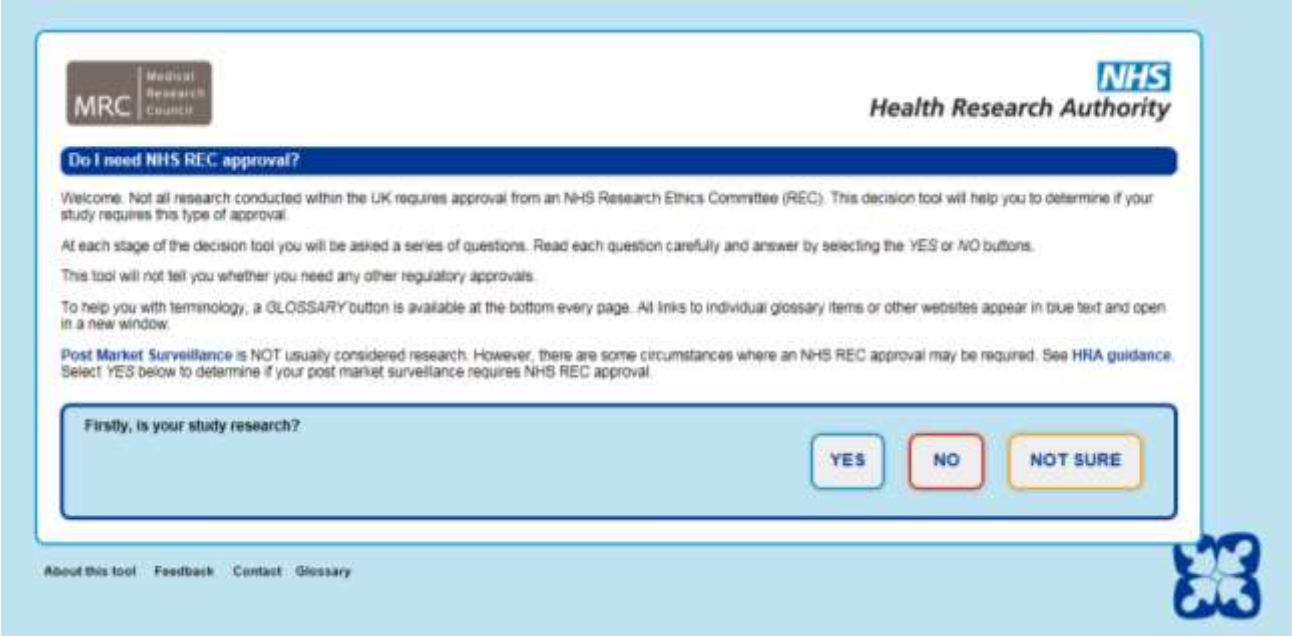
Professor Andrew W. Bradbury, BSc MB ChB (Hons) MD MBA FEBVS FRCSEd FRCSEng
Sampson Gamgee Professor of Vascular Surgery, University of Birmingham, UK *and* Consultant Vascular and Endovascular Surgeon, Heart of England NHS Foundation Trust, Birmingham, UK.

Appendix 1: Health Research Authority (HRA) Decision Tools

Definition of Research (http://www.hra-decisiontools.org.uk/research/)



Requirement for NHS REC Approval (http://www.hra-decisiontools.org.uk/ethics/)



Appendix 2: Fibrovein PASS Proforma 1 (procedure-related neurological AE)

Centre, date and patient details ***(please complete a form for each patient and each leg)***

Centre number: ☐☐ Date (dd/mmm/yy): ☐☐ / ☐☐☐ / ☐☐ Initials: ☐☐☐

Age ☐☐ M ☐ F ☐ Height (m): ☐.☐☐ Weight (kg): ☐☐☐ BMI: ☐☐.☐

Patient history ***(please tick all that apply)***

Migraine ☐ if yes, aura? ☐ TIA ☐ Stroke ☐ Smoker ☐ Diabetes ☐ High BP ☐

DVT ☐ if yes, same leg? ☐ Known PFO: ☐ if yes, is it symptomatic? ☐

Details of treatment – which leg? R ☐ L ☐ ***(please complete a separate form for each leg)***

CEAP: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐

Foam only Y ☐ N ☐ If no, what other?

RFA ☐ LASER ☐ phlebectomy ☐

liquid sclerotherapy ☐ other ☐

Vein treated	Primary	Recurrent
GSVAK	☐	☐
GSVBK	☐	☐
AASV	☐	☐
SSV	☐	☐

Deep veins normal: Y ☐ N ☐

Previous Fibrovein foam treatments:

1 ☐ 2 ☐ 3 ☐ ≥4 ☐

Preparation: Tessari ☐ Double syringe ☐

Tessari + 5 micron filter ☐

Steriven ☐ Easyfoam ☐ Other ☐

Liquid to gas ratio 1 to: 2 ☐ 3 ☐ 4 ☐ 5 ☐

Air ☐ CO_2/O_2 ☐ Other gas ☐

Total volume foam (ml) 3% ☐☐ 1% ☐☐

Number of injection sites ☐☐

Aliquot size: 2-3ml ☐ 3-5ml ☐ >5ml ☐

Compression type: Bandage ☐ Stocking ☐

Stocking compression class: 1 ☐ 2 ☐

Duration (days): Bandage☐☐ Stocking☐☐

Was there a procedure-related neurological AE? Y ☐ N ☐

If, yes please inform the UK Co-ordinating Centre and complete rest of the form

Migraine ☐ Headache ☐ Scotoma ☐ Other visual ☐ One eye ☐ Both eyes ☐

Stroke ☐ TIA ☐ Hemiparesis ☐ Language disturbances ☐ Loss of consciousness ☐

Outcome: Recovered without sequelae ☐ Recovered with sequelae ☐ Recovering ☐

Not recovered ☐ Died due to the adverse event ☐ Unknown ☐

Signed: Date (dd/mmm/yy): / /

Please report SAE to the UK Co-ordinating centre WITHIN 1 WORKING DAY

+44 (0)121 424 5570 or fibroveinpass@heartofengland.nhs.uk

Appendix 3: Fibrovein PASS Proforma 2 (SAE)

Centre, date and patient details
Centre number: ☐☐ Date (dd/mmm/yy): ☐☐ / ☐☐☐ / ☐☐
Patient ID ☐☐☐☐☐☐☐☐☐☐ Initials: ☐☐☐ Age ☐☐ M ☐ F ☐
Details of SAE: patient outcome, comments & follow up taken
Treatment date: ☐☐ / ☐☐☐ / ☐☐ Date of reaction: ☐☐ / ☐☐☐ / ☐☐ Description of SAE:
Outcome: Recovered without sequelae ☐ Recovered with sequelae ☐ Recovering ☐ Not recovered ☐ Died due to the adverse event ☐ Unknown ☐
Signed: Date (dd/mmm/yy): ☐☐ / ☐☐☐ / ☐☐
Please report SAE to the UK Co-ordinating centre WITHIN 1 WORKING DAY **+44 (0)121 424 5570 or fibroveinpass@heartofengland.nhs.uk**

Appendix 4: Instructions for completing Fibrovein PASS Proforma 1 and 2

Fibrovein Post Authorisation Safety Study Form 1 - Instructions

Centre number, date and patient details:

Centre number: please insert specific two-digit number

Date: please enter date of treatment in dd/mmm/yy (e.g. 01/JAN/15) format

Patient initials: please enter initials e.g. Joe John Bloggs (JJB)

Height: please enter height in metres

Weight: please enter weight in kilograms

BMI: please insert, if known (weight(kg)/height(m)^2)

Patient History (please tick all that apply):

Migraine: does your patient have a history of migraine, if so do they get an aura?

TIA: does your patient have a history of transient ischaemic attack?

Stroke: does your patient have a history of stroke?

Diabetes: does your patient have a history of diabetes?

High BP: does your patient have a history of hypertension?

DVT: does your patient have a history of deep vein thrombosis; if so, was it in the same leg as you are treating?

PFO: is your patient known to have patent foramen ovale; if so, is it symptomatic?

Details of Treatment (please complete separate form for each leg):

CEAP: please tick the correct CEAP clinical score (please tick only one box for the most severe clinical grade)

1. Telangiectasia or reticular veins
2. Varicose veins
3. Oedema
4. Skin changes (venous eczema / haemosiderin deposition / lipodermatosclerosis)
5. Healed venous ulcer
6. Open venous ulcer

Foam only: Have you treated your patient today using Fibrovein UGFS only? If not, please tick ALL other treatments used at the same time (RFA = radiofrequency ablation, LASER = endovenous laser ablation)

Vein treated: please tick ALL the veins you have treated today and tell us whether they were primary or recurrent:

- GSVAK: great saphenous vein - above knee
- GSVBK: great saphenous vein - below knee
- AASV: anterior accessory saphenous vein
- SSV: small saphenous vein

Deep veins normal: are your patient's deep veins normal?

Previous foam treatments: please record the number of previous Fibrovein UGFS treatments your patient has had (either leg)

Preparation: please tick the box corresponding to the method of foam preparation you used for this treatment

Liquid to gas ratio: please record the average ratio of liquid to gas that you used for this treatment

Gas used: please record if you used air, a CO_2/O_2 mixture, or another gas?

Total volume of foam: please tell us how many mls of 3%, and how many mls of 1%, Fibrovein **foam** you used for this treatment?

Number of injection sites: how many injection sites did you use for this treatment?

Aliquot size: on average how many mls of foam did you inject each time you injected foam during this treatment?

Compression type: did you a apply bandage or stocking, or both, after the UGFS?

Stocking compression class: if you applied a stocking, what class did you use?

Duration: please tell us how long you advised your patient to keep the stocking, bandage, or both, on after their UGFS

Were there any procedure-related neurological AE?

Please tell us yes or no

If yes, please tell us how your patient was affected (tick all that apply) and the outcome

Please contact us about the neurological AE as soon as you can

- Telephone: +44 (0)121 424 5570
- Email: fibroveinpass@heartofengland.nhs.uk

Were there any SAE?

If your patient has an SAE during UGFS, or if you become aware that your patient has had an SAE after the UGFS please let us know WITHIN ONE WORKING DAY by

1. Completing and returning the Fibrovein PASS Proforma 2
2. Contacting the UK Co-ordinating centre
    a. Telephone: +44 (0)121 424 5570
    b. Email: fibroveinpass@heartofengland.nhs.uk

Just to remind you that SAE are defined by the UK Medicines and Healthcare Products Regulatory Agency (MRHA) (www.mhra.gov.uk) as those that:

1. Results in death
2. Are immediately life threatening
3. Require in-patient hospitalisation or prolongation of existing hospitalisation
4. Result in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
5. Are a congenital abnormality or birth defect
6. Represent an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

Life threatening means the patient was at immediate risk of death from the AE as it occurred or it is suspected that continued use of the product would result in the subject's death. Life threatening **does not** mean that had the AE occurred in a more severe form it might have caused death.

With regard to hospitalisation, hospital admissions and or procedures planned before the treatment with foam sclerotherapy are not considered SAEs, provided the condition did not deteriorate in an unexpected way after the administration of Fibrovein.

Out-patient treatment in accident and emergency is not an SAE in itself; however, the reason for attendance may be (e.g. bronchospasm or laryngeal oedema).