Infant and Child European Cryoablation Project

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Study Protocol

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STUDY INVESTIGATOR(S)

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1. SUMMARY

A registry to audit the current range of applications, technical success rate, safety profile, complication rate and efficacy of cryoablation procedures being performed in children in the United Kingdom.

2. BACKGROUND

Cryoablation involves image-guided insertion of single-use specialised needles or probes through the skin into a soft tissue or bone lesion. The base unit is connected to the probe(s) and generates cyclical freezing and thawing of the tissues at the probe tip(s) via exchange of highly pressurised gases through the probe lumen(s). Extreme freezing and thawing of the lesion causes permanent tissue destruction through both mechanical disruption of tissue membranes and one or more secondary immune responses.
Cryoablation is one of several minimally invasive ablative techniques used to reduce the size of or to eradicate soft tissue and bone lesions. Ablative techniques are now an accepted standard of care for many benign and malignant lesions in adult practice. Cryoablation is widely used in the management of renal cell carcinoma, as recognised by NICE, with long-term outcomes matching surgical resection [1].

The advantages of cryoablation over surgery, particularly in a paediatric population, are:

- Minimally invasive approach, therefore suitable for day case procedures and almost scarless
- Significantly faster recovery times compared to complex surgical debulking
- Minimal complication rates compared to surgery (less risk to nerves, blood vessels and critical solid organ)
- Affords excellent pain relief (has an independent role in chronic pain management)

To date the use of cryoablation in children remains novel and under reported [2,3].

The purpose of this registry is to audit the current range of applications, technical success rate, safety profile, complication rate and efficacy of cryoablation procedures in children. This registry will, as a minimum, clarify current practice and outcomes within individual centres, allowing teams to audit and benchmark their own procedures and aims to align practice amongst individual hospitals. A registry will provide a body of evidence to establish parameters for best practice and may highlight conditions that respond better or worse than others to this novel therapy. The audit may lead to a clinical trial for the treatment of one or more specific conditions but in the interim aims to provide evidence for the efficacy and safety of the procedure and protect against indiscriminate use of this treatment modality in children in the future.

References:

1. *www.nice.org.uk/guidanceIPG402*
2. Shaikh R, Alomari AI, Kerr CL, Miller P, Spencer SA. Cryoablation in fibro-adipose vascular anomaly (FAVA): a minimally invasive treatment option. Pediatr Radiol. 2016 Jul;46(8):1179-86
3. Whitmore M, Hawkins C, Prologo J, et al. Cryoablation of osteoid osteoma in the pediatric and adolescent population. J Vasc Interv Radiol 2016 Feb;27(2):232-7

3. AIM(S) OF STUDY

Principle aim:	Establish feasibility and safety of cryoablation in children
Secondary aims:	Assess response to treatment (as measured by change in lesion size and/or change in symptomatology) post treatment

4. OBJECTIVES

1. To identify all cryoablation procedures in children in our institution.
2. Invite other centres offering cryoablation in children to participate by submitting data via the online registry
3. To collect data via an online registry
4. To analyse the data to establish the safety and efficacy of this procedure in children and to identify trends in outcomes for different conditions treated
5. To establish guidelines for best practice regarding cryoablation treatment in children

5. STUDY DESIGN

This is a prospective multi-centre, open, non-controlled repeat treatment registry and data collection in collaboration with other individual hospitals. The registry is based

with Great Ormond Street Hospital NHS Foundation Trust; other centres in the UK and Europe will be invited to participate. All such centres will be subject to their institution's audit and ethics processes

The registry will consist of a robust, multi-centre data collection system to support and establish the treatment pathway, safety parameters and outcomes of paediatric cryoablation. The registry aims to collect standardised data from all centres performing cryoablation in children to allow robust audit of this procedure and its outcomes. Multiple data sets will be collected and entered into an anonymised web-based host. The registry is designed with the patient at the centre of the data collection. Anonymised data will be analysed collectively but will ultimately be owned and retained by individual Trusts.

6. STUDY SETTING/LOCATION

The registry is based at Great Ormond Street Hospital for Children NHS Foundation Trust. Data from all cryoablation procedures will be entered in this registry. Other Trusts will be encouraged to submit data to the same registry.

7. STUDY POPULATION

All children in whom a clinical decision is made to treat with percutaneous cryoablation

8. ELIGIBILITY CRITERIA

8a. Inclusion criteria

All children in whom a clinical decision is made to treat with percutaneous cryoablation, to include those in whom cryoablation was not technically or clinically possible at any stage.

8b. Exclusion criteria

1. Subjects over the age of 18 years.
2. Any subject whose clinical management evolves so that treatment modalities other than cryoablation are offered instead.

9. STUDY OUTCOMES

9a. Primary Outcome

Occurrence and severity of complications arising from cryoablation treatment

9b. Secondary Outcome(s)

1. Occurrence and causes of procedural/technical failure of the procedure

2. Where relevant, change in maximal diameter of lesion following treatment, as measured on ultrasound or MRI, comparing pre-treatment diameter to diameter at 2 years.
3. Where relevant, change in symptomatology post treatment, as assessed by quality of life questionnaires and visual analog scales.
4. Where relevant, change in function post treatment, as assessed by clinical review and physiotherapy assessment.

10. STUDY PROCEDURES

10a. Recruitment of participants

Data from all cryoablation procedures performed in our institution will be entered into the registry. Data from procedures at other UK institutions may also be submitted.

10b. Randomisation

This is a non-randomised study.

10c. Study procedure

Data will be entered into an online-based registry designed for this study. The registry is designed and managed by Obsidian Health Ltd and funded by Biocompatibles UK Ltd.

The following dataset is an indication of the data items that will be collected within the registry. The registry is not limited to these items and the items and data format can be changed before or during the registry.

Schema

- Patient
- Patient has Diagnosis
- Patient has one or more Treatments
- Patient has one or more Follow-ups
- Patient has one or more Complications
- Patient has one or more Post-ops

Data items

Data item	Data type
Patient	
Patient identifier	Local pseudonym
Date of Birth (0 - 18)	Month and year only
Gender	List
Weight (Kg)	Float

ASA score (anaesthetic risk) 1 - 4	Integer

Diagnosis

Diagnosis	List
Comorbidities	List
Biopsy proven?	Y/N
Snomed code	List
Lesion anatomical site: limb, thorax, head and neck, abdomen, pelvis (need more detail here)	List
Lesion tissue involvement: Fat/bone/muscle/other	LIst
Pre-operative information	
Length of symptoms already	Months
Imaging (MRI, US, other)	List
Symptoms	List
Other treatments tried	List
Treatment	
Treatment date	Date
Pre-op	List
Size of lesion	Float [possibly 3 floats]
Symptoms	List
No of probes	Integer
Freeze time*	Float
Thaw time*	Float
Cryoablation system probe type(s)	List [may need updating as new systems come onto market]
No. of freeze/thaw cycles	Radio
Thaw type [active or passive]	Radio
% power during freeze cycle	
*freeze and thaw time for *each* cycle	

Technical success	Binary
If technical success no - reason	List +/- text
Length of inpatient stay	
Any medical support required (list, such as iv analgesia)	
Immediate complications	Multi-list
Follow-up at 3 mths, 6 mths, 1 year, 2 years	
Follow-up date	Date
Imaging	List
Size of lesion	Float
Symptoms	List
Complications at follow up	
Complication	Multi-list
Onset Duration of problem Any treatment given Resolved?	

10e. Patient safety

Any adverse events related to a cryoablation procedure will be medically managed as per clinical need. All such events will be recorded, reported and managed according to the institution's risk management system, alongside any data collection pertaining to this study.

10f. Adverse events, Serious Adverse Events and Product Malfunctions

An adverse event (AE) is defined as any untoward or unfavourable medical occurrence in a human patient or clinical trial subject administered a medicinal product, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the patient's participation in the research, and which does not necessarily have a causal relationship with this treatment (study medication, application of the study device, etc.) or study participation. It includes all adverse events regardless of seriousness or relatedness.

A serious adverse event (SAE) is defined as an adverse event that

a) Results in death

b) Led to a serious deterioration in health that either:
    I. Results in a life-threatening illness or injury, or
    II. Results in a permanent impairment of a body structure or a body function, or
    III. Requires in-patient hospitalization or prolongation of existing hospitalization, or
    IV. Results in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
    V. Results in a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
c) Led to fetal distress, foetal death or a congenital abnormality or birth defect

A product malfunction is defined as a failure of the device to meet its performance specifications, essential function or otherwise perform as intended. Performance specifications include all claims made in the labelling for the device. The essential function of a device refers not only to the device's labelled use, but for any use widely prescribed within the practice of medicine.

Reporting of Adverse Events, Serious Adverse Events and Device Malfunctions

The Institution and/or the Sponsor-Investigator shall report all and any serious adverse events, product malfunctions or quality complaints (regardless of causality) that they become aware of in relation to the Product and/or the investigation to BTG.

All reports will be exchanged in English and Sponsor-Investigator will also provide BTG with such information and reasonable assistance as may be requested by BTG to allow BTG to comply with their obligations.

The Institution and/or the Sponsor-Investigator shall report all SAEs and incidents impacting patient safety to ICardioQAComplaints@bsci.com.

SAEs

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SAEs

The Sponsor-Investigator will report SAEs within **one business day** to enable BTG to comply with their obligations as the device manufacturer, under applicable laws and regulations.
All reports will contain the following, if available:

- Study title and name of the Sponsor-Investigator.
- Patient number
- Adverse event number
- Date of event occurrence/date notified
- Product details
    - Product name/ part number
    - Size / dose
    - Batch / lot number
- Adverse event details along with comprehensive event description
- Action(s) taken to treat or resolve the event

- Outcome
- Investigators opinion of causality of event i.e. related to
    - Drug
    - Device
    - Procedure
- Product returned to Galil if applicable

Device Malfunctions

The Institution and/or the Sponsor-Investigator shall report all device malfunctions and/or quality complaints to ICardioQAComplaints@bsci.com within one business day of becoming aware of the issue.

10g. Data monitoring

Data will be reviewed by the co-investigators at a minimum of 6 month intervals. Procedural data will be collected for 3 years and follow up data will continue to be collected for a further 2 years. The registry plans to close after 5 years but this could be extended. Data analysis will be completed by 6 months post closure of the registry.

See Appendix 1 [Obsidian Data Security Protocol] for details of data storage and management by Obsidian Health Ltd.

11. STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

Upon completion of recruitment and follow up, the data will be subject to uni-variate and multi-variate analysis. Statistical analysis support will be provided by Obsidian Health Ltd but may also include other sources of statistical advice and expertise.

12. ETHICAL CONSIDERATIONS

We will conduct this study in full conformance with principles of the “Declaration of Helsinki”, Good Clinical Practice (GCP) and within the laws and regulations of the United Kingdom.

The study is registered with the institution’s audit program; the institution’s audit committee have confirmed that formal ethics approval is not required for this study as it is an audit not a research study.

See Appendix 1 [Obsidian Data Security Protocol] for details of data storage and management by Obsidian Health Ltd.

We have considered the potential risks and proposed benefits of the study procedures, the priority of the participants’ interests over those of science or of society and how those interests will be safeguarded. All subjects will be offered cryoablation based on clinical need, as assessed by the multidisciplinary clinical team in our institution and as discussed and agreed with the patient and their family/guardian. The cryoablation procedure, its timing and its risks will not be altered

by entry into this registry. Children and families may be concerned that if they decline to participate in the study, this may affect the subject's clinical care. They will be actively reassured that this is not the case; age-appropriate fact sheets and consent forms have been designed to make this clear and will be used throughout the study.

13. OUTCOMES AND SIGNIFICANCE

The results of this study will be shared with other participating centres and selected anonymised data will be made available to Boston Scientific Corporation, as owner of it's subsidiary Biocompatibles UK Ltd, who fund the study. The data will be used to establish best practice. Adverse outcomes will be investigated and used to modify the technique for future procedures. The study aims to highlight any conditions that respond significantly well or not to this procedure and will promote any such findings to ensure children are offered the best treatment available.

The co-investigators plan to present the outcomes at the annual scientific meeting of the Society for Pediatric Interventional Radiology and other relevant scientific forums and publish the outcomes in relevant scientific journal(s).

14. APPENDICES

1. Obsidian Health Ltd Data Security Protocol