PROTOCOL

Study Title:	Feasibility of ambulatory pleurodesis
Chief Investigator:	Kevin Conroy
Sponsor:	TVRA
Funder:	TVRA

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1. STUDY SUMMARY:

Overall Aim:	Is the study protocol deliverable?
Primary Objective:	• Can patients with malignant pleural effusions undergo chest drainage and talc. Pleurodesis on an ambulatory basis
Secondary Objective	• What are the patient perspectives of this protocol?
Target Accrual:	10 patients
Inclusion & Exclusion Criteria:	Inclusion • Malignant pleural effusion • Life expectancy >30 days • WHO PS 1-2 (3 if due to exertional dyspnoea) Exclusion • Previous failed pleurodesis • Known non-expansile lung

	• Pregnancy • Age <18
Data Collection Summary:	•
Anticipated Duration of Recruitment	12 months
Duration of Patient Follow-up	30 days
Definition of End of Trial	Drain removal and completion of d+30 questionnaire

2. BACKGROUND

AIMS AND OUTCOMES:
Patients with malignant pleural disease often experience a significant symptom burden and a short life expectancy. The cornerstone of their treatment is relieving breathlessness by draining fluid from around the lungs and attempting to prevent further fluid build up. Inpatient chest drainage and talc pleurodesis remains the most successful method of stopping the fluid build up but this often requires an average hospital stay of four days. This can be an inappropriate length of time for this patient group. Our study would investigate whether this treatment could be provided on an ambulatory basis and facilitate a greater quality of life.

We would assess deliverability of the trial protocol and collect patient feedback to see if our patients consider it an acceptable and worthwhile intervention.

3. Primary Objective

Can patients with malignant pleural effusions undergo chest drainage and talc. Pleurodesis on an ambulatory basis

Secondary Objective
What are the patient perspectives of this protocol?

Primary Outcome Measure:
Success delivery of study protocol

Secondary Outcome Measure:
Patient questionnaire

4. OVERVIEW OF STUDY PATHWAY:

Eligible patients will be offered enrolment in the trial along with standard of care options.

If patients agree to participate in the trial they would be consented for chest drain, talc pleurodesis on an ambulatory pathway.

On day 1:

- A standard chest drain would be inserted in the morning and large volume fluid removal would commence using an underwater seal bottle- as per standard care. We would remove 1000mls of fluid (stopping earlier if not tolerated) and the clamp the drain for one hour.
- We would then open the drain again and drain up to 500mls before again clamping for one hour.
- We would repeat this process as frequently as possible until the end of the working day.
- The drain would then be connected to an ambulatory bag and left in the open position.
- The patient would then be sent home to return on day 2.

On day 2:

- The drain would be flushed, aspirated and the output assessed.
- If there is still fluid output we would drain up to 500mls and close the drain for an hour and repeat.
- If there is no further output we would arrange a chest x ray to ensure the effusion has resolved and the lung has fully inflated.
- If it has we would proceed to talc slurry instillation (with 20mls 1% lidocaine as per standard practice) and clamp the drain for 2 hours.
- After this we would open the drain again and drain up to 500mls and close the drain for an hour.
- We would repeat this as required and again the patient would return home with an ambulatory bag left open.
- If the effusion has resolved but the lung has not fully expanded due to underlying disease then we would simply remove the chest drain as pleurodesis will not be possible.

On day 3:

- The drain would be flushed, aspirated and the output assessed.
- If there is still fluid output we would drain up to 500mls and close the drain for an hour and repeat.
- If there is no further output we would arrange a chest x ray to ensure the effusion has resolved.

- We would then remove the drain and repeat the x-ray to confirm there have been no complications.
- We would then consider the intervention complete and revert to standard care

If there was still significant fluid output we would repeatedly drain 500ml volumes of fluid and clamp the drain for an hour after each 500ml until dry.

We would ask patients to complete a very brief questionnaire (visual analogue scale) on breathlessness and chest pain on day 1 - before intervention, 1 hour post drain insertion, at the end of the day and on day 2 and 3 on first encounter and at the end of the day. We would also repeat the questionnaire on day 30 along with their satisfaction with the protocol.

DAY 1	DAY 2	DAY 3	DAY 4
Seldinger 16Fg drain inserted	Assess output - aspirate and flush drain. Proceed to D3 if no out put.	Assess output - aspirate and flush drain. Repeat Day 2 protocol if required	Assess output: if >240mls / 24 hours repeat Day 2 protocol
Thoracocentecis – up to 1000mls or patient tolerance	Thoracocentecis – up to 500mls or patient tolerance	CXR to confirm >75% pleural apposition	Seldinger drain removed
Clamp for 1 hour	Clamp for 1 hour	Instil 4g steritalc with 3mg/kg Lidocaine and 50ml 0.9% NaCL flush	CXR to confirm >75% pleural apposition
Thoracocentecis – up to 500mls or patient tolerance	Thoracocentecis – up to 500mls or patient tolerance	Clamp for 2 hour	
Repeat as able	Repeat as able	Connect to ambulatory bag and leave 'open'	
Connect to ambulatory bag and leave 'open'	Connect to ambulatory bag and leave 'open'		

5. SELECTION OF PATIENTS:

Inclusion criteria:

- Malignant pleural effusion
- Life expectancy >30 days
- WHO PS 0-2 (3 if due to exertional dyspnoea)

Patient exclusion criteria:

- Previous failed pleurodesis
- Known non-expansile lung

- Pregnancy
- Age <18

Screening and Informed Consent:

Potential candidates will be referred to the respiratory (pleural) team for standard care. Eligible candidates will be offered trial enrolment as an additional option by the PI/CI or delegates and undergo written consent.

SAMPLE SIZE

Number of participants and records
10 patients

Statistical analysis plan
Thematic analysis of patient feedback

6. STUDY PROCEDURES

Study protocol outlined above. Additionally, we will collect Patient related outcome measures relating to breathlessness and pain each day and at day +30. We will also seek patient feedback on the protocol at this point.

7. DATA COLLECTION

Data will be collected by the trials team longitudinally. Patients surveys will be collected and the 30 day survey will be conducted via telephone consultant or face to face by the trial team

8. DATA MANAGEMENT AND CONFIDENTIALITY

Investigators are required to maintain on file the accurate, complete, and current records relating to this Study. Data will be stored securely in a locked office in a trial file. Digital information will be stored on an NHS computer in a locked office. Only authorized personnel and their designees will have access to these confidential files.

PROTOCOL DEVIATIONS

Protocol deviations should be reported to the sponsor and Chief Investigator using the provided reporting form. The Sponsor and Chief Investigator should then review the details

to assess the impact on the research dataset and also to assess if there are learning points to help prevent a repeat deviation.

MISSING DATA AND DATA QUERIES

Missing data will be included in the analysis. The trials team, CI or an appropriate designee will address any emergent data queries.

9. SAFETY REPORTING

Definitions

Adverse Event (AE) Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to the intervention under study.

Adverse Reaction (AR) An untoward or unintended response in a participant to which is related to the intervention under study i.e. that a causal relationship between the trial intervention and an AE is at least a reasonable possibility and the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial intervention qualify as adverse reaction.

Serious adverse Event (SAE) is any untoward medical occurrence that; results in death, is life threatening or requires inpatient hospitalisation.

Serious adverse reaction (SAR) is an event that is both serious and in the opinion of the investigator, believed with reasonable probability to be due to the trial intervention.
Unexpected Serious Adverse Reaction (USAR) is a serious adverse reaction, the nature and severity of which is not consistent with the known information about the intervention under study.

9.2. Recording and Reporting AEs and SAEs

For each SAE the following information will be collected:

· Full details in medical terms and case description
· Event duration (start and end dates, if applicable)
· Action taken
· Outcome
· Seriousness criteria
· Causality in the opinion of the investigator
· Whether the event is considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the [Sponsor/GCTU] as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

9.3. Recording and Reporting USARs

All USARs occurring from the intervention until 6 months post termination of trial treatment must be reported to the NHS REC. The Sponsor will perform this reporting. The assessment of expectedness will be performed by the PI against the known information for the trial. USARs must be reported no later than 15 calendar days after the Sponsor has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report. As soon as a site suspects that a SAR may be a USAR they must contact the CI, sponsor representative and the trial manager immediately. The reporting timeframe starts at day 0 when the Sponsor is in receipt of a minimum set of information:

· Sponsor trial reference and trial name
· Patient trial number and date of birth
· Date of notification of the event
· Medical description of the event
· Date and time of the onset of the event (including event end date if applicable)
· Causality assessment
· Seriousness of the event, particularly if life threatening or fatal
· An identifiable reporter (e.g., Principal Investigator)

This information must be provided on USAR report form. The site is expected to fully cooperate with the Sponsor in order that a full and detailed report can be submitted to the NHS REC within the required timelines.

PIs will be informed of all USARs by the Sponsor and CI.

Responsibilities

Principal Investigator

· Checking for AEs and ARs when participants attend for treatment or follow up

· Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness of events.

· Ensuring that all SAEs and SARs, including USARs, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.

· Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator

· Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.

· Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.

· Using medical judgement in assigning expectedness to SARs.

· Immediate review of all USARs.

· Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.

Sponsor

· Assessment of expectedness of any USARs

· Expedited reporting of USARs to the REC within required timelines

·Notification of all investigator sites of any USAR that occurs

9.6. Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the Sponsor must be notified immediately and details of the USM given. The Sponsor must inform the NHS REC within 3 days of the USM taking place in accordance with the Sponsor's standard operating procedures.

10. TRIAL MANAGEMENT AND OVERSIGHT

The monitoring team employs a risk-based approach to monitoring. This approach focuses efforts on the most crucial data and process elements to allow for more efficient monitoring practices while maintaining the quality of the overall study conduct.

The team will employ remote monitoring of clinical trial with a focus on safety, study endpoints, data completion and data outliers. Source documentation, including study logs, Informed Consent Log, Protocol Violation/Deviation Log and the Serious Adverse Event Report log will monitored to ensure that the sites are adhering to the study protocol and procedures.

In collaboration with the data management team, the monitor will create and utilize reports outlining data totality and timeliness, missing values to generate queries and optimize reconciliation of data.

Clinical sites will maintain copies of all source documents, which may be either paper or electronic, at each site. The monitors will review the source documents to determine whether the data reported is complete and accurate. They will also verify that all adverse events exist on the source documents, are consistent with the protocol, and are documented in the appropriate format.

Source documents include medical charts, initial hospital admission reports, operative procedure records, discharge and re-admission reports, consult notes and other study-related notes. At an on-site visit, the study monitors reserve the right to copy de-identified records in support of all adverse events and outcomes.

The monitors will also confirm that the regulatory binder is complete and that all associated documents are up to date. The regulatory binder should include but is not limited to all revisions of the protocol and informed consent, approvals for all of the above documents, and correspondence; investigator's agreement and agreement amendments; DOA log;, CVs and appropriate training certificates of all study personnel and monitor site visit log.

If problems are identified during the monitoring visit missing study documents, etc., the monitor will assist the site in resolving the issues.

11. WITHDRAWAL OF PATIENTS FROM THE TRIAL

Participants are free to withdraw from the trial at any point and return to stand care. This can be done by contacting the trial team in writing, telephone or in person. Patient information up to that point would be included with patient consent. We would also seek to record the reasons for their withdrawal with their consent.

12. TRIAL FUNDING

There is no specific funding sought for this trial due to the small sample size.

13. DISSEMINATION

Publication and presentations

The results will be presented locally, nationally and internationally; where any personal information is necessary for the data analysis (use of demographic data) this will be presented in a way to ensure that individuals cannot be identified and the patients will be informed in advance of giving their consent to participate in the study.

REFERENCES

1. Davies HE, Mishra EK, Kahan BC, Wrightson JM, Stanton AE, Guhan A, Davies CW, Grayez J, Harrison R, Prasad A, Crosthwaite N, Lee YC, Davies RJ, Miller RF, Rahman NM. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA. 2012 Jun 13;307(22):2383-9. doi: 10.1001/jama.2012.5535. PMID: 22610520.