The INTERnational MultIcenTer STudy of PlEural INfecTion (INTERMITTENT): a point prevalence survey of the global aetiology, management and outcomes of pleural infection

UK localised Protocol
Short Study Title: INTERMITTENT
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Sponsor: Global Principal Investigators: Federico Mei, Steven Walker, Jane Shaw, Uffe Christian Steinholtz Bødtger

This protocol has regard for the HRA guidance.

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Study Summary

Study Title	The INTERnational MultIcenTer STudy of PlEural INfecTion (INTERMITTENT): a point prevalence survey of the global aetiology, management and outcomes of pleural infection
Short Title	INTERMITTENT study
Study design	International, multicentre point prevalence study
Study participants	Population of interest: adults who have required a pleural procedure for the management of pleural infection.
UK sample size	100 patients.
Planned study period	1 year, with two 4-week periods of data collection, one in the summer and one in the winter
Study objectives:	Primary Objective: To identify and describe international variations in terms of burden of disease and aetiology of pleural infection. Secondary Objectives: To establish the number of pleural infections and to assess variations in prevalence by geographic location and seasonality. To establish the causative microorganisms of pleural infection in an international cohort and describe variations in microbiology by geographic location and seasonality. To describe demographic, clinical, and management strategies for pleural infections. To associate management strategies with clinical outcomes.
Inclusion criteria	Any patient aged 18 or over who underwent a pleural procedure for suspected pleural infection, with pleural fluid culture and chemistry, within the previous 4 weeks
Exclusion criteria	Exclusion: Patient is younger than 18 years. Patient has suspected pleural infection as a result of recent thoracic trauma or surgery.

Funding

This study will not receive external funding and will not burden the facility's costs or the National Health Service (SSN). Once the study has started, any changes in this regard will be submitted for review by the competent ethics committee.

Role of Sponsor

The University of Bristol is the Sponsor for this study. The Sponsor has had input into the design of the study but overall responsibility for the design lies with the chief investigator. The Sponsor is responsible for authorising the initial submission to the research ethics committee (REC) and health research authority (HRA) and subsequent amendments, ensuring appropriate agreements and indemnity arrangements are in place, overseeing the conduct of the study and ensuring it adheres to the principles of good clinical practice (GCP) and the UK Policy Framework for Health and Social Care Research, and for archiving at the end of the study. The Sponsor is not responsible for and has no involvement in the data analysis or interpretation, or for writing manuscripts.

Roles and Responsibilities of the Trial Management Group

The Trial Management Group will be composed of the chief investigator, study coordinator and members of the International Multicentre Pleural Research Collaborative (IMPACT)steering group. The TMG will write the protocol and statistical analysis, obtain relevant approvals from an NHS research ethics committee (REC) and the Health Research Authority (HRA), coordinate with NHS Trusts to set up sites and ensure the study is conducted according to the principles of GCP and the UK Policy Framework for Health and Social Care. The TMG will meet every 2 months, at minimum, to manage the day-to-day running of the study, monitor safety, key performance indicators and discuss and resolve emerging issues. Members of the TMG will analyse the data, interpret the analyses, and submit manuscripts to peer-reviewed journals.

Background and Rationale

Pleural effusion caused by an infectious organism is a common clinical condition which has potentially fatal outcomes. In Europe, up to 50% of people with pneumonia have a pleural effusion, which is associated with a 3-6-fold increase in mortality (1). In the United States, the annual incidence of hospitalised empyema is 11.7 per 100000, with an in-hospital mortality up to 7.2%, and a mean annual cost close to a billion USD(2, 3). In England, the annual incidence rate of hospitalised empyema was 8.38 per 100 000 hospital admissions in 2017, with a mortality rate of approximately 14% over a ten-year period (4). In Africa, tuberculous effusions are highly prevalent, but – as with other low-middle income regions – the epidemiology of pleural infection from other organisms is unknown(5). However, wherever you are in the world, the incidence of pleural infection seems to be increasing, and the burden on the healthcare system is substantial(6, 7, 8).

The term 'pleural infection' describes a spectrum of conditions. These include a simple parapneumonic effusion, where an uninfected pleural exudate is associated with lung parenchymal infection; a complicated parapneumonic effusion, where the effusion has become infected and therefore requires drainage; and an empyema (derived from the Greek term '*empyein*', meaning 'to suppurate'), where there is frank pus in the pleural space (9).

True pleural infection, which is often identified indirectly through pleural fluid pH or chemistry, is not uniformly managed. The age and comorbid status of the patient, the infecting organism, the presence of septae and loculations, a thick pleural peel or rind, and the availability of treatment may all alter the management approach(7). While the RAPID score is a validated tool for predicting the outcome of pleural infection using some of these parameters (urea as an indicator of renal dysfunction, age, fluid purulence, community or nosocomial infection, and albumin level), because of the lack of high-quality evidence on many of the interventions which are available for pleural infection, common clinical practice still varies widely.

These gaps in the evidence have been highlighted by a recent joint statement from the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (7). In their statement they say that research efforts should focus on comprehensive characterization of the burden of pleural infection in immunocompromised hosts and other neglected populations, and on documenting the microbiological patterns at a local level, on a global scale. Patients with pleural infection in low- middle income countries are an important neglected population.

The International Multicentre Pleural Research Collaborative (IMPACT) is a global network of clinicians with an interest in pleural disease, which is hosted by the ERS. IMPACT represents the second phase of the International Collaborative Effusion Database (ICEdb), an ERS Clinical Research Collaboration founded in 2016, which has produced the largest retrospective case series in neglected pleural diseases including non-specific pleuritis (10), chylothorax (11), benign pleural effusions (12), and eosinophilic effusions (manuscript still under review). With members in 24 countries on five continents, IMPACT is positioned to answer many of the important research questions on pleural infection.

Study Objectives

Primary Objective:

To identify and describe international variations in terms of burden of disease and aetiology of pleural infection.

Secondary Objectives:

- To establish the number of pleural infections and to assess variations in prevalence by geographic location and seasonality.
- To establish the causative microorganisms of pleural infection in an international cohort and describe variations in microbiology by geographic location and seasonality.
- To describe demographic, clinical, and management strategies for pleural infections.
- To associate management strategies with clinical outcomes.

Study Design

This will be an international, multicentre point prevalence survey (PPS).

There will be two limited data collection periods during one year: one in winter and one in summer. During this time, participating clinicians will collect data on all patients with pleural infection seen in their centre. These data will be uploaded to a central REDCap database, and analysed for the outcomes defined above.

Inclusion criteria

1. Any patient aged 18 or over who underwent a pleural procedure for suspected pleural infection, with pleural fluid culture and chemistry, within the previous 4 weeks.

Definitions:

1.1. Suspected pleural infection will be identified by the treating/participating clinician, based on:

Symptoms and signs suggestive of an infectious process including, but not limited to, one or more of:

- malaise,
- fever,
- chest pain,
- cough,
- raised white cell count,
- raised C-reactive protein (CRP) or other inflammatory/infectious marker in blood

AND

Chest imaging evidence of a pleural effusion

1.2. A pleural procedure will be any procedure during which pleural fluid is aspirated from an effusion, in a patient fulfilling the criteria for suspected pleural infection above.

1.3. Pleural procedures where pleural fluid is aspirated but not sent for microbiologic testing will not be included, except when the fluid is frank pus and another culture of blood or sputum has been sent.

1.4. Inpatients and outpatients may be included, and patients admitted to a high care or intensive care unit.

Exclusion criteria

1. Patient is younger than 18 years.
2. Patient has suspected pleural infection as a result of recent thoracic trauma or surgery.
   2.1. Note on an exception: patients who have suspected pleural infection and a recent pleural biopsy will still be included, provided there was a preexisting pleural effusion.
3. Patient is culture-positive for pulmonary or pleural Mycobacterium tuberculosis (TB)*.
4. Known pleural malignancy (pleural fluid cytology positive for malignant cells or known thoracic malignancy or metastases).

**It is recognised that patients from areas of high incidence of TB, pleural infection can present similarly to TB pleuritis. Patients will not be excluded solely based on high pre-test probability of TB. Patients who are included initially and eventually diagnosed with pleural TB will be dealt with separately in the analysis*

Data Collection

Data collection will be over two 4-week periods within 12 months, from 1st to 28th February and 1st July to 28th July.

There are two timepoints for data collection for each patient: at baseline and at 12 weeks. All data collection will be performed by a member of the clinical team. At the 12-week timepoint data will be collected retrospectively from the hospital clinical records.

The following variables will be captured for each patient:

Baseline Assessment:

The baseline assessment for all patients will incorporate routinely collected clinical information, such as:

Basic demographics	▪ Age ▪ Sex ▪ Geographic location (country, city) ▪ Outpatient only ▪ If Inpatient: • Ward type (medical, surgical, specialist pulmonology or thoracic surgery, intensive care or high care) if inpatient
Medical history and comorbidities	All major comorbidities will be noted, but specifically capturing the presence of conditions known to be associated with pleural infection: ▪ Diabetes Mellitus ▪ HIV ▪ COPD ▪ Cancer ▪ Hypertension ▪ Stroke ▪ Ischaemic heart disease ▪ Chronic kidney disease ▪ Active pulmonary tuberculosis ▪ Alcohol abuse ▪ Illicit substance use or abuse ▪ Other forms of immunosuppression ▪ Current indwelling pleural catheter. ▪ Previous thoracic surgery or trauma (unrelated to the current presentation)

12-weeks Post-enrollment:

The following data relating to the 3 months after enrolment will be collected when they become available or retrospectively:

Details of the pleural procedure	▪ Date ▪ Type ▪ 1st/2nd procedure ▪ Indication ▪ Complications ▪ Ultrasound guided or blind ▪ Ultrasound appearance (loculations/depth/echogenicity etc)
Pleural fluid results	▪ Culture, Microscopy (with sensitivities if available) ▪ Appearance ▪ pH ▪ Biochemistry: protein, lactate dehydrogenase, glucose, adenosine deaminase ▪ Cell count/differential ▪ Mycobacterial culture and microscopy ▪ Other relevant pleural fluid test results
Blood test results (within 1 week of the pleural aspiration)	▪ Albumin ▪ Urea ▪ WCC ▪ Platelets ▪ CRP ▪ PCT
Radiology (within 1 week of the pleural aspiration)	▪ Size on plain CXR (lights scale) ▪ Laterality ▪ Other features (pneumonia/mass/loculated/air fluid level) using standardized reporting tool ▪ CT findings (pleural enhancement/thickening etc) using standardized reporting tool ▪ Upload DICOM of chest radiograph (for quality control purposes)
Treatment of pleural infection (13,14)	1. Antibiotic(s): ▪ Drug(s) ▪ Regimen (dose, frequency, duration) ▪ Start date(s) ▪ Stop date(s) 2. Intercostal drain(s) ▪ Type (standard tube vs. body cavity drain vs other) ▪ Gauge/size ▪ Seldinger/blunt ▪ Start date

	▪ Stop date 3. Surgery: ▪ Type ▪ Date 4. Intrapleural enzyme therapy: ▪ Drug(s) ▪ Regimen (dose, frequency, duration) ▪ Start date ▪ Stop date 5. Medical thoracoscopy: ▪ Indication ▪ Date ▪ Findings
RAPID score	calculation coded by REDCAP using above information
Outcomes at 12 weeks	▪ Duration of hospital stay ▪ Mortality ▪ Need for surgery ▪ Ambulatory follow-up ▪ Re-admission ▪ Return to work within 30-days

Site-specific Information:

In addition to the patient-specific information above, the study will also collect information from each site on the methods of pleural fluid collection and culture, as these may affect the outcome.

Variables include (but not limited to):

- Container for pleural fluid specimen collection (blood culture bottles, vs sterile specimen container vs other)
- Volume of pleural fluid sent for culture
- Laboratory processing of pleural fluid for culture
- Culture method (plating, liquid culture – especially for Mtb isolates)
- Sensitivity testing method (phenotypic, genotypic, NAAT etc)

Definition of End of Study

The study will last approximately two years from the first patient enrollment.
Data will only be collected for the 12-week period after the enrolment date, even if the episode of pleural infection is ongoing at the time of end of study.

The end of the study as a whole will be after the12-week post-enrolment data have been collected for all patients, all data queries have been resolved, the database locked for analysis.

Statistical Analysis

Sample Size:

Data suggest that approximately 40% of patients hospitalized for CAP may develop pleural infection. Using global estimates of lower respiratory tract infections (4,350 cases per 100,000 annually) [15], it is hypothesized that the incidence of pleural infections could be around 1,600 cases per 100,000 in winter and approximately half that (800 cases per 100,000) during the summer. To estimate the sample size required to compare these seasonal differences, we assumed a difference (Δ\DeltaΔ) of 0.008 between the winter (16%) and summer (8%) prevalences. Using a significance level (α\alphaα) of 0.05 for a 95% confidence interval and a power (1−β1-\beta1−β) of 80%, and applying a z-test for proportions, the required sample size was calculated as approximately 1,452 participants per group. Therefore, a total of 2,904 participants is needed to detect this difference with acceptable precision and statistical power.

Analysis Plan:

The statistical analysis for the INTERMITTENT study will involve a detailed examination of the data to meet each of the specific study objectives. Descriptive and inferential statistical techniques will be employed, depending on the type of data and research questions addressed. Below is a breakdown of the planned statistical analyses for each objective:

Objective 1: To establish the burden of disease in terms of pleural infection cases in an international cohort and describe variations in burden by geographic location and seasonality.

1. **Descriptive Statistics**:
    - **Point-prevalence**: For each site and time period (winter and summer), the total number of pleural infection cases will be identified.
    - **Geographic location**: total number of cases will be also stratified by country and region to examine each country's contribution.
    - **Seasonality**: Comparisons of burden between winter and summer periods will be performed to explore seasonal variations.
2. **Inferential Statistics**:
    - **Chi-square test or Fisher's exact test**: These will be used to assess differences in prevalence across geographic regions and between the two data collection periods (seasonality).
    - **Logistic regression**: A logistic regression model will be used to adjust for potential confounding factors (such as patient demographics or comorbidities) and identify independent predictors of pleural infection prevalence across different regions and seasons.

Objective 2: To establish the causative microorganisms of pleural infection in an international cohort and describe variations in microbiology by geographic location and seasonality.

1. **Descriptive Statistics**:
    - The frequency of specific microorganisms (e.g., *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*) isolated from pleural fluid cultures will be summarized.
    - Geographic and seasonal stratification of the data will show variations in the prevalence of specific microorganisms.
2. **Inferential Statistics**:
    - **Chi-square test or Fisher's exact test**: These will be applied to compare the distribution of microorganisms across different geographic regions and between winter and summer periods.
    - **Multinomial logistic regression**: This model will be employed to assess the association between geographic location, seasonality, and the type of microorganism identified,

adjusting for potential confounders such as antibiotic use and patient demographics.

Objective 3: To describe the demographic characteristics, clinical presentation, comorbidities, and pleural effusion characteristics of the patients with pleural infection in an international cohort and describe variations by geographic location and seasonality.

1. **Descriptive Statistics**:
    - Demographic characteristics (age, sex), clinical presentation (symptoms, severity of infection), and comorbidities (e.g., diabetes, HIV, cancer) will be summarized for the entire cohort and stratified by geographic location and seasonality.
    - The characteristics of pleural effusion (e.g., pH, glucose, protein, lactate dehydrogenase, cell count) will also be summarized and compared across regions and seasons.
2. **Inferential Statistics**:
    - **ANOVA or Kruskal-Wallis test**: Continuous variables such as age, pleural fluid chemistry, and blood markers will be compared across regions and seasons.
    - **Chi-square test or Fisher's exact test**: Categorical variables such as comorbidities and clinical presentation will be analyzed to detect differences across geographic regions and between seasons.
    - **Multivariate regression models**: These will be used to evaluate the relationship between demographic and clinical factors (e.g., age, sex, comorbidities) and the characteristics of pleural infection, adjusting for geographic and seasonal variations.

Objective 4: To describe management strategies of pleural infection in a diverse international cohort, stratified by the type of pleural infection and geographic location.

1. **Descriptive Statistics**:
    - The management strategies (e.g., antibiotics used, duration of therapy, use of drainage procedures, surgery, and intrapleural enzyme therapy) will be summarized and stratified by type of pleural infection (simple parapneumonic effusion, empyema) and by geographic location.
2. **Inferential Statistics**:
    - **Chi-square test or Fisher's exact test**: These will be used to compare the use of different management strategies across geographic regions.
    - **Multivariable logistic regression**: This will assess the factors associated with the choice of management strategy (e.g., intercostal drainage vs. medical management), adjusting for confounding factors such as pleural fluid characteristics, patient comorbidities, and region.

Objective 5: To associate management strategies with clinical outcomes, where possible within the timeframe of the project.

1. **Descriptive Statistics**:
    - Clinical outcomes of interest (e.g., duration of hospital stay, mortality, need for surgery, re-admission, return to work) will be summarized for the overall cohort and stratified by management strategy (e.g., antibiotic regimen, surgical intervention) and by geographic location.
2. **Inferential Statistics**:
    - **Survival analysis**: Kaplan-Meier survival curves will be used to estimate time-to-event outcomes such as time to discharge, time to recovery, and survival. The log-rank test will compare survival curves based on different management strategies.
    - **Cox proportional hazards regression**: This model will assess the association between management strategies (e.g., type of antibiotic, use of surgical intervention) and time-to-event outcomes (e.g., survival, time to recovery), adjusting for covariates such as patient

demographics, comorbidities, and pleural fluid characteristics.

- **Multivariable logistic regression**: This will be used to identify factors associated with binary outcomes such as mortality, re-admission, and the need for surgery. Independent variables will include management strategies, patient demographics, comorbidities, and pleural fluid characteristics.

Data Handling and Record Keeping

Data will be retained for seven years, or longer if justified and approved by relevant ethical guidelines.

1. Data collection tools and source document identification

   Source data will be routine clinical records, either electronic from local hospital computer systems or paper files depending on local practice. These include patients' medical records, laboratory test results, and radiology reports. These data will be entered onto an eCRF in a study- specific REDCap database. Where sites are unable to do direct entry onto the eCRF, paper source may be generated from the REDCap forms and subsequently entered onto the eCRF by study staff. Each patient that is enrolled on the study will be assigned a study-specific ID, which will be used for the CRFs and on all study-related documents.

2. Data handling and record keeping

   Data will be retained for seven years, or longer if justified and approved by relevant ethical guidelines.

   Data entry at will use a bespoke study database housed on the Polytechnic University of Marche server, built using the validated open-source REDCap system and regularly backed up. The study investigator will facilitate data entry into the database via an electronic case report form (eCRF) with the support of the clinical team. Each participant will be allocated an unambiguous participant identification code (study patient ID). It is also possible to download the data for all records in this project in a single PDF file that could be printed and retained with the TMF. This file contains the actual page format as you would see it on the data entry page or survey and includes all data for all records for all data collection instruments. Sites will sign a data sharing agreement where local regulations require.

3. Quality assurance

   REDCap includes data validation checks which are inbuilt into the database build and a data query management system to allow management of data quality throughout the study. The INTERMITTENT database will be validated as part of the Database Activation process and final data quality checks will be incorporated as part of the Database Lock process.

   During the study, the REDCap database will be regularly assessed for completeness and accuracy of data entry, according to a predetermined quality control plan. The study quality control officer will contact sites and study staff responsible for data entry to complete missing data or correct mistakes within a reasonable time from data entry, to minimise the chances of incorrect data collection.

4. Access to Data, Data Protection and Confidentiality

All data will be stored in line with Good Clinical Practice (GCP) requirements and the General Data Protection Regulation (GDPR), and University of Bristol's Data Protection Policy and Information Security Policy. All study documentation will be kept secure in an access restricted environment and only accessible by INTERMITTENT study staff and authorised representatives from the Sponsor and regulatory authorities to permit study-related monitoring, audits and inspection. Patient data will be kept confidential. On all study-specific documents the patient will be referred to only by the study-specific patient ID. Only the usual care team will have access to identifiable data.
REDCap is password protected with only approved users having access. User access can be restricted to different levels by assigning users with limited permissions based on their role (i.e., data entry only). Interaction with the software automatically creates an access log data trail, ensuring that the access of data can be audited to ensure data protection (e.g. by data point, function or individual user).

5. Archiving

   Once all study data has been successfully downloaded by Polytechnic University of Marche REDCap team, they will delete the study data from the REDCap project but keep the metadata and put this into archived status. This way, the project can still be brought back to life if needed (by uploading the data from long term storage) but it no longer exists on the REDCap server. Data will be retained as per AOU delle Marche archiving policy.

Data Dissemination Plan and Publication of Results

The results of this study will be disseminated at international conferences including the European Respiratory Society Congress, any local conferences of the investigators pending agreement by the group, and in publication format. Authorship of publications will follow COPE guidelines. A plain English summary will be prepared and disseminated with the help of our ELF (European Lung foundation) patient group.

Ethical Conduct of the Study

All participating sites and clinician must be compliant with international and local regulations and guidelines applicable to research involving human participants, and in accordance with the International Conference on Harmonisation (ICH)Good Clinical Practice (GCP). If said regulations differ between countries the more restrictive regulations will apply.

This protocol and any subsequent modifications will be reviewed and approved by the NHS Research Ethics Committee and Health Research Authority.

1. Participant Information and Informed Consent

   This study will collect anonymised routine clinical data at baseline, with the remaining information collected retrospectively from hospital records. Personal data will only be accessed by the direct care team and will be de-identified for upload to the REDCap database. There will be no intervention, and the data collection will not affect any decisions regarding the patient's management strategy.
   As such, patients will not be required to provide consent.

2. Confidentiality

   Data will be handled according to the 'data handling and record keeping' section above. Records which identify the patient or link them to the data collected by the study will be kept confidential, at the site they were collected from, and not be made publicly available. The data will be entered into a secure access-controlled REDCap database. Only PIs and specific collaborators will have access to these data. Data may be reviewed by representatives of the IRB/IEC, and by others tasked with duties of monitoring and quality assurance. Research and clinical information relating to patients on the study may be shared with other researchers through lectures or publications, but the patients will not be identified by name. Any images (including Chest radiograph, computed tomography and ultrasound images) used for analysis or publication will be anonymised before use. All study- related documents with participants' names, hospital numbers, or addresses, will be stored separately from their clinical information, and in secure access-controlled facilities at the sites.

Safety Reporting

This is an observational study therefore there is no necessity for safety reporting.

Breach Reporting

Breach reporting will be conducted in line with the University of Bristol Research Governance Standard Operating Procedure.

In the event of a breach of protocol or the principles of GCP the event should be assessed and reported by the study team to the sponsor within 24 hours of becoming aware of it.

A serious breach is defined as ""the conditions and principles of good clinical practice in connection with that [study or] the protocol relating to that [study that was] likely to effect to a significant degree – (a) the safety or physical or mental integrity of the subjects of the [study]; or (b) the scientific value of the [study]" (Medicines for Human Use (Clinical Trials) Regulations 2004). A serious breach will require onward reporting by the Sponsor to the REC within 7 days of the Sponsor being made aware of it.

In the event of a personal data breach, the Research Governance Team will refer this to the Information Governance Team at the University of Bristol.

Timelines

After appropriate staff to run the study have been recruited, the study timeline spans just under two years, including time for setup and training of the sites staff. Training will be virtual, with online meetings of the whole study group for protocol training, and REDCap-specific training only for those who will perform database entry.

	[6 mo]	[2 mo]	[4 mo]	[2mo]	[2mo]	[3mo]	[3mo]
Setup and logistics: Ethical approvals, Local institutional approvals, Database, development, Staff training	X						
Data collection 1		X					
Data cleaning and quality control 1			X				
Data collection 2				X			
Data cleaning and quality control 2; database lock and export					X		
Analysis						X	
Manuscript drafting							X

Authorship Eligibility Guidelines

We will follow the International Committee of Medical Journal Editors (ICMJE) authorship criteria for outcome papers:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

An authorship plan will be agreed prior to the drafting of outcome papers. We do not plan to engage the use of professional writers for this study.

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