Official study title:

The APPLAUS trial - evaluating the use of an **app** in **pl**eural disease: **a**lgorithm-supported clinical decision making versus **us**ual care: a multicentre, stepped-wedge cluster-randomised controlled trial to reduce number of days in hospital

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Zealand University Hospital

Primary investigator:

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Ultrashort description

Pleural diseases is a frequent cause of disease and admission to hospital, with a negative impact on quality of life for patients. With the APPLAUS trial, we aim to investigate if a guideline-based, algorithm can support and improve physicians' decision making – from admission to discharge. We aim to develop and design a novel app, available, free of charge, via the App' store, based on recently published, international guidelines regarding diagnosing and treating pleural diseases. We will conduct a stepped-wedged cluster, randomized trial, involving all regions of Denmark, with the aim of reduce days in hospital for patients, number of procedures applied, mortality, overall costs as well as the frequency of which rescue surgery is needed.

Background

Pleural disease encompasses four disease entities (pleural effusion, malignancy, infection and pneumothorax) and is associated with poor survival, large disease burden, low quality of life, acute admissions and prolonged hospital stay (1-3, 5-8). The incidence of pleural disease is increasing globally, and is estimated to 360 pr 100,000 inhabitants, corresponding to around 1.2 million patients annually in the United States and 20,000 in Denmark (4). Annual costs amount to 10 billion USD in the US and 150 million USD in Denmark (2). Pleural infection, pleural malignancy, recurrent pleural effusion, and spontaneous pneumothorax are each associated with poor survival and prolonged hospital admissions (1, 5-8). The median duration of hospital stay varies with type of pleural disease from 4-7 days with spontaneous pneumothorax to 12-17 days with pleural infection (9-12). However, admission duration is a right-skewed curve with a subgroup with >20 days in hospital due to prolonged air-leak of spontaneous pneumothorax or difficult-to-control pleural infection (1, 10, 13). Early diagnosis and guidelines-based treatment reduce days in hospital (9, 14, 15). Evidence is increasingly based on multiple, large, well-conducted multicentre trials published in high-impact journals (9-11, 16-23). These studies are integrated in the recently updated 2023 version of the British Thoracic Society (BTS) pleural disease guidelines (1), since the previous version from 2010 (24). However, patients with pleural disease are treated mainly in emergency departments without respiratory physicians or other experts in pleural disease. Dissemination of evidence-based guidelines from specialists to generalists is a well-known hurdle that is effectively addressed by easy access to clinical decision-supporting tools (25-27). The complexity of managing pleural disease has in the United Kingdom lead to establishment of dedicated pleural clinics across major hospitals (28, 29). A shift from in-patient to ambulatory service has reduced number of days in hospital and costs without impairing safety (9, 30-32). Pleural clinics are virtually non-existing in Denmark, and the gap between pleural guidelines and pleural disease management is evident in a recent survey conducted by the Danish Respiratory Society Pleural Interest group among all departments involved in pleural care (mostly Emergency, Medical and Surgical departments) (33). Few hospitals had clear patient pathways for early diagnosis and treatment or for management of treatment failure of e.g.

pleural infection or spontaneous pneumothorax (33). Almost no hospitals follow guidelines' recommendation of needle aspiration as first-line treatment of stable patients with symptomatic spontaneous pneumothorax (1, 24), which reduces hospital admission by 2.7 days compared to chest tube insertion, the Danish standard (14, 34, 35). The demonstrated underuse of current pleural guidelines by Danish hospitals suggests that a clinical, guideline-based decision supporting tool has the potential benefit to significantly improve pleural care, demonstrated by reduction in days in hospital (26, 33, 36). Therefore, this study aims to provide an easy-to-access guideline-based algorithm to support physicians' clinical decision making in departments involved in pleural disease management from admission to discharge to provide early and individualised guideline-based pleural care, both in early diagnosis and therapy, and in treatment failure management.

Methods

Study design:

Open-label, nationwide, stepped-wedge cluster-randomised controlled trial.

Participants (target group):

Patients undergoing thoracentesis or chest tube drainage during in-hospital management for non-traumatic, symptomatic pleural effusion and/or spontaneous pneumothorax.

Inclusion criteria:

Acute admission to emergency department or acute medical unit, AND at least one of the following related to the admission:
a) a diagnosis of pleural effusion (DJ90, DJ91, DC782), pleural infection (DJ86) or pneumothorax (DJ93),
b) procedural codes of thoracentesis (KTGA30) or chest tube insertion (KGAA10),
c) pleural fluid cytology, culture and/or biochemistry.

Exclusion criteria:

Traumatic pleural effusion/haemothorax or pneumothorax including iatrogenic injury, such as but not limited to traffic road accident, cardiac or lung surgery, insertion of central venous catheters.

Iatrogenic injury related to workup of non-traumatic pleural effusion or pneumothorax is not an exclusion criterion, e.g. pneumothorax after aspiration of a non-traumatic pleural effusion.

Randomisation and masking:

According to the stepped-wedge cluster-randomised trial design, all centres (clusters) initially provide standard care (the control group) before switching to algorithm-based treatment (the intervention group), thus at the end of the trial, all centres are in the intervention group (26, 36, 37). Randomisation concerns the timing of this cross-over to algorithm-based treatment and is done by an independent statistician using a computer-generated scheme. The randomisation order is stratified to ensure that low–medium-volume centres alternate with high-volume centres. Randomisation order is concealed from patients and the investigators, except for the local principal investigator, who is informed before trial onset of the time of crossover for that centre. Neither patients nor physicians are masked to treatment (26, 36, 37).

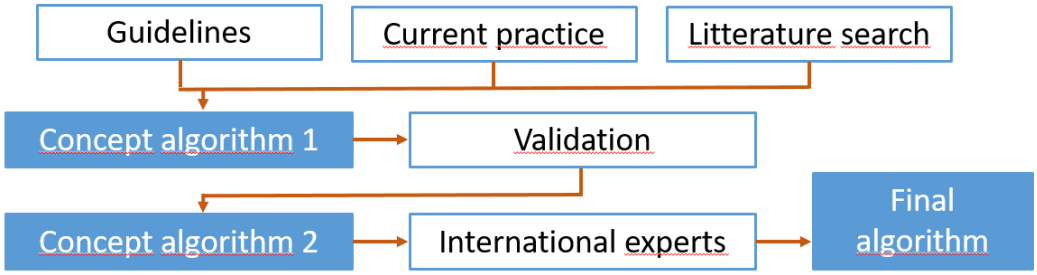

Figure 1: Algorithm development

Procedures

The process of designing the APPLAUS algorithms will include an inventory of the guidelines on pleural effusion, pleural infection and spontaneous pneumothorax, as well as consensus meetings with international experts on pleural diseases (1, 5, 6, 8, 38). The process is illustrated in figure 1. To reduce the risk of contamination of usual care, only one expert in pleural disease from each centre is involved in the algorithm design. The final evidence-based algorithm will be reviewed by an advisory committee of three international pleural experts from high-volume centres outside Denmark.

After crossover, clinicians will be trained in how to use the algorithm during a 4-week wash-in period (36). Training consists of on-site presentations for all physicians in all clinical departments involved in management of pleural effusion, pleural infection and spontaneous pneumothorax: Emergency Departments and Acute Medical Units, Departments of Medicine including Respiratory Medicine, and Departments of Surgery. A nationwide online expert panel of investigators who are pleural specialists are available to assess clinical cases and to advise on how to proceed with the management. The APPLAUS algorithms focus on both early diagnosis and management, early recognition of in-hospital treatment failure, and early recurrence

prevention. For each patient, daily evaluation using the algorithm is done from admission to discharge. The algorithm will integrate standardised information data on clinical observations (including vital signs and chest drain output), imaging results, and serum inflammatory markers. The algorithm will be available for clinician as a smartphone application. The concept of the app is illustrated in figure 2 below.

After entering data in the smartphone app, the algorithm produces advice on the indication for pleural procedures, antibiotic treatment, removal of chest drains, timing of thoracic surgical assistance in case of

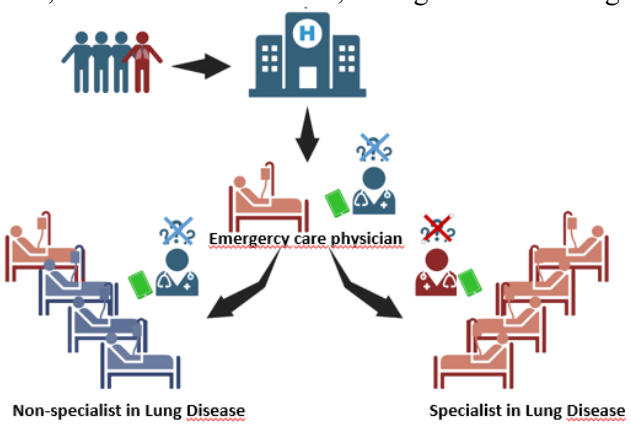

Figure 2: Pictogram illustrating the application of the smartphone app

treatment failure (e.g. persistent air-leak, uncontrolled pleural infection), timing of thoracic surgery or permanent pleural procedures to prevent recurrence (e.g. indwelling pleural catheters or pleurodesis for pleural effusion, or pleurodesis or bullectomy for primary spontaneous pneumothorax), and life-style changes (e.g. smoking cessation). A version of the Pleural Disease management smartphone app will be launched for daily clinical use. During the study, access to the app will be restricted to physicians in included sites after cross-over to intervention. Restrictions include personalised passwords. After successful study completion, the app will become publicly accessible.

Outcomes

Primary and secondary outcomes are briefly outlined. For in-depth description of primary and secondary outcomes, please see ‘Appendix 1’.

Primary outcome

- Days in-hospital

The primary outcome was chosen on the basis of previous data suggesting that guideline-based treatment shortens total length of hospital stay regardless of pleural disease types (effusion, infection, pneumothorax) without compromising safety (9-11). Likewise, the 42-day point was chosen on the basis of same data suggesting that most patients treated conservatively are discharged within 25 days, and thus outcomes measured at 42 days are considered reliably to capture all related re-admissions (9-11).

Secondary outcomes

Other secondary outcomes include the following and will be analysed regarding the subtypes of pleural disease (pneumothorax, pleural effusion, pleural infection):

- Number of readmissions
- Amount of treatment failure
- Number of pleural procedures (excluding thoracic surgery)
- Referral for thoracic surgery
- Referral to out-patient clinic
- Overall incidence of death

Secondary outcomes, specific for subtype of pleural disease include the following:

Pneumothorax

- Amount of subtyping
- Managing strategies
- Proportion of air leak
- HRCT-scans performed

Pleural effusion

- Amount of imaging and pleural effusion lab results
- Definitive pleural procedure with-in 90 days of admission
- Definitive diagnosis of pleural effusion
- Malignant pleural effusion

Infection

- Diagnostic work-up
- Culture positive pleural effusion
- Intrapleural therapy applied

- Systemic, antibiotic therapy administered

All data are collected using a web-based predefined case record form and checked for accuracy and completeness of the source data by researchers not involved in clinical care.

Clusters

We define a cluster as a distinct ED and the relevant clinical departments that receives patients with pleural disease from that ED. Patients admitted for pleural disease are often managed at multiple departments with acute admission at the Emergency Department and from there transference patterns to in-hospital management depend on type of pleural disease, such as:

Spontaneous pneumothorax: Department of Surgery, or Respiratory Medicine.
Pleural infection: Department of Internal Medicine, Respiratory Medicine, or Thoracic Surgery
Pleural effusion (non-infectious): Department of Internal Medicine, or Respiratory Medicine (39).

Consideration on ethical aspects

The study will be reported to the National Ethics committee with an application to waiver the need for informed patient consent, due to the stepped-wedge design(37, 40):
1) the study aims an intervention on an institutional and not a patient level,
2) the intervention is not experimental but a treatment-decision tool to deliver guidelines-based best practice, which is the goal of standard of care,
3) asking for informed consent would lead to refusal of patients in the intervention arm only, since standard practice does not require consent, which would skew the patient population, and
4) implementation would be less successful if not done in all patients in the entire department as standard procedure.

Statistical analysis

Estimated annual Danish incidences of pleural diseases are: 700 cases of pleural infection, 800 cases of spontaneous pneumothorax, and 19,000 cases of pleural effusion including 4,000 cases of malignant pleural effusion (4). Pleural infection and spontaneous pneumothorax are managed in-hospital, and we estimate that at least 25% of patients with pleural effusion are managed during admission due to the very low access to ambulatory pleural clinics in Denmark. This leaves >5,000 potentially eligible patients annually.

We expect to recruit ten hospitals (clusters) ie. two from each of the five Danish administrative Regions. The clusters will be randomised in 5 steps of 2 clusters/step. We expect a mean difference in days-in-hospital of 2 days (SD 5) between usual care group and intervention group (9-11). The intracluster correlation is considered medium (0.1), and with a variation of cluster size coefficient of 0,5, alpha of 0.05, and power (1-beta) to 0.90, 12 patients per cluster/period (41, 42). Table 1 shows that there with 10 clusters and 6 data capture periods, this translates into 12 x 10 x 6 = 720 patients. To anticipate 15% attrition due to underuse of the app or other loss of data, we aim to include a total 828 patient, equalling a mean of 83 patients per hospital.

Control Run-in Intervention

		Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7
Step 1	Cluster 1							
	Cluster 2							
Step 2	Cluster 3							
	Cluster 4							
Step 3	Cluster 5							
	Cluster 6							
Step 4	Cluster 7							
	Cluster 8							
Step 5	Cluster 9							
	Cluster 10							

Feasibility, Work plan and Time schedule

The APPLAUS trial is feasible concerning pleural disease incidence of ~20,000/year: infection 700, spontaneous pneumothorax 800, pleural effusion 19,000 including malignant cause 4,000 (4). The limited access to pleural clinics in Denmark restricts ambulatory management. Thus, a highly conservative estimate is that 25% (5,000) are admitted to one of the 21 Danish hospitals with emergency departments (48). About half (2,500 patients) are admitted to the trial's 10 hospitals. The work plan and time schedule is shown in the Gantt chart below (Figure 4).

Figure 4. Gantt chart showing timeline for the APPLAUS project. Q1 starts 01 February 2024.

	Year 1				**Year 2**				**Year 3**			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Project 1: algorithm												
Algorithm draft												
Validation												
Expert committee												

Publication protocol												
Project 2: APP construction												
App construction												
Validation												
Publication												
Project 3: multicentre trial												
National symposium on new guidelines												
Site recruitment and contracts												
Recruitment of local project nurses												
Data collection												
Data analysis												
Publication												

Role of the funding source

The funders have no role in study design, data collection, data analysis, data interpretation, or reporting results.

Supervisor group

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Appendix 1.

Box 1: **Definitions of the primary and secondary clinical outcomes**	
Outcome	**Definition**
Primary outcome	
Days in-hospital	Number of in-hospital days of any cause within 42 days after admission, including re-admissions.(1) Planned day-case treatment is considered as 0 days. Admission with discharge the same day is considered as 0 days.
Secondary clinical outcomes	
Primary endpoint stratified by pleural disease subtype	
Other secondary outcomes*	Each outcome also analyzed per pleural disease subtype (effusion, infection, pneumothorax)
Pleural diagnoses	Number in total and for each subtype (i.e pleural effusion, pneumothorax, pleural infection, malignant, pleural effusion)
Readmissions	
All causes	Number of emergency, non-planned re-admissions within 42 days
Involving pleural procedures	Number of emergency, non-planned re-admissions, within 42 days, requiring a renewed, pleural procedure
Treatment failure	Defined as admission for >1 day (pleural effusion), >7 days (pneumothorax) and >14 days (pleural infection)
Pleural procedures (excluding thoracic surgery)	
Number (mean pr patient)	
Type	i.e surgical chest-tube, non-surgical chest-tube or needle aspiration
Time from admission to procedure	Time from admission to pleural procedure is performed
Performed out of normal working hours	Numbers of procedures performed evening, nights and/or weekends
Referral for surgery	
In-patients: time from admission	time from admission to referral and type of surgery
In-patients: type	Type of surgery referred to
Out-patients: time from admission	time from admission to referral and type of surgery
Out-patients: type	Type of surgery referred to
Referral for ambulatory treatment	
Type	Type of device used for ambulatory management
Death	All-cause death occurring within 90 days after admission, including all-cause due to treatment failure.
Secondary outcomes specific for pleural disease subtypes	
Effusion	
Imaging and pleural effusion lab results	% having a chest CT, % having pleural effusion sent for cytology, culture and biochemistry
Definitive pleural procedures within 90 days	amount of either indwelling catheters and/or talc pleuradesis and/or surgical pleuradesis with-in 90 days for initial admission
Final diagnoses	final diagnosis of aetiology of pleural effusion
Malignant pleural effusion	Cytology-positive pleural effusion, or no other likely cause than known malignancy. Proportion and no. of cancer subtypes.
Infection	
Diagnostic workup	Diagnosis of pleural infection made by: effusion inspection or pH or culture, imaging, clinical presentation
Culture-positive pleural effusion	Proportion, and microbe types
Intrapleural therapy	Saline irrigation (TDS), DNAse+TPA.
Systemic antibiotic therapy	type of antibiotic, time from admission to administration of first dose, % of cares with pleural, diagnostic tests ahead of initiation of antibiotic treatment
Spontaneous pneumothorax	

Air-leak	Subgroup without a chest-CT scan 12 months prior to admission: number of patients with HRCT 90 days after discharge (1)
Subtypes	Number classified as PSP or SSP during admission.
HRCT	Subgroup without a chest CT within preceding 12 months: no./% with an HRCT within 90 days
SP management strategies	Either conservative, ambulatory device or in-patients treatment with chest-tube

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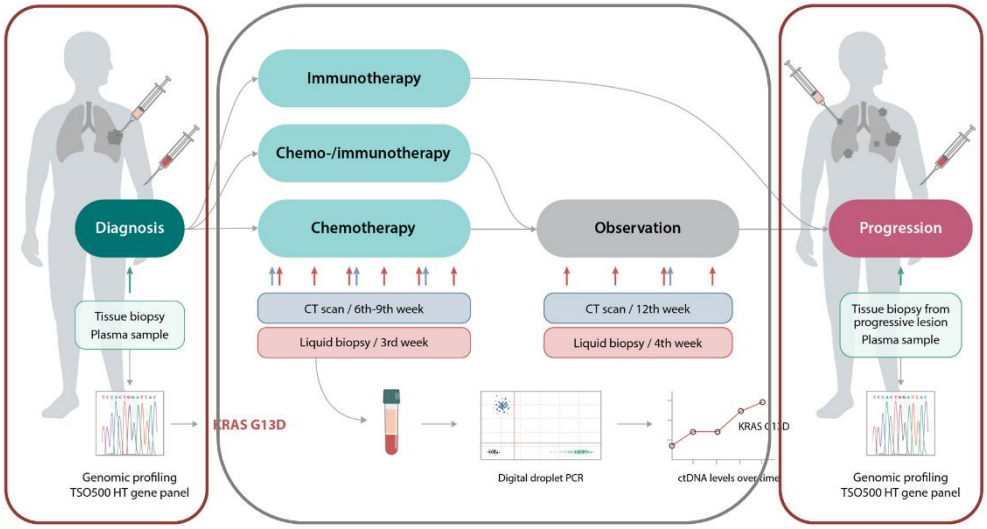
Inspiration til figure. Kan overhovedet ikke kopieres 1:1 men layout kan inspirere.



Jeg forestiller mig at vi til venstre har en pt med pleurasygdom aka spontan pneumothorax eller pleuraeffusion. Dvs. til venstre har man ”early disease management” med et stiliseret billede af et sygehus og en app samt pile viser enten til indlæggelse (mod midten) eller udskrivelse/ambulant.

I midten til venstre (svt de 3 grønne felter): beslutning om indlæggelse eller udskrivelse. Den øverste arm hedder ”control” (sv.t”immunotherapy” i figuren ovenfor) med vandret pil til indlæggelse og en anden til udskrivelse. Under ”Control” en arm som hedder ”invervention” (sv.t ”Chemotherapy” i figuren). Under den Gentagne pile og stiliseret app = dagligt brug af app til at erkende tidligt behandlingssvigt.

Måske skal feltet til højre vise ”behandlingssvigt” eller måske skal der ikke være noget til højre.