Universitat de Girona
Facultat de Medicina

Hospital Universitari de Girona
Doctor Josep Trueta

FINAL DEGREE PROJECT

INTENSIVE CARE TELEMEDICINE VERSUS NEED – BASED TELEPHONE CONSULTATION IN PEDIATRIC PATIENTS WITH RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS

MULTICENTER RANDOMIZED OPEN – LABEL CLINICAL TRIAL

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2. ABBREVIATIONS AND ACRONYMS

AEC	Airway epithelial cells
ARDS	Acute Respiratory Distress Syndrome
BPM	Beats per minute
BROSJOD	Bronchiolitis Score of Sant Joan de Déu
CPAP	Continuous positive airway pressure
EMS	Emergency Medical Services
FiO2	Fraction of inspired oxygen
HFNC	High – Flow Nasal Cannula
HIPAA	Health Insurance Portability and Accountability Act
HUDJT	Hospital Universitari Doctor Josep Trueta
IMV	Invasive mechanical ventilation
LFNC	Low – Flow Nasal Cannula
LOS	Length of stay
NIPPV	Noninvasive positive pressure ventilation
NIV	Non – invasive ventilation
PCR	Polymerase chain reaction
PEEP	Positive end – expiratory pressure
PICU	Pediatric Intensive Care Unit
PPE	Personal protective equipment
RNA	Ribonucleic Acid
RPM	Respirations per minute
RSV	Respiratory Syncytial Virus
SaO2	Oxygen saturation

3. ABSTRACT

BACKGROUND: Bronchiolitis is a common infection of the lower respiratory tract among the pediatric population, representing a major cause of hospitalization. Patients from regional hospitals often require intensive care support and so the assistance from referral centers. The inter – hospital transferring, during the peak infection period, takes around 24 – 48 hours due to pediatric ambulances saturation. The assistance by an intensivist through telemedicine during this time interval would minimize the territorial differences nowadays existing and therefore, avoid the delay of the treatment.

OBJECTIVES: Our main objective is to decrease the length of stay of critically ill patients with RSV bronchiolitis from regional hospitals with telemedicine intensivist support meanwhile they are not transferred to referral centers.

DESIGN: A prospective randomized, controlled, multicentered, open-label clinical trial performed in regional and referral hospitals from Girona, Tarragona and, Terres de l'Ebre Health region.

PARTICIPANTS: Participants included in the clinical trial are patients under 12 months old diagnosed with RSV bronchiolitis from the regional hospital with criteria to be transferred to the referral center. A consecutive non-probabilistic model will be used.

METHODS: The study will include 168 participants, 84 will be assisted through need – based telephone consultation and the other 84 will receive telemedicine intensivist support from the referral center during the period the patient cannot be transferred from the regional hospital because there are no ambulances available. Data about the length of stay, clinical complications, provider satisfaction, economic cost, and covariables will be collected and statistically analyzed to avoid confounding factors.

KEYWORDS: RSV bronchiolitis, telephone consultation, telemedicine, tele – ICU, regional hospital, referral hospital.

4. INTRODUCTION

4.1. BRONCHIOLITIS

Bronchiolitis is a common infection in the small airways that causes inflammation and congestion of the bronchioles, affecting especially patients under 2 years old (1). Firstly, the main symptoms of the disease are suggestive of an upper respiratory tract infection, with rhinorrhea and nasal congestion, but subsequently, lower respiratory tract symptoms are manifested, with difficulty in breathing, sometimes requiring respiratory support (2).

It supposes a potentially life – threatening condition that carries a significant burden at primary health, hospital, and intensive care unit in the most severe cases (3).

4.1.1. EPIDEMIOLOGY

Bronchiolitis is the most common infection of the lower respiratory tract in patients under 12 months, affecting children younger than five years old (4,5).

It is the leading cause of admission in the infant population. Almost 18% of the total hospitalizations in the pediatric unit are because of bronchiolitis (5,6).

In Spain, up to 87% of patients with acute bronchiolitis are treated in primary care. Among all children diagnosed, around 2 – 5% are admitted to hospital, and of those, up to 20% require intensive care assistance (7,8). Estimated mortality between the hospitalized infants is around 1 – 2% (8).

4.1.2. ETIOLOGY AND PATHOGENESIS

The respiratory pathogens are mostly viral, being in 80% of bronchiolitis Respiratory Syncytial Virus (RSV) the causative agent. Other viruses are rhinovirus, bocavirus, adenovirus, metapneumovirus, Influenza A and B, and parainfluenza (5,9). In immunosuppressed children, it is important to consider cytomegalovirus (8).

Co-infection is common, especially RSV together with rhinovirus (4).

Exceptionally, bacterium agents such as *Mycoplasma pneumoniae* can also cause bronchiolitis (2).

4.1.2.1. RESPIRATORY SYNCYTIAL VIRUS

RSV accounts for most of the cases of bronchiolitis. Almost 75% of infants under 12 months are infected during the first year of life, especially in the second and third months after birth. From the age of two, 90% of children have suffered from RSV bronchiolitis (1,5).

Mortality from RSV is declining in developed countries thanks to accessible respiratory care. It is under 1%, although it can reach 3% in the higher-risk population (5,10). RSV acute bronchiolitis represents the second leading cause of mortality after malaria in children under 12 months old (5).

The disease causes seasonal outbreaks, between October and May, with the maximum peak between December and February months. However, because of SARS – CoV – 2, the typical seasonal pattern of bronchiolitis changed, and the incidence decreased in the last year 2020. Currently, due to the relaxation of the social – distancing measures, the trend is normalizing again (10,11) .

The infection is transmitted by the inhalation of someone's RSV – nasal secretions or by contaminated surfaces contact. After incubation of approximately 5 days, RSV replicates in the nasal epithelium and there is a and a cell – to – cell transfer, from the nasal mucosa to the respiratory tract (12,13). In the first days, the patient suffers from rhinorrhea and nasal congestion, due to the upper respiratory tract affection. In one – third of the infected patients, RSV disseminate to lower respiratory airways (14).

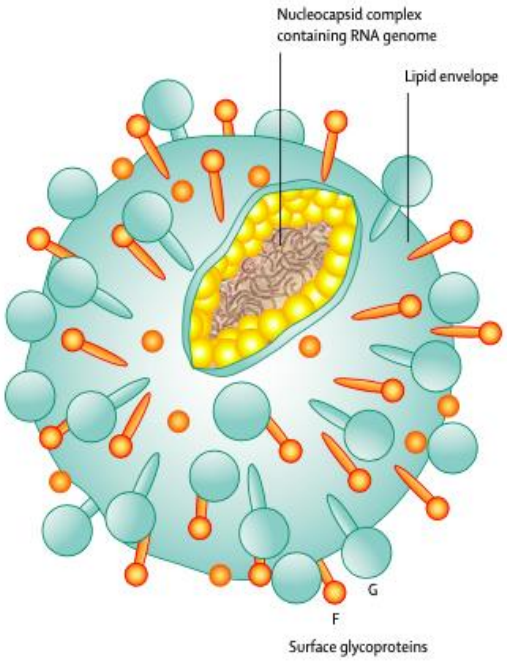

Figure 1. *Representation of RSV structure* (3)

RSV belongs to the *Pneumovirus genus,* a member of the *Paramyxoviridae* subfamily. It is a single – stranded negative – polarity protein virus with an enveloped RNA. There is

only one serotype of RSV, but two groups are described according to their antigenic composition: A and B. In addition, different genotypes have been defined for RSV A and B according to G and F glycoproteins (1,12).

RSV interaction with airway epithelial cells (AEC), the main target cells for RSV, is aided by G and F virus surface proteins. There is a fusion between RSV and host cell membranes, near to cholesterol - rich domains. After that, viral genome transcription and replication take place (13).

When the host cell is infected by the virus, there is an innate immune response in which macrophages, dendritic cells, and AEC are very important. Toll – like – receptors (TLR4 and TLR6), retinoic acid – inducible gene I – like receptor and NOD – like receptors, among others, activate a cascade that stimulates the production of cytokines and other inflammatory molecules (tumor necrosis factor - α, interleukin – 6, chemokine ligand 3, chemokine ligand 5). Such molecules promote the recruitment of immune cells such as monocytes, neutrophils, and eosinophils. Although CD8 and CD4 T cells contribute to the adaptative immune response, this one is weak, reason why the risk of re-infection is common (5).

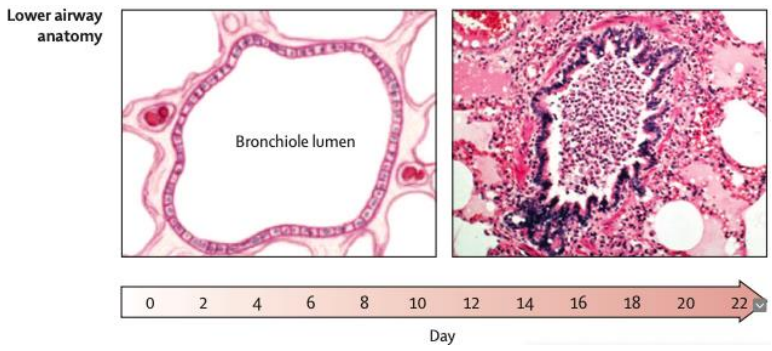

Figure 2. *Inflammatory reaction in bronchioles due to viral bronchiolitis* (4).

Most of the bronchiolitis symptoms are related to this immune response and not because of the infection at all. It causes ciliated epithelial cell necrosis and a whole set of inflammatory reaction, with significant mucus secretion and edema that obstructs bronchioles and increases airways' resistance. In the infant, a little increase of the bronchiolar wall supposes a very significant alteration of airflow, especially during exhalation, when the diameter of the bronchioles is physiologically smaller. For this

reason, there is early air trapping, hyper-insufflation, and atelectasis in the worst cases (8,13,14).

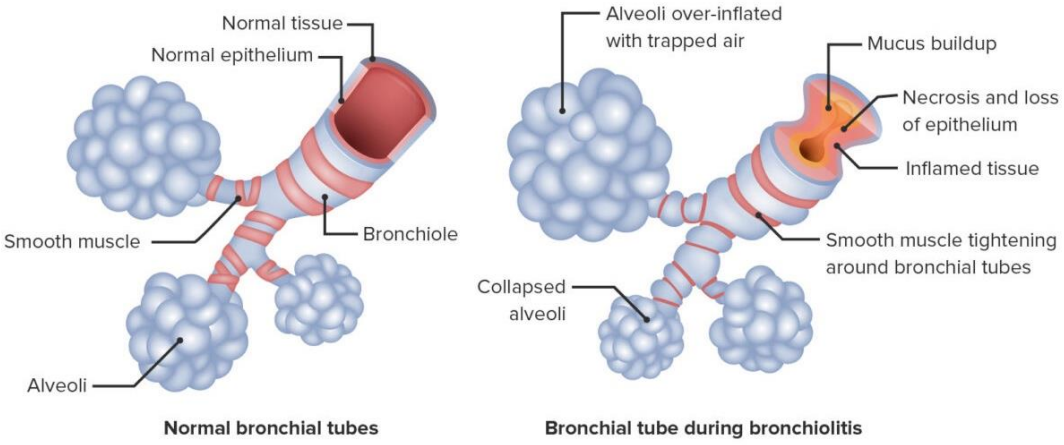

Figure 3. *Typical pathophysiology of bronchiolitis. Source: Lecturio Medical Concept*

As a result of this bronchoconstriction, the patient can be tachypneic with an increase of the breathing work, using accessory muscles, which can lead to acute respiratory failure, due to the mismatch between ventilation and perfusion and hypoxemia (14).

4.1.3. RISK FACTORS

Although most of the infants are infected by RSV during the first years of life and it is a self – limited disease, some of them suffer a severe clinical presentation. The main factors that influence children's risk for a worse evolution bronchiolitis are:

- **Host factors** (1,8,14,15)
    - Sex: boys have a higher risk for severe illness than girls.
    - Age: especially between 1 and 3 months.
    - Prematurity: due to immature lung development, especially those < 32 weeks' gestation.
    - Low birthweight (<2500 gr).
    - Neuromuscular disorders.
    - Chronic lung disease: bronchopulmonary dysplasia, cystic fibrosis and airway malformations.
    - Hemodynamically significant congenital heart disease, especially non-cyanotic congenital cardiopathies.

- Immunodeficiency diseases, either natural or acquired.
- Genetic and chromosomic abnormalities, such as trisomy 21.

- **Environmental factors** (1,8,14)
  - Lack of breastfeeding.
  - School – aged siblings.
  - Air pollution.
  - Smoking during pregnancy and exposure to passive smoke.
  - Geographic area.

4.1.4. CLINICAL MANIFESTATIONS

Commonly, the infection starts with rhinorrhea, congestion, and sneezing due to upper respiratory tract involvement, and progresses to cough, tachypnea, and an increase of breathing work (with intercostal and supraclavicular retractions and abdominal muscles use) that makes feeding difficult because of lower respiratory tract affection (4,16).

Dry cough is the predominant symptom and may take up 3 – 4 weeks to disappear (5).

Fever can be present among the children affected with bronchiolitis, although it is not common temperature over 39ºC (8).

The duration of the bronchiolitis episode depends on multiple factors. In mild cases, symptomatology disappears in a few days. In moderate and severe conditions, the respiratory distress gets worse mainly in the first 24 – 48 hours, the moment when most of the infants require hospitalization, and lasts approximately for 10 days (5,8).

However, it is important to highlight that those clinical findings are submitted to a minute – to – minute variation, as child circumstance varies from one moment to the other, being calm and sleeping to agitated and crying in a short period of time *(Figure 4)* (4).

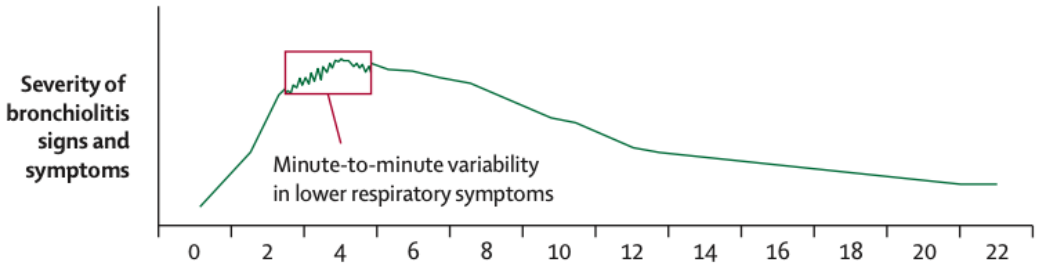

Figure 4. *Typical clinical course of viral bronchiolitis* (4).

4.1.5. COMPLICATIONS

Patients with severe bronchiolitis can develop both pulmonary and extrapulmonary complications as the virus can affect distant organs using hematogenous pathways:

- **Apneas**: Respiratory pauses can be the initial clinical form of presentation or appear after some days of evolution but are more frequent in premature patients or newborns because of pulmonary immaturity. This is one of the main causes of mechanical ventilation in patients with bronchiolitis (8,16).
- **Dehydration**: It is frequent due to tachypnea, fever, and decreased feeding and drinking because of respiratory distress (8).
- **Bacterial and viral coinfections:** bacterial co-infection occurs in 1% of the hospitalized patients, except for otitis media, which is more frequent. Prevalent pathogens are *Staphylococcus Aureus, Pseudomonas aeruginosa,* or *Streptococcus pneumoniae*, among others (17,18).
- **Aspiration pneumonia:** the increase of inspiratory muscles work lead to an ascend of gastric juices into the esophagus and consequently, into the airways (18).
- **Respiratory failure and Acute Respiratory Distress Syndrome** (ARDS): Hypoxemia is common in bronchiolitis and it usually responds to oxygen. Sometimes it is associated with hypercapnia, due to muscle fatigue, and additional respiratory support is necessary. ARDS is an entity consisting of severe acute injury of the lung with hypoxia, diffuse bilateral infiltrates in radiography together with a decrease of lung compliance and edema. In this case, there is a mortality rate of 40% among the patients affected (18,19).
- **Pneumothorax and pneumomediastinum**, especially to consider in patients with a sudden worsening (20).

- **Cardiovascular complications**, such as ventricular tachycardia, ventricular fibrillation, pericardial effusion, or myocarditis, also in children without congenital heart disease. In patients with elevated viral load is frequent sinoatrial blocking. Elevated cardiac troponin T is a good indicator of myocadiac damage (13).
- **Hepatitis**, associated with elevated transaminase levels and coagulation disorders (13).
- **Hyponatremia**, due to endocrine system disorders and high levels of antidiuretic hormone (ADH) (13).
- **Neurological alterations**, such as central apnea, lethargy, tone abnormalities, status epilepticus, and encephalopathy, among others. Central apnea can affect up to 21% of the infants hospitalized because of RSV bronchiolitis (13).

4.1.6. DIAGNOSIS

Bronchiolitis diagnosis is essentially clinical, based on anamnesis and physical examination. According to McConnochie criteria, it is considered when there is a first episode of viral airways infection (fever, rhinorrhea, coryza or otitis media) in children under 2 years old, associated with expiratory wheezing on auscultation, in absence of other cause that could originate it (5) .

Patients with typical bronchiolitis manifestations do not require laboratory or radiologic studies as the evidence demonstrates that benefits do not exceed costs (4).

- **Anamnesis**: It is very important to interrogate about all the factors related to a higher risk of severe illness, such as prematurity, chronic illnesses, smoking environment, non – breastfeeding, and low birth weight. It is also relevant to indagate about the evolution of the current episode (5).
- **Physical examination**: It is necessary to realize a complete examination of the patient, with special emphasis on the dehydration and breathing difficulty signs (5). The evaluation must be continuous, as there can be changes in a short period of time (14). Inspection and auscultation can reveal important signs.
    - Through the inspection, we can appreciate (8,14,16):

        - Signs of respiratory distress, such as subcostal and intercostal retractions and nasal flaring.
        - Tachypnea.
        - A distended thorax distended and sometimes a palpable liver and spleen, as the diaphragm is descended due to pulmonary hyperinflation.
        - Signs suggestive of dehydration are tachycardia, delayed capillary refill, dry mucous membranes, and a sunken fontanelle.
    - The auscultation reveals (5,8):
        - Wheezing sounds during inspiration and expiration.
        - A prolonged expiratory phase.
        - Crackles sounds.
        - Hypoventilated zones.

- **Pulse oximetry**: It is a non-invasive method to determine oxygen saturation. It is useful for the initial evaluation of the acute bronchiolitis patient. However, it should not be the only criteria, as arbitrary pulse oximetry can lead to unnecessary admissions and hospital length stay prolongation (4). It is also necessary when clinical changes are observed, but continuous monitoring is not justified (5).
- **Arterial blood gas analysis**: It measures arterial gases such as oxygen (pO_2), carbon dioxide (pCO_2) and pH from a blood sample of the radial artery, femoral artery, or arterial catheter, for example. It is not routinely used but is helpful in patients with severe respiratory distress about to suffer acute respiratory failure (4,5).
- **Virological test**: Although the etiological diagnosis of bronchiolitis is epidemiologically very important and it is useful to indicate patient's isolation, it does not have much influence on the management of the episode, especially during the epidemic outbreak and those patients under one year of life, as RSV is the main viral agent, and the incidence of other pathogens is less common (5,16). There are different types of diagnostic tests:

- Molecular tests: It is based on the polymerase chain reaction (PCR) to detect the virus in the nasopharynx. It has a sensibility of around 95% but it is expensive (4,5).
    - FilmArray respiratory panel: It analyses the presence of around 20 viruses and bacterium that cause upper respiratory tract infections with a sensitivity and specificity of 95% to 99% respectively through a multiple PCR system. It is the one used nowadays in the clinical practice.
- Antigen detection tests: It is more available, economic and the result is immediate (5). Some examples of rapid tests are direct immunofluorescence assays or enzyme immunoassays (3). The specificity of these tests is 100% but sensitivity is between 80 - 90% (21). A positive result on the virological test confirms the etiology, but a negative test does not make it possible to safely discard infection (8).

- **Blood test:** It is important to determine C – reactive protein level when bacterial superinfection is suspected, especially in those patients with high temperatures. Electrolyte serum concentrations determinations are useful to diagnose dehydration or other electrolytic discordances (5,16).
- **Urine test:** Between 1 – 7% of the patients with bronchiolitis develop urinary tract infections. For this reason, it is important to obtain urinalysis and urine culture from those patients with risk factors to this type of infection or with a suggestive clinical manifestation, such as persistent temperature over a long period of time (4).
- **Radiographic studies**: In mild cases, chest radiography can be normal or can evidence peri-bronchial thickening and trapping air signs, with atelectasis. It is only indicated in patients with severe affection and symptoms progressing not according to what is expected or with diagnostic doubts (5).

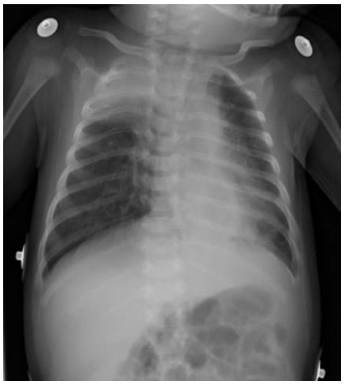

Figure 5. *Chest radiography from RSV bronchiolitis patient* (16).

In *Figure 5* we can see an imaging from a patient with RSV bronchiolitis affection who has bilateral hyperinflation, air trapping, atelectasis and peribronchial thickening on the chest radiography.

4.1.7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of an infant under 2 years old with cough and respiratory symptomatology should include infectious and non – infectious pathologies (5).

The diagnostic that is more easily confused with bronchiolitis is asthma since the first episode of this disease can be together with an infection of the lower respiratory tract. However, in asthma, it would be common family history, skin atopy, repeated episodes, and response to bronchodilators. Other illnesses that can initially manifest simultaneously with bronchiolitis are cystic fibrosis, airway malformations, cardiac disease, and bronchiolitis obliterans, among others (8).

Whooping cough, also known as pertussis, should be suspected when there is paroxysmal cough. It is also important to discard other bacterial pneumonia, that, unlike viral bronchiolitis, the patient would have a higher temperature and a worse course of the disease (4).

Vascular ring or foreign body aspiration should be contemplated in a patient without upper respiratory symptoms (4).

Aspiration pneumonia, usually due to gastroesophageal reflux, is manifested with cyanosis and coughing during feedings. It can also be caused by bronchiolitis itself (18).

4.1.8. SCORES

When a patient is diagnosed with bronchiolitis, it is important to determine the severity of the episode using a score to predict the evolution, the hospital length of stay and the need of respiratory support or intensive care unit assistance using an objective system (22).

Before using this diagnostic tool, airways secretions must be aspirated in order not to falsely worsen the severity of the score (2).

There are different scores for acute bronchiolitis. Sant Joan de Déu Hospital (SJDH) designed a score in 1999 with the main objective to classify the patient severity into different degrees (mild, moderate or severe) and decide according that the treatment and the respiratory support needed (Table 1) (22).

Table 1. *Bronchiolitis score of Sant Joan de Déu Hospital (BROSJOD)* (22).

	0	**1**	**2**	**3**
Wheezes / rales	No	Expiratory wheezes, inspiratory rales	Expiratory and inspiratory wheezes / rales	-
Indrawing	No	Subcostal, lower intercostal	Previous + supraclavicular + nasal flaring	Previous + upper intercostal + tracheal tug
Air entry	Normal	Regular and symmetric	Asymmetric	Very reduced
Oxygen saturation				
Without O_2	>95%	91 – 94%	<91%	
With O_2	Without O_2	>94% with FiO_2 < 40%	<94% with FiO_2 > 40%	
Respiratory rate (rpm)				
< 3 month	<40	40 – 60	60 – 70	>70
3 – 12 month	<30	30 – 50	50 – 60	>60
12 – 24 months	<30	30 – 40	40 – 50	>50
Heart rate (bpm)				
< 1 year	< 130	130 – 150	150 – 170	>170
1 – 2 years	<110	110 – 120	120 – 140	>140

The score is based on a scale from 1 to 16, from less to more severe disease. The resultant score has been classified into three groups according to mild (punctuation between 1 – 5), moderate (6 – 10) or severe bronchiolitis (11 to 16) (22).

Wood - Downes clinical score modified by Ferres is also used, although it was initially for asthmatic patients (Table 2) (2,22)

Table 2. *Wood - Downes clinical score modified by Ferres* (2,22).

	0	**1**	**2**	**3**
Wheezing	None	End expiration	Entire expiratory phase	Inspiration and expiration
Retractions	None	Subcostal or lower intercostal	1 + supraclavicular + nasal flaring	2 + suprasternal + lower intercostal
Respiratory rate	< 30	31 – 45	46 – 50	>60
Heart rate	<120	>120	-	-
Inspiratory breath sounds	Normal	Regular, symmetrical	Markedly silent, symmetrical	Silent thorax, no wheezing
Cyanosis	Not present	Present	-	-

A score between 1 – 3 is classified as a mild bronchiolitis, between 4 – 7 as a moderate bronchiolitis and between 8 – 14 as a severe bronchiolitis.

4.1.9. TREATMENT

4.1.9.1. PATIENT ASSESSMENT AND HOSPITALIZATION ADMISSION CRITERIA

Most of the infants that suffer from mild bronchiolitis can be assisted in primary care and treated at home. However, moderate and severe bronchiolitis require hospitalization and the need of respiratory support between those patients is common (5).

The admission criteria for hospitalization according to *Sociedad Española de Neumología Pediátrica* are (5):

- Poor feeding (intake of < 50% of usual).
- Dehydration, lethargy, or general condition affectation.
- Story of apneas.
- Tachypnea or respiratory rate > 60 – 70.

- Moderate or severe respiratory distress (cyanosis, intercostal retractions).
- Hypoxemia (SaO_2 < 92 – 94%).
- Moderate bronchiolitis unresponsive to general measures.
- Severe bronchiolitis: BROSJOD Score > 7 - 8 (Table 1) or Wood - Downes clinical score modified by Ferres > 6 – 7 (Table 2).
- Diagnostic doubts.
- Comorbidities.
- Less than 72 hours of evolution, due to the risk of worsening.
- Socioeconomic or geographic context that does not allow a good following-up of the patient.

The patient will be attended to their regional hospital, except for the following cases that will be moved into the referral center via Pediatric Emergency Medical Service (EMS) (8):

- Infant under 4 – 6 weeks old with a moderate bronchiolitis not responding to general measures.
- Infant with high – risk factors (immunodeficiencies, congenital cardiopathies) and moderate bronchiolitis.
- Infants with apneas, important lethargy or toxic appearance.
- Severe bronchiolitis not responding to treatment.

The admission criteria for Pediatric Intensive Care Unit (PICU) assistance in Hospital Universitari Doctor Josep Trueta (HUDJT) are (2,8):

- Severe bronchiolitis (BROSJOD Score >10).
- Important O_2 requirement: SaO_2 < 92% with a FiO_2 > 50%.
- Respiratory and/or metabolic acidosis with pH < 7,25.
- Extrapulmonary complications: arrhythmias, hemodynamic instability, dehydration, or severe electrolytic alteration.
- Rapidly progressive disease
- Recurrent apneas episodes, with SaO_2 affectation.

In the hospital environment, awareness about nosocomial infection prevention among professionals is needed to avoid virus transmission. Some of these measures include (8):

- Contact isolation measures.
- Use of using single - use gloves and gowns.
- Use of surgical mask if any intervention is realized.
- Stethoscope cleaning before and after the examination of the patient.
- Restriction of external visits.

4.1.9.2. SUPPORTIVE TREATMENT

Viral bronchiolitis treatment is symptomatic and is based on supportive care. The use of drugs is rarely indicated. Supportive treatment is essential in both, domiciliary and hospitalized patients with a lower respiratory tract infection. It is the primary therapeutic step to ensure the stability of the patient, guaranteeing a proper oxygenation and hydration (1,2).

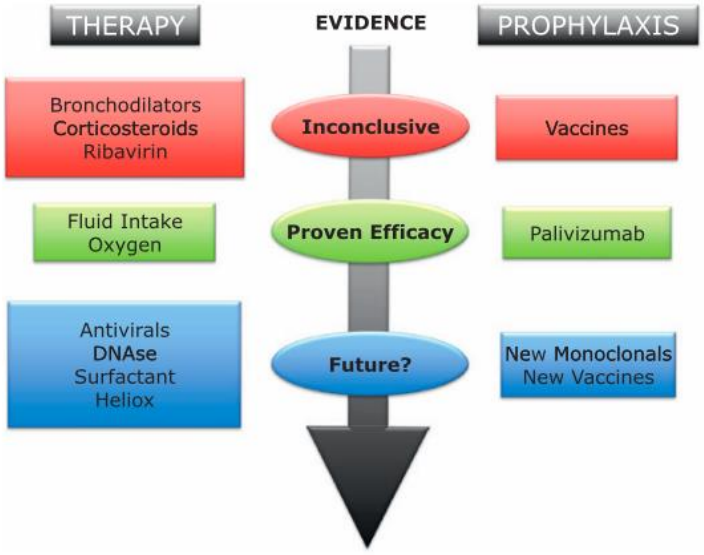

Figure 6. *Management of viral bronchiolitis based on recent evidence* (16)*.*

As it is described on Figure 6, the only therapy for viral bronchiolitis that have scientific evidence is supportive care.

Nasal clearing

The airways must be kept permeable with physiological saline solution washing and mechanical aspiration. This procedure can help to prevent complications such as otitis.

It is recommended to do it before feeding, when clinical obstruction signs are observed (an increase of respiratory sounds or breathing effort), or before severity score evaluation (5,7).

Postural habits

The patient should be placed in a 30º semi-fowler position (7).

Nutrition and hydration

Fluid replacement in the patient with acute bronchiolitis is important as there is a risk of dehydration because needs requirements are higher due to fever and tachycardia and there is a decreased intake when there is respiratory failure.

The options of feeding are different depending on the patient condition (5,23)

- **Fractionated food administration**, which consists of small but frequent feeding, especially indicated in mild bronchiolitis.
- **Nasogastric feeding**, prescribed in moderate or severe bronchiolitis, especially when the respiratory frequency is elevated and there is nasal congestion, as aspiration risk increases. It is also recommended to those patients with an intake < 50% of the usual according to the age.
- **Parenteral nutrition,** using intravenous administration when proper hydration is not achieved with other resources. It is important to control the secretion of the antidiuretic hormone as in these patients can be inadequate.

Respiratory support

The different types of respiratory support used to assist patients with bronchiolitis and respiratory difficulties are:

- **Low – Flow Nasal Cannula (LFNC) Oxygen Therapy:** It consists of supplemental oxygen administrated by nasal cannula. It is indicated in patients with SaO_2 < 92%. It can be weaned when SaO_2 > 94%, but after that, it is necessary to monitor the patient to ensure correct stabilization (5).
- **High – Flow Nasal Cannula (HFNC) Oxygen Therapy**: It is based on humid oxygen at body temperature at high pressure. It permits a high inspired gas flow of

maximum up to 2 litres/kg, which levels are independent of the oxygen concentration administrated. It decreases the breathing work, as well as the need for FiO_2. It has demonstrated a reduction in the intubation rates of around 9%, also decreasing the number of days a patient is admitted to the pediatric ICU (5,8).

It is recommended in case of:

- Supplemental oxygen therapy failure
- Patients with hypoxemia without hypercapnia who require high amounts of oxygen or FiO_2>35%.
- Respiratory distress progress or severe according to SJDH score.
- SaO_2 < 88%.

- **Non-invasive ventilation** (NIV):
  - Nasal continuous positive airway pressure (nCPAP): This system administrates a continuous level of pressure which is always the same to airways during both, inspiration, and expiration, without considering the respiratory cycle but permitting the spontaneous breathing of the patient. In this case, it is important to regulate positive end – expiratory pressure (PEEP) according to the status of the patient. This value refers to the pressure of the end of exhalation. It is usually applied a PEEP between 4 – 6 (8,24).
  - Nasal Bi-level Positive Airway Pressure (nBIPAP): This mechanism delivers two different constant pressures, higher and lower but both positive, allowing the spontaneous breathing of the patient but reducing the respiratory work. Inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) settings are modified according to the patient's condition. The first one is to modify ventilation and the second one, to modify oxygenation (5,24).
- **Invasive Mechanical ventilation** (IMV): Patients with worsening respiratory distress although the measures described above require endotracheal intubation (23).

The first step in a patient that requires respiratory support is HFNC oxygen therapy, except for those who have a severe respiratory failure or frequent apneas, to whom NIV is preferred. If there is no improvement (decrease of RPM and BPM, breathing work, and O_2 requirements), it is necessary to use NIV. Initially, CPAP will be applied, and later if the patient is worsening, BIPAP is considered. Finally, those who do not have a good evolution will need invasive mechanical ventilation (8).

4.1.9.3. PHARMACOLOGICAL TREATMENT

- **Bronchodilators**: Most of the clinical practice guidelines do not recommend bronchodilators for acute bronchiolitis treatment, as no evidence demonstrates a significant efficiency of this group of drugs (25).
    - β_2 – agonists, such as salbutamol: Although it is demonstrated salbutamol produces a moderate clinical improvement, it should not be administrated systematically as it does not reduce hospitalization days or admissions. If the administration is considered opportune, it is necessary to carry out a therapeutic test before. It consists of the inhalation of salbutamol through a chamber (2 - 6 inhalations). After 20 minutes, it is necessary to reevaluate the score. If there is an improvement of about 2 points on the score or SaO_2 gets better, the response is considered optimum, and it can be used. Regarding the way of administration, the evidence refers to the inhaled route, not considering others (8,25).
    - Nebulized epinephrine: No studies demonstrate the routinary use, reason why it is only administrated as a rescue medication. It is needed a therapeutic test to evaluate the patient's response (25).
    - Xanthines: caffeine, theophylline, or aminophylline can be used in case of acute bronchiolitis associated with apneas, especially in infants with history of prematurity (25)
- **Saline hypertonic serum**: The administration of 3% saline hypertonic serum has demonstrated better clinical evolution and a decrease in the total hospitalization length of stay (25).
- **Antibiotics**: Indicated if there is suspicion of bacterial superinfection (otitis, urinary tract infection) (25).

- **Others** (8,25):
    - Surfactant: The evidence of surfactant administration is not enough. It could be administrated in those patients with mechanical ventilation or newborn with severe illness.
    - Helium: Mixture of oxygen and helium gas used for rescue in severe cases. It could be useful in patients with moderate or severe bronchiolitis but there are not enough studies that reveal that.
    - Ribavirin: Antiviral drug indicated in severe bronchiolitis for RSV in immunosuppressed infants.

The following pharmacological treatment is not recommended in acute bronchiolitis (25):

- Mucolytics, cough suppressants, and nasal decongestants.
- Antihistamics.
- Anti – leukotrienes, such as montelukast.
- Glucocorticoids: Although this drug is used in other respiratory diseases, no evidence demonstrates its effectiveness in bronchiolitis.

In *Annex 1* the management of acute bronchiolitis is summarized.

4.1.9.4. MONITORIZATION AND FOLLOWING – UP

At primary care, the following – up should be constant as the patient may get worse at any time. The same happens at the hospital, where is necessary the monitorization of the vital signs (RR, BR, SaO_2, and respiratory distress signs). Moreover, depending on the condition, especially in ICU patients, it can also be necessary to evaluate the temperature, blood pressure, diuresis control, or arterial gases (5,8).

4.1.10. PREVENTION

Reinfection risk may reduce with good patient and family education. It is necessary to highlight the importance of hygienic measures, the disinfection with alcohol or soap and water, the elimination of smoking exposure and the contact with other infected infants (1,10).

Apart from the hygienic measures, that are basic for all the infants susceptible to a respiratory tract infection, for high – risk patients there are pharmacological interventions for RSV prophylaxis. Firstly, it was used polyclonal intravenous immunoglobulin, but currently, palivizumab is administrated (10,16).

Palivizumab is humanized IgG1 monoclonal antibody, targeting RSV fusion F protein. It is administrated every month during the RSV outbreak as an intramuscular dose of 15 mg/kg maximum for 5 months. The indications for the administration of palivizumab according to *American Academy of Pediatrics Guidance* are (16):

- First-year of birth of patients born before 29 weeks' gestation.
- First-year of birth of patients born before 32 weeks' gestation with chronic lung disease.
- Second-year of birth of patients with chronic lung disease that still require oxygen support or pharmacological treatment, such as corticoids or diuretics.
- Patients with hemodynamically congenital heart defects, immunodeficiency, and pulmonary or neuromuscular disease.

The dose of the drug accumulates over each month's administration, and it is not protective until several applications. Therefore, there is a higher incidence of bronchiolitis among the patients that only have taken the first injections (16).

4.1.11. PROGNOSIS

It is described in the literature and there is scientific evidence of a clear association between bronchiolitis and asthma, which increases whether the causative agent is RSV or rhinovirus. This relationship implies not only that bronchiolitis may cause asthma because of the damage and alteration of the lung function but also that it is a marker of increased predisposition to asthma, due to individual risk factors (4,5).

Moreover, lower respiratory tract infection is also associated with recurrent wheezing, which intensity decreases with age (5).

4.2. TELEMEDICINE

The prefix “tele” means “at a distance”. However, it can also be referred to data or electronic devices. This word can be applied in different areas, but in medical terms, it is used when different telecommunication technologies are employed to exchange information and connect patients with healthcare providers, especially when there is a geographical barrier. This enables doctors and health professionals to offer services at distance (26). *Telemedicine* and *telehealth* can be used as synonyms nowadays.

Telemedicine has multiple indications. The most important are (27):

- **Tele-education**: Tele-education provides the formation of both, students and professionals, and patients and families. It allows real – time interaction between the provider and the learner.
- **Tele-consultation**: It is a good tool for the deliberation of clinical situations to other subspecialists from a different community or area, especially in those hospitals with limited expertise, breaking down distance and time barriers.
- **Tele-practice**: It establishes a connection between doctors and patients separated in distance. This involves a decrease in health care system costs and fewer displacements but without replacing the patient attendance.
- **Tele-research**: It encourages the investigation among the health professionals but also it is a good way to disseminate the research findings. Moreover, it is a tool useful for clinical trials, as it permits recruiting patients.

4.2.1. INFRASTRUCTURE

The basis for telemedicine is connectivity to the Internet, the software platform and hardware that enables a connection between the two sides.

4.2.1.1. SYSTEM DESIGN

The equipment needed for implementing a telehealth system will depend on the type of program needed. The two models that can be practiced are (27):

- **Synchronous** or **live telemedicine**: It implies a real – time interaction between persons connected from different places.

- **Asynchronous** or **store – and – forward telemedicine**: It consists of the recording of information in one place from one professional and transferring it later to another place and person.

Moreover, the selecting platform used will depend on the specific use offered (28):

- **Remote monitoring**: Health platform used for monitoring patients, especially those with chronic illness. The medical measurements taken are saved in the network and are processed by algorithms that indicate if the values are in the correct range or not. Doctors and other health professionals have access to the information to be aware of any alteration. The system is used to have information about patients' vital signs, and it is not normally associated with videoconferencing.
- **Consultative visits**: Telecommunication for deliberation between two clinical professionals or directly with the patient using video. In this case, diagnostic instruments are not used, and the meeting has only a consulting purpose.

  Some manners to deliver videoconferencing are programs installed such as Zoom, Skype for business, Join Me or Cisco, Clik Meeting, among others. Another option is buying the services to the vendor, who guarantees the preservation and the upgrades of the system. Moreover, there are programs created for smartphones or PC ideated because patients have the possibility to concern visits.
- **Facilitated visits**: When it is necessary to do a physical exam, complex medical devices are needed. In this case, it is required an exclusive platform that can offer it apart from videoconferencing. Apart from viewing the patient, these applications have integrated clinical information through monitors, compatible stethoscopes to listen to patient's breathing sounds, or even an ultrasound, among many other possibilities. However, in this case, apart from the professional who is behind the screen observing, it is necessary a clinician with the patient to do the examination.

  Some examples of these programs are:
  - AGNES by AMD Telemedicine
  - Intouch Health

- Avizia telemedicine
- Idonia software (29)

4.2.1.2. EQUIPMENT

The technological supplies needed for the telemedicine consultation are (30):

- **Technical setup**: Videoconferencing ideally requires two screens, one for the video software and patient recording and the other for consulting all the available information in the medical history. A computer and a webcam will be also necessary .
- **Audio and video**: It is very important to ensure a good sound and video quality. This can be achieved with property speakers, earphones, microphone, and webcam. The professional should be located in a room without noises.
- **Connectivity**: The quality of telemedicine will depend especially on the connection between the places that are linked. For this reason, is very important that the institution or the hospital guarantees a high – speed connectivity (27).

Moreover, it is important to have a technical staff for solving all the problems resulting from those users not being able to operate with the telemedicine system. The support should be offered during all the hours the service is provided (28).

4.2.1.3. PRIVACY AND SECURITY

Security can be guaranteed through establishing a point – to – point encryption between the equipment connected and using a private internet network. Moreover, it is important to create safeguards for accessing data (27).

In United States, the Health Insurance Portability and Accountability Act (HIPAA) objective is to ensure the privacy of the health information. This represents using software with an end – to end encryption, which is not guaranteed in public platforms such as Facebook Live or Twich (31,32).

4.2.2. LEGAL ISSUES

Telehealth implementation varies from one state to the other, reason why it is relevant to have into consideration that the patient's physical location will determine the laws and regulations that the provider will have to follow (33).

Nevertheless, there is a set of regulations about how to keep personal data that is important to consider when executing a telemedicine system:

- **International regulations** (34):
    - According to Article 12 of Universal Declaration of Human Rights, "no one shall be subjected to arbitrary interference with his privacy, family, home or correspondence, nor to attacks upon his honor or reputation".
    - Referring to Article 8 of the Declaration of the Rights of Patients made in Lisbon, "Patient's has a right to expect from a physician, to respect the confidentiality of all medical information about his private life".
    - Remitting to the Declaration on the Promotion of Patients' Rights in Europe, Article 4 determines that "protection of personal information, even after death, protect patients' identity, the protection of patients' records from third parties".
    - The American Medical Association (AMA) adopted new guidance for telehealth services in 2016 to facilitate advice to providers so they can deal with telemedicine limitations and get the most advantage of telecommunications (35,36).
- **National regulations** (37):
    - El Código de Ética y Deontologia from the Spanish Medical Association does not deal specifically with telemedicine, but it evidences that the general code of ethics must be applied to telemedicine. Article 22.1 mentions the importance to use telemedicine as a supplement, but never as a substitute of the face – to face meetings and direct contact.

So, in telemedicine, the respect for the dignity of the patient is imposed over technology. Nowadays, telehealth policies are guided by general ethics.

4.2.3. TELEMEDICINE BARRIERS

The increasing use of telemedicine demonstrates that it is an essential tool in a globalized world. This can be appreciated in its wide use in the different disciplines of medicine, and more specifically in the different pediatrics subspecialities, such as its application in neonatology, critical care, and chronic diseases, among others (27).

Nevertheless, there are different limitations when using this system:

- **Personal limitations**, both provider and patients: Telemedicine requires the acceptance of the people affiliated with the system, especially patients, who may doubt about their privacy and ability to work with technology or refuse the idea of not having a face – to face interaction with the doctor or other health professionals. It is also very important that the members have the capacity of managing the network, reason why training is necessary.
- **Technological limitations**: System failure or connectivity loss can happen in the worst cases. This limitation must be stated on the informed consent.
- **Legal and licensing barriers**: It refers not only to the possibility of negligent actions by the health professional who is practicing telemedicine but also all the security policies and procedures that are needed to guarantee patients' confidentiality.

4.2.4. FINANCIAL IMPACT

Implementing a telemedicine system at the end supposes cost savings and financial gain although the impact of planning a new program is a substantial expense (33). Fixed costs, such as the equipment, the licensing fees, or software updates, will depend basically on the technology required and the intervention used. Among the variable costs, it is important to consider the preservation of the technology, the training of the users, and the technical support, among others multiple factors (27).

Although at the beginning it is necessary a technology purchase, at the moment the system is executed, the costs are similar or even less than not using telemedicine. There are no transport costs for the patient, and in most of cases, it supposes less time for the provider (33).

4.2.5. INTENSIVE CARE TELEMEDICINE APPLICATIONS

Both adults and pediatric patients who are critically ill require highly specialized physicians. It is evidenced that it reduces the mortality, ICU, and hospital length of stay (LOS). However, due to geographic factors and lack of professionals, there are disparities in access and not all critical patients are treated with the conditions needed (38).

The application of a telemedicine system in the ICU is known as Tele – ICU. It supposes the involvement of critical care physicians in the attention of critical patients located in remote areas to provide the assistance required (38).

The main difference between telephone consultation and tele – ICU assistance is that the health professional has available all the information of the patient, including monitors with vital constants of the precise moment, the medical history, and a video recording of the patient (38).

The Tele – ICU model can be intermittent, for needed consultations from the regional hospital to the referring hospital or integrated with the continuous monitorization of the patient, what is known as tele – presence ICU system (38,39).

The main objective of the Tele – ICU system is far from substituting bedside attention, but it is necessary when that cannot be done and there is no alternative. The aim is that all patients receive the same quality service, especially those patients from remote hospitals with deficiencies in infrastructures, less experimented professionals or without available subspecialists, or also during the critical care transport to the referral centers. It is also essential for preparing the patients' arrival and all the resources that will be needed in the referring hospital (38,40).

So, the purpose of telemedicine is the correct management of the critical patient, avoiding delayed diagnoses or non – efficient treatments which would suppose a worse prognosis for the patient (38).

4.2.5.1. TELE – ICTUS

A patient suffering a stroke is in a very critical condition and his affection depends basically on the time elapsed until he is being treated. In Catalonia, to provide a rapid

response to patients located in areas distant from referral hospitals, Tele – Ictus system was implemented in 2007. The main objective was to establish communication channels to assist regional centers from neurological experts on call able to treat acute cerebral vascular accidents (41).

In 2013, the system evolved as Tele – Ictus 2.0 and it also included videoconferencing and a medical imaging sharing platform (42,43).

The software used for the telecommunication between hospitals in Tele –Ictus is *Idonia* and it is compatible with the hospital's current computer system. The network allows videoconference assistance, image transferring, and centralizes all the communications (29,44).

This system is powered by Departament de Salut, Servei Català de la Salut (Cat Salut), TicSalut foundation, i2CAT foundation and Agència de Qualitat i evaluació sanitària de Catalunya (AQuAS) (43).

5. JUSTIFICATION

Acute bronchiolitis caused by RSV is the most common infection of the respiratory tract in children under 12 months. Although it has a low mortality rate, it supposes a substantial cause of admission in hospitals and PICUs during the seasonal peak. This implies an important percentage of hospital and ICU pediatric beds occupancy during the periods of highest incidence, reaching saturation levels in some cases and consuming a great amount of health care resources.

Some of the patients affected suffer from moderate or severe illness, and the ones living in non-urban communities that need critical care assistance are transferred to a hospital with PICU. The pediatric critical care services are even more regionalized than the adults' ones in tertiary care hospitals. In Girona health region the only PICU available is in Hospital Universitari Doctor Josep Trueta, meanwhile in Camp de Tarragona and Terres de l'Ebre health region the only center with the resources to assist the pediatric critically ill patient is Hospital Universitari de Tarragona Joan XXIII. Moreover, during the RSV outbreak, the pediatric EMS, which is centralized in Barcelona, is full of capacity and it takes a long time to do the transferring, sometimes up to 24 – 48 hours.

A telemedicine intensivist support meanwhile the critically ill infant is not at the referring center would be of great importance for not delaying the patient management and eliminating the territorial disparities among patients.

This study is relevant as there is no research on the application of a telemedicine system in the critically ill pediatric patient with RSV bronchiolitis, even less in Girona, Camp de Tarragona and Terres de l'Ebre Health region.

A telemedicine system applied in the most severe cases of RSV bronchiolitis is about to be executed in Girona health region but firstly it is important to evaluate if it is worthwhile and if there is a significant difference in implementing it.

Moreover, once it is executed and professionals are used with the system, it can be used for other pathologies.

6. HYPOTHESIS

MAIN HYPOTHESIS

- Critically ill pediatric patients with RSV bronchiolitis from regional hospitals with telemedicine intensivist support are on average fewer days in PICU than those who are assisted by clinician need – based telephone consultation.

SECONDARY HYPOTHESIS

- Critically ill pediatric patients with RSV bronchiolitis from regional hospitals with telemedicine intensivist support are on average fewer days hospitalized in total than those who are assisted by clinician need – based telephone consultation.
- Pediatric patients with severe RSV bronchiolitis from regional hospitals with telemedicine intensivist support develop fewer complications than those who are assisted by clinician need – based telephone consultation.
- The health care professionals from regional hospitals who receive telemedicine intensivist support with critically ill pediatric patients who suffer from RSV bronchiolitis are satisfied.
- The economic cost of pediatric patients with RSV bronchiolitis from regional hospitals with intensive care telemedicine support is lower than those who are assisted by clinician need – based telephone consultation.

7. OBJECTIVES

MAIN OBJECTIVE

- Compare the PICU length of stay (LOS) of critically ill pediatric patients with RSV bronchiolitis from regional hospitals who receive intensive care telemedicine to those who are assisted by clinician need – based telephone consultation.

SECONDARY OBJECTIVES

- Compare the total hospitalization LOS of critically ill pediatric patients with RSV bronchiolitis from regional hospitals who receive intensive care telemedicine to those who are assisted by clinician need – based telephone consultation.
- Analyze the complications of pediatric patients with severe RSV bronchiolitis from regional hospitals supported with intensive care telemedicine compared to those who are assisted by clinician need – based telephone consultation.
- Analyze the satisfaction of health care professionals in regional hospitals assisted by telemedicine intensivist support from referral centers when treating pediatric patients with severe bronchiolitis.
- Quantify the direct economic cost of pediatric patients with severe RSV bronchiolitis from regional hospital with telemedicine intensivist support compared to those who are assisted by clinician need – based telephone consultation.

8. SUBJECTS AND METHODS

8.1. STUDY DESIGN

A prospective randomized, controlled, multicentered, open-label clinical trial.

The study is designed to compare the application and non – application of a continuous telemedicine model in critically ill pediatric patients under 12 months with RSV bronchiolitis hospitalized in regional hospitals meanwhile they are not transferred to the referral center. All the patients will be treated following the current protocol, but one group will receive telemedicine support and the other will be assisted by clinician need – based telephone consultation, as it is done nowadays.

8.2. STUDY SETTING

The study will be carried out simultaneously in Girona, Camp de Tarragona and Terres de l'Ebre health regions.

The referral hospital of each region will do the intervention on their respective regional hospitals, as it is the only center with the resources to assist pediatric critically ill patients. The hospitals where the intervention will be implemented are the regional hospitals that do not have pediatric ICU assistance.

In Girona health region, the referral hospital is Hospital Universitari Doctor Josep Trueta, meanwhile in Tarragona and Terres de l'Ebre health region, it is Hospital Universitari de Tarragona Joan XXIII. The patients who are part of the basic referral hospital population will not be enrolled on the clinical trial as it is the center that does the intervention and applying telemedicine on them has no sense. According to data from *Table 3* and

Table 4*,* 21% of the total population of the Girona health region belongs to the basic population of Hospital Universitari Doctor Josep Trueta. In Tarragona and Terres de l'Ebre Health region, the proportion of the basic population that pertains to the referral center is around 26%.

The tables below (*Table 3* and *Table 4*) describe the characteristics of the hospitals included in the study: their localization, the distance in kilometers (km) to the referral

hospital using the shortest route and an approximation of the basic population that attends each hospital.

Table 3. *Characteristics of hospitals from Girona health region included in the study*

	Hospital	Localization	Distance (km)	Basic population
Referral hospital	Hospital Universitari Doctor Josep Trueta	Girona	-	159.633
Regional hospitals	Hospital de Figueres	Figueres	47,6 km	140.000
	Hospital de Palamós	Palamós	50,5 km	133.000
	Hospital d'Olot i comarcal de la Garrotxa	Olot	55,4 km	60.000
	Hospital de Santa Caterina	Salt	5 km	147.222
	Hospital de Campdevànol	Campdevànol	85,4 km	26.000
	Hospital Comarcal de Blanes	Blanes	46,1 km	100.000

Table 4. *Characteristics of hospitals from Camp de Tarragona and Terres de l'Ebre health region included in the study*

	Hospital	Localization	Distance (km)	Basic population
Referral hospital	Hospital Universitari Joan XXIII de Tarragona	Tarragona	-	200.000
Regional hospitals	Pius Hospital de Valls	Valls	22,8 km	64.000
	Hospital Universitari de Sant Joan de Reus	Reus	12 km	175.000
	Hospital del Vendrell	El Vendrell	35,4 km	73.000
	Hospital Sant Pau i Santa Tecla	Tarragona	4 km	86.806
	Hospital Verge de la Cinta de Tortosa	Tortosa	88,1 km	73.000

	Hospital Comarcal d'Amposta	Amposta	80,9 km	54.000
	Hospital Comarcal Mora d'Ebre	Móra d'Ebre	62,9 km	25.000

We will do two groups of regional hospitals in each health region for then randomly apply the intervention. The relevant hospital characteristics that we will consider for making the groups because are important when applying telemedicine, are:

- The level of complexity of the hospital, as the patients' assistance must be the same in all the hospitals to compare the intervention.
- The basic population that assumes the hospital, to have a comparable number of patients in each group.
- The kilometers between the regional and referral hospital, as patients will be transferred from one place to the other and the distance may be different between the centers compared.

Referring to the level of complexity, all the regional hospitals have the same possibilities when attending patients with acute bronchiolitis. Therefore, this aspect shall not interfere when making the groups as it is the same for all of them. Among the referral hospitals, Hospital Universitari Doctor Josep Trueta pediatric ICU has a level of complexity III, meanwhile Hospital Joan XXIII de Tarragona is level II. Therefore, it does not intervene on the care of patients with RSV bronchiolitis, which is the same in both hospitals, as all have the same resources for treating this type of pathology.

Considering the distance between the regional hospital and the referral hospital and the population that assumes each hospital, we have made two groups of hospitals in every health region as homogeneous as possible. However, it is much more important that the groups have a comparable population size than similar distance between the centers, as this second aspect will only interfere with a time variation of less than one hour at the most.

Several combinations of regional hospitals have been made according to the factors mentioned above to make the two groups in each health region. We selected the most

homogeneous groups, which are those shown in the following figures (*Figure 7* and *Figure 8*).

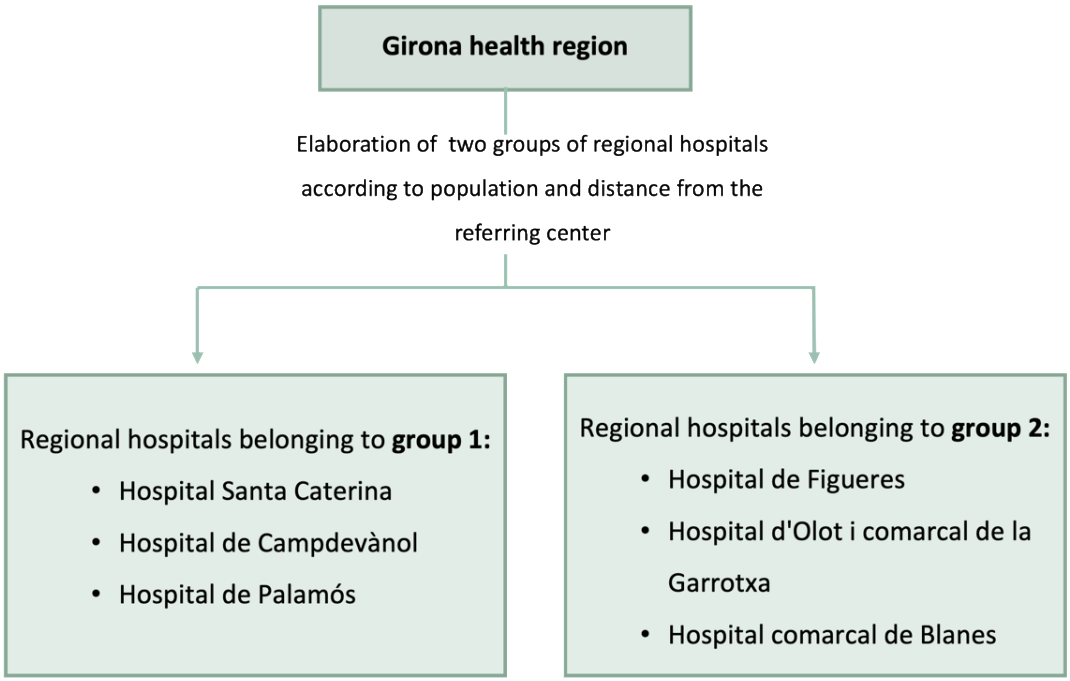

Figure 7. *Girona health region study groups*

In Girona health region, two groups of hospitals with similar population between them (300.000 inhabitants approximately) have been set up.

It is true that we put two regional hospitals with disparate distances in the same group, as Hospital de Campdevànol is far away, and Hospital de Santa Caterina is close to referral hospital.

Although, at the end, the difference of the time the ambulance takes to do the transferring between these two regional hospitals and referring center is only one hour apart and we do not expect this time interferes significantly, it is the best option. If they were in separated groups, the final conclusions could be falsely positive or negative depending on the intervention allocation. In this way, we ensure that this does not happen.

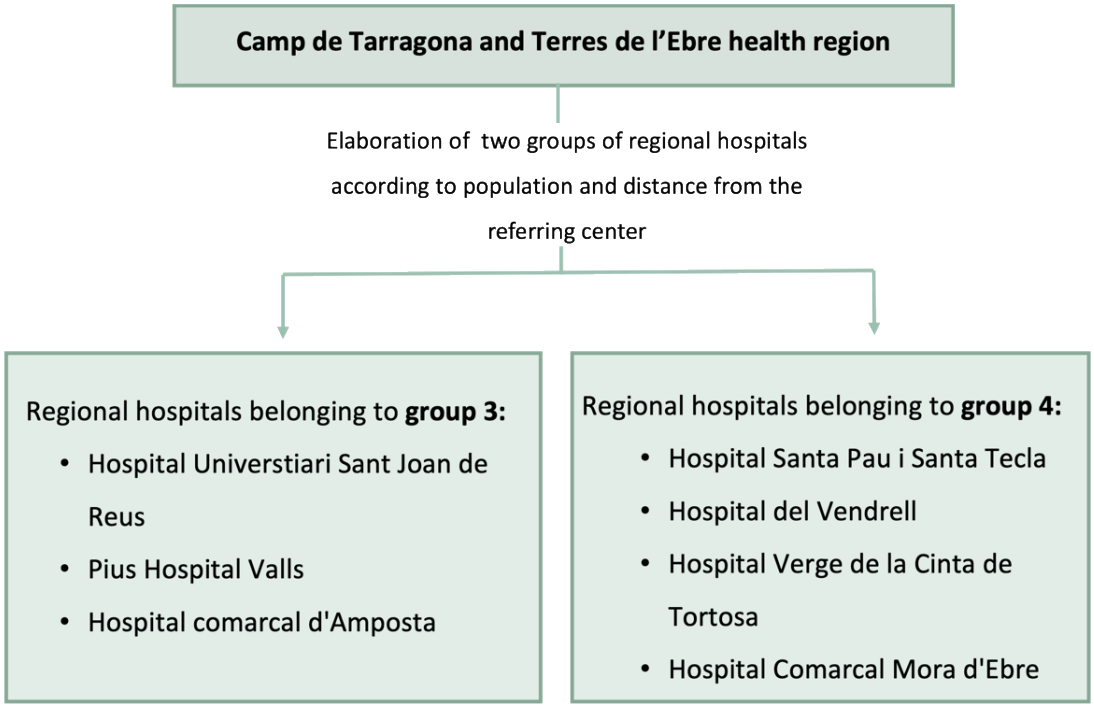

Figure 8. *Tarragona and Terres de l'Ebre health region study groups*

Both groups of regional hospitals in Camp de Tarragona and Terres de l'Ebre health regions have is a short-distance hospital (Hospital Universitari Sant Joan de Reus and Hospital Sant Pau i Santa Tecla), a medium-distance hospital (Pius Hospital de Valls and Hospital del Vendrell) and a long-distance hospital (Hospital d'Amposta and Hospital Verge de la Cinta de Tortosa). In addition, there is a group with a fourth hospital (Hospital Comarcal de Mora d'Ebre), which is also medium-distance hospital. Both groups attend an approximate population between 260.000 and 290.000 inhabitants.

8.3. STUDY POPULATION

The study population will include patients under 12 months from regional hospitals diagnosed with RSV acute bronchiolitis with criteria to be transferred to the referral hospital. Therefore, inclusion criteria will be based on indications for admission to PICU.

8.3.1. INCLUSION CRITERIA

- Patients aged under 12 months hospitalized in a regional hospital diagnosed with acute bronchiolitis caused by RSV and any of the following criteria:
    - Severe bronchiolitis (BROSJOD Score >10).
    - Important O_2 requirement: SaO_2 < 92% with a FiO_2 > 50%.

- Respiratory and/or metabolic acidosis with pH < 7,25.
- Extrapulmonary complications: arrhythmias, hemodynamic instability, dehydration, or severe electrolytic alteration.
- Rapidly progressive disease.
- Infants with recurrent apneas episodes, important lethargy or toxic appearance.
- Infant under 4 – 6 weeks old with a moderate bronchiolitis not responding to general measures.

8.3.2. EXCLUSION CRITERIA

- Patients aged over 12 months.
- Patients diagnosed with acute bronchiolitis not caused by RSV.
- Patients without parental or legal guardian authorization for participating in the clinical trial.
- Patients with any of the following high-risk factors for developing severe bronchiolitis:
  - Patients with congenital airways malformations
  - Patients with neuromuscular disorders.
  - Patients with hemodynamically significant congenital heart disease.
  - Patients with immunodeficiency diseases.
  - Patient with trisomy 21

8.3.3. WITHDRAWAL CRITERIA

Patients that at any time of the clinical trial meet an exclusion criteria because it was developed after his inclusion or it was not recognized previously and those whose parents present a revocation of the informed consent will be removed from the study.

8.4. SAMPLING

8.4.1. SAMPLE SELECTION

As RSV bronchiolitis is an acute disease and the incidence depends especially on environmental factors, it is impossible to predict the moment when an infant is going

suffer from a bronchiolitis. A non-probabilistic consecutive method of recruitment will be used in this study.

8.4.2. SAMPLE SIZE

There are no similar studies for the estimation of the size of the sample. The most analogous studies that exist are based on the application and non-application of telemedicine in the critically ill patient admitted to the ICU for pathologies with very high mortality rates. In the RSV, mortality is not remarkable, reason why it cannot be compared with these studies.

For this reason, we have relied on the recommendations of experts and non-published data from Hospital Universtiari Josep Trueta to calculate the sample.

We used GRANMO software to calculate the size of the sample for the clinical trial. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, **84** subjects are necessary in first group and **84** in the second to recognize as statistically significant a difference greater than or equal to 2 units. The common standard deviation is assumed to be 4.5. It has been anticipated a drop-out rate of 5%.

As the sample is based on approximate data, once we have information from approximately 20% of the patients, we will recalculate the sample size needed based on the mean and standard deviation of these patients for the main variable. In case we need more population to obtain the minimum difference deserved, we would include part of Catalunya Central and Barcelona health region, with Hospital Parc Taulí as the referral hospital and the respective regional hospitals (Hospital Sant Bernabé Berga, Hospital Althaia Manresa, Hospital Sant Celoni, Hospital Granollers, Hospital de Mollet, Hospital de Terrassa and Mutua de Tarrassa).

8.4.3. TIME OF RECRUITMENT

Time of recruitment has been estimated based on the data from 2019 before the pandemic, as RSV incidence was influenced because of Coronavirus (Sars – CoV – 2) infection the last year 2020.

In Girona health region, in 2019 there was a total population of 6.688 people aged < 12 months according to *Insituto Nacional de Estadística de España*. Considering that 21% of them belong to the basic population of Hospital Universitari Doctor Josep Trueta, the population under 12 months corresponding to the regional hospitals is around 5.283. According to epidemiological data, 75% of them will be infected in this first year of life, which corresponds to 3.962. Of these, 5% will require hospitalization, totaling 198 patients, of which 20% will require admission to the ICU, approximately 39 patients per year.

In Tarragona and Terres de l'Ebre health region, in 2019 there was a total population of 6.486 patients, of which 4.799 of them pertain to the regional hospitals. If we make the same calculations as we have done with Girona health region, we have that 3.599 of them are infected for RSV in the first 12 months, 179 require hospitalization and 35 of them will require pediatric ICU assistance.

Therefore, considering the required sample and the number of patients each year with the characteristics of the study, the time of recruitment need will be 2 years and a half.

8.5. STUDY VARIABLES AND MEASUREMENTS

8.5.1. INDEPENDENT VARIABLE

The independent variable is the intervention of the study, which is the application of a **telemedicine system** in patients with severe RSV bronchiolitis. It is a dichotomic nominal qualitative variable expressed as yes /no.

8.5.2. DEPENDENT VARIABLES

MAIN DEPENDENT VARIABLE

- The main dependent variable is the **total pediatric intensive care unit length of stay** in the referring hospital, from the time the patient arrives with the pediatric ambulance until is discharged at the hospitalization plant. It is a discrete quantitative variable measured in number of days.

SECONDARY DEPENDENT VARIABLES

- **Total length of stay in hospital**: From the day the patient from the regional hospital meets the inclusion criteria and the intervention is applied until the child is discharged at home, including the days hospitalized in pediatric ICU. We will not consider the days of hospitalization before the intervention is initiated. This is a discrete quantitative variable measured in number of days.
- Presence of pulmonary and extrapulmonary **complications** developed once the telemedicine system is initiated. It is a discrete quantitative variable, expressed in numbers from 0 to 9, which represents the sum of each of the following dichotomous nominal qualitative variables expressed with yes /no:
    - Apneas: Continuous monitoring will be very helpful for detecting apnea. Recurrent apneas are an alarm sign that the patient is worsening.
    - Dehydration: Tachycardia, delayed capillary refill, dry mucous membranes and sunken fontanelle are indicative of dehydration.
    - Bacterial coinfection: We will suspect it with a worsening of the patient's general condition and fever and increased CRP in the blood test.
    - Respiratory Failure: Physical examination will be essential to detect respiratory distress. If there is respiratory failure, arterial blood gas analysis will be very altered, with severe hypoxemia and, in some cases, hypercapnia.
    - Cardiovascular complications: It will be necessary a complete cardiological examination and electrocardiogram when we suspect ventricular tachycardia, ventricular fibrillation, pericardial effusion or myocarditis.
    - Hepatitis: In this case, we will find elevated transaminase levels and coagulation disorders on the blood test.
    - Hyponatremia: It will be necessary a blood test when we suspect electrolyte imbalance. Serum sodium levels under 135 mEq/L are abnormal.
    - Neurological alterations: Periodic neurological examinations will be required to detect central apnea, lethargy and tone abnormalities. In

some case it will be necessary an electroencephalogram to detect status epilepticus or encephalopathy.

- **Provider satisfaction**: The measuring instrument of the clinician's satisfaction is the Telehealth Usability Questionnaire (TUC) (*Annex 2*). It can be answered by both, professionals, and patients, but in this case the professionals of the regional hospital who takes care of the patient included in the study will be who fill it in according to their telecommunication experience with the referral hospital and the intensivist located there. It should be completed at the moment the patient is on the ambulance transferred to the referral hospital.

  It measures the usability in telemedicine valuating how useful it is for the members (usefulness), how easy or difficult is learning the system (ease of use and learnability), how good is the engagement with the technologies (interface quality) and the interaction with the referral center (interaction quality), the problem-solving capacity of the system (reliability) and the satisfaction of the user and future use of it. The answers of each question are 1 – strongly disagree, 2 – disagree, 3 – somewhat disagree, 4 – neither agree nor disagree, 5 – somewhat agree, 6 – agree and 7 – strongly agree. The final result will be the total of all the questions and the average. A higher result on the total score or a good overall average indicates a greater degree of satisfaction and usability of the telemedicine technology of the professionals who use it. It is a discrete quantitative variable, measured with a numeric punctuation.

  The Telehealth Usability Questionnaire has a strong validity as it includes the most relevant items from other studies validated used previously. It will be necessary to translate it into Catalan by experts and validate it before being answered.

- Direct **economic cost** of the total hospitalization days: It is a continuous quantitative variable measured in euros (€). It will be calculated as the average of the sum of the cost per patient of the hospital days. A bed in a PICU costs approximately 1400 euros/day, meanwhile a bed in a pediatric hospital costs approximately 310 euros/day, including laboratory and imaging, use of oxygen, medical supplies, health professional who are attending and blood transfusions, among others.

8.5.3. COVARIABLES

The probability that a VRS bronchiolitis causes greater affection is conditioned by:

- **Patient susceptibility**:
    - Sex: It is a dichotomous nominal qualitative variable, expressed in male or female.
    - Age: It is a discrete quantitative variable, expressed in months.
    - Low birthweight: Patients born with a weight under 2.500 gr. It is a dichotomic nominal qualitative variable, expressed with yes / no.
    - History of prematurity: patients born with a prematurity < 32 weeks' gestation. It is a dichotomic nominal qualitative variable, expressed with yes / no.
    - Chronic lung disease: presence of bronchopulmonary dysplasia or cystic fibrosis. It is a dichotomous nominal qualitative variable, expressed with yes/no.

- **Time** since the transfer is requested in the regional hospital until the patient arrives at the referral hospital, as it is the time the intervention is applied. It is a discrete quantitative variable, expressed in hours.

Table 5. *Characteristics of the variables*

	Variable	Type of data	Categories or values	Measuring instrument
Independent variable	Continuous telemedicine model	Dichotomic nominal qualitative variable	Yes / No	Use of the intervention
Dependent variable	Total ICU LOS	Discrete quantitative variable	Number of days	Case report form
Secondary dependent variables	Total LOS	Discrete quantitative variable	Number of days	Case report form
	Complications	Discrete quantitative variable	Number of complications	Physical examination, blood test or imaging.
	Provider satisfaction	Discrete quantitative variable	Questionnaire	TUC Questionnaire
	Economic cost	Continuous quantitative variable	Euros (€)	Case report form
Covariables	Sex	Dichotomous nominal qualitative variable	Male / Female	Medical history
	Age	Discrete quantitative variable	Months	Medical history
	Low birthweight	Dichotomic nominal qualitative variable	Yes / No	Medical history
	History of prematurity	Dichotomic nominal qualitative variable	Yes / No	Medical history
	Chronic lung disease	Dichotomic nominal qualitative variable	Yes / No	Medical history
	Time since the transfer is requested until the patient arrives at the referral hospital.	Discrete quantitative variable	Hours	Case report form / medical history

8.6. STUDY INTERVENTION

8.6.1. ENROLLEMENT

The patients with RSV bronchiolitis from the regional hospital who reunite the inclusion criteria and do not have any exclusion criteria will be considered for the clinical trial. Their parents or legal guardians will be informed about the possibility to participate in the clinical trial. It will be explained to them what it is about, what it involves and the consequences that it has and we will provide them the information document *(Annex 3)* If progenitors accept and sign the informed consent (*Annex 4),* the patient will enter in the clinical trial.

Patients will be selected following a non – probablisitic consecutive method.

8.6.2. RANDOMIZATION AND MASKING TECHNIQUE

The clinical trial will be executed simultaneously in Girona, Camp de Tarragona and Terres de l'Ebre health region. In each province, two groups of regional hospital will be done considering the population assumed and the distance from the two hospitals connected.

All the patients with acute bronchiolitis will be treated according to the protocol from *Sociedad Española de Neumologia Pediátrica*, but depending on the regional hospitals they are hospitalized, they will receive telemedicine intensivist support or clinician need – based telephone consultation from the referral hospital.

Whether a group of hospitals from a health region is assisted by clinician need – based telephone consultation or telemedicine intensivist assistance will be randomly selected:

- The control group (**group A**) is formed by patients from regional hospitals assisted with need – based telephone consultation, as it is done nowadays.
- The experimental group (**group B**) are patients from regional hospitals assisted with a continuous care model of telemedicine.

In *Figure 9* the randomization of the intervention is schemed.

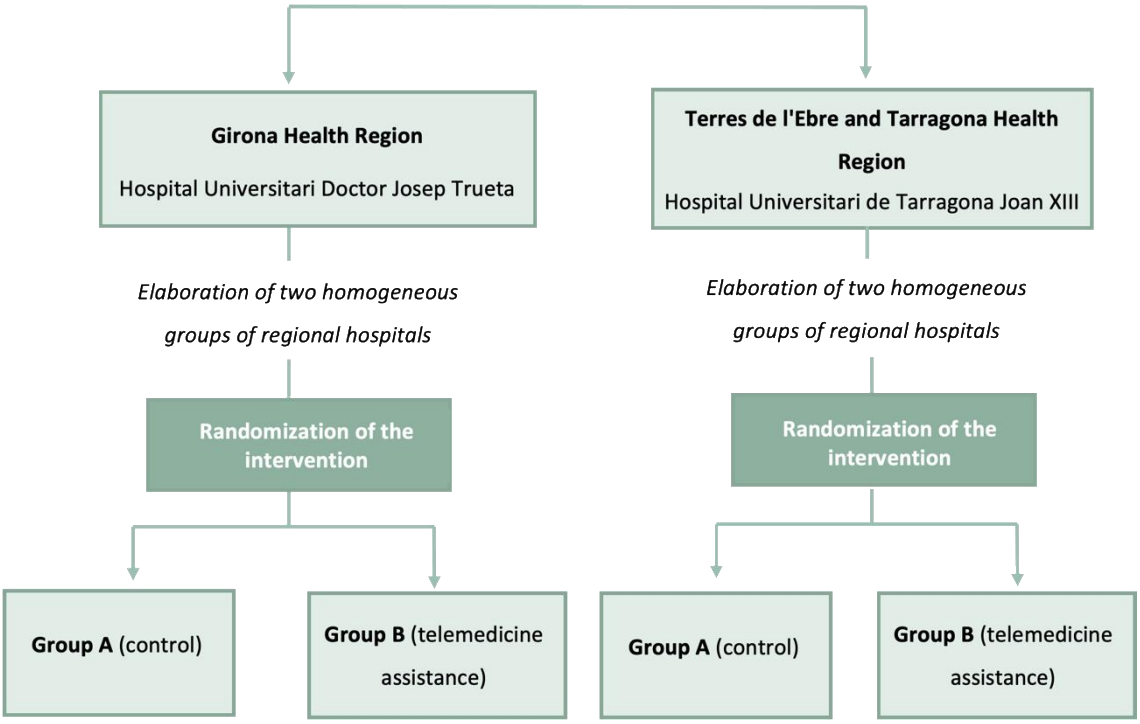

Figure 9. *Randomization of the intervention*

Our study will be open – labelled as the intervention is telemedicine and it is necessary to use several technological devices. Therefore, health professionals will know which patients receive the assistance, and the parents of the patients too.

8.6.3. INTERVENTION

It will be necessary that those patients included in the clinical trial are diagnosed of RSV infection using FilmArray™, a respiratory panel that uses multiple PCR to detect the causal agent. In a very quickly way it analyzes up to 20 of the most common pathogens implied in respiratory infections.

At the moment it is indicated the transferring of a critically ill pediatric patient with RSV bronchiolitis from a regional hospital to referral center because there is a criteria to be admitted in the PICU and pediatric EMS is notified, the intervention is initiated.

Clinician needed – based telephone consultations (**group A**) or a continuous telemedicine model (**group B**) with referral hospital will be carried out while the patient hospitalized in the regional hospital is waiting for the pediatric ambulance, time that can take up to 24 - 48 hours during seasonal RSV outbreaks.

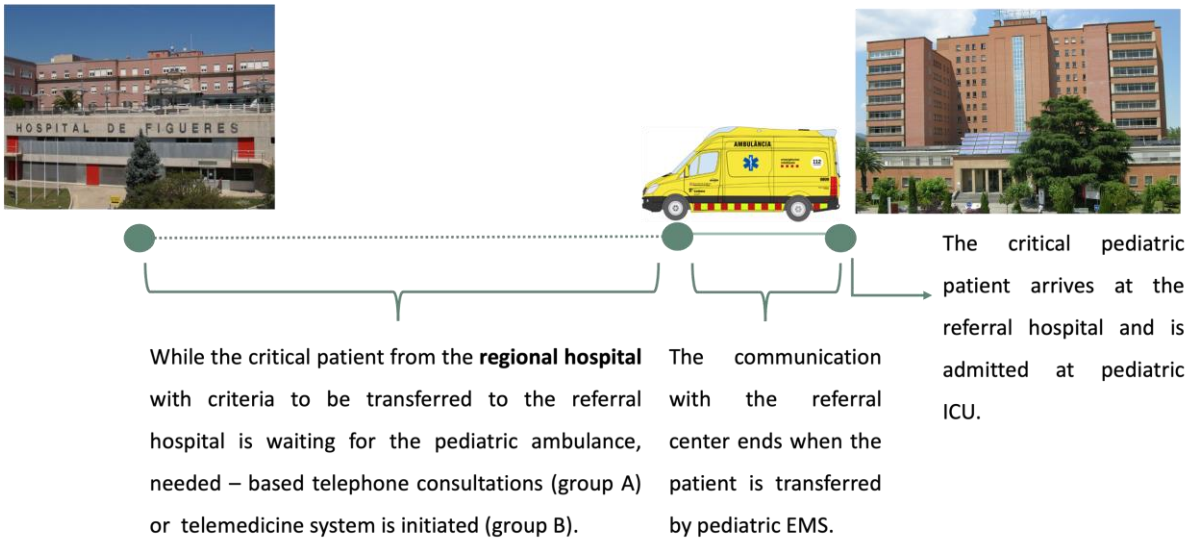

Figure 10. *Overview of the intervention*

The patient will be always managed according to the current protocol for acute bronchiolitis. It is based on supporting measures, hydration, and respiratory assistance according to patients' requirements. In specific cases or as a rescue, pharmacological treatment can be used too *(Annex 1).*

Once the pediatric ambulance takes the child to the referral hospital, the patient will be admitted to the PICU.

8.6.3.1. NEEDED – BASED TELEPHONE CONSULTATION VS TELE – ICU ASSITANCE

Meanwhile a patient from a hospital that is part of group A is not transferred to the referral hospital because the pediatric ambulance system is saturated, health care professionals from regional hospitals that are in charge will be assisted by telephone if they have any consultation. They will be able to call the intensivist on call from the referral hospital of the region to solve specific doubts, as it is done nowadays.

It will not be possible for the expert to see the patient by videoconference or have the continuous monitoring of the patient, but it will be useful.

8.6.3.2. TELE – ICU ASSITANCE

When a patient pertaining of a hospital from group B meets the inclusion criteria and requires ICU assistance, a pediatric critical care telemedicine program based on a

continuous model will be initiated util the patient is transferred by the pediatric EMS, connecting the regional hospital to the referral hospital.

The intensivist on duty at the referral hospital will observe the patient's appearance by videoconference, will have available all the radiological images taken through the platform and dispose of all the vital parameters displayed through the monitor. In addition, the intensivist in charge will be able to see all the patient's medical history using shared clinical history. As mentioned above, patient follow-up will be continuous.

The health professionals that are at patient's bedside will provide all necessary information from the physical exploration needed and will follow the instructions about the management of the patient from the expertise who is in the referral hospital until the patient is transferred by pediatric ambulance.

The **technological equipment** needed will be different depending on the type of center:

- In the referral center, two screens (one for the patients' medical history and monitoring and another for videoconferencing), a computer, a webcam and audio source will be essential.
- In the regional hospital it will be necessary a computer, a web cam, audio source and a monitor with the vital parameters of the patient homologated with the program.

It will be essential that both centers have a good internet connection to enable the exchange of information.

The telemedicine **software** that is going to be employed is *Idonia*, which is the same that is being used in many hospitals in Catalunya for Tele – Ictus. In fact, it is already implemented in centers included in our clinical trial, such as Hospital de Figueres, Hospital de Palamós, Hospital de Campdevànol and Hospital Comarcal de Mora d'Ebre.

The system offers videoconference and all the radiological images of the patient available. Moreover, we will homologate ICU monitors with *Idonia* software in order to obtain information of all vital parameters. The vital constants that will appear on the

monitor because are necessary for the follow-up of the acute RSV bronchiolitis patients are:

- Heart rate and respiratory rate
- Blood pressure
- Body temperature
- Electrocardiogram waveform
- Oxygen saturation
- In the most critical patient, it will be also necessary hemodynamic monitoring using the radial artery and a central venous catheter for information of the central venous pressure.

We have chosen this system because the fact that it is already being used in other acute pathologies such as stroke provides guarantees of safety and operation. Moreover, it is already implemented in many of the hospitals that are part of our clinical trial and therefore the economic cost will be lower.

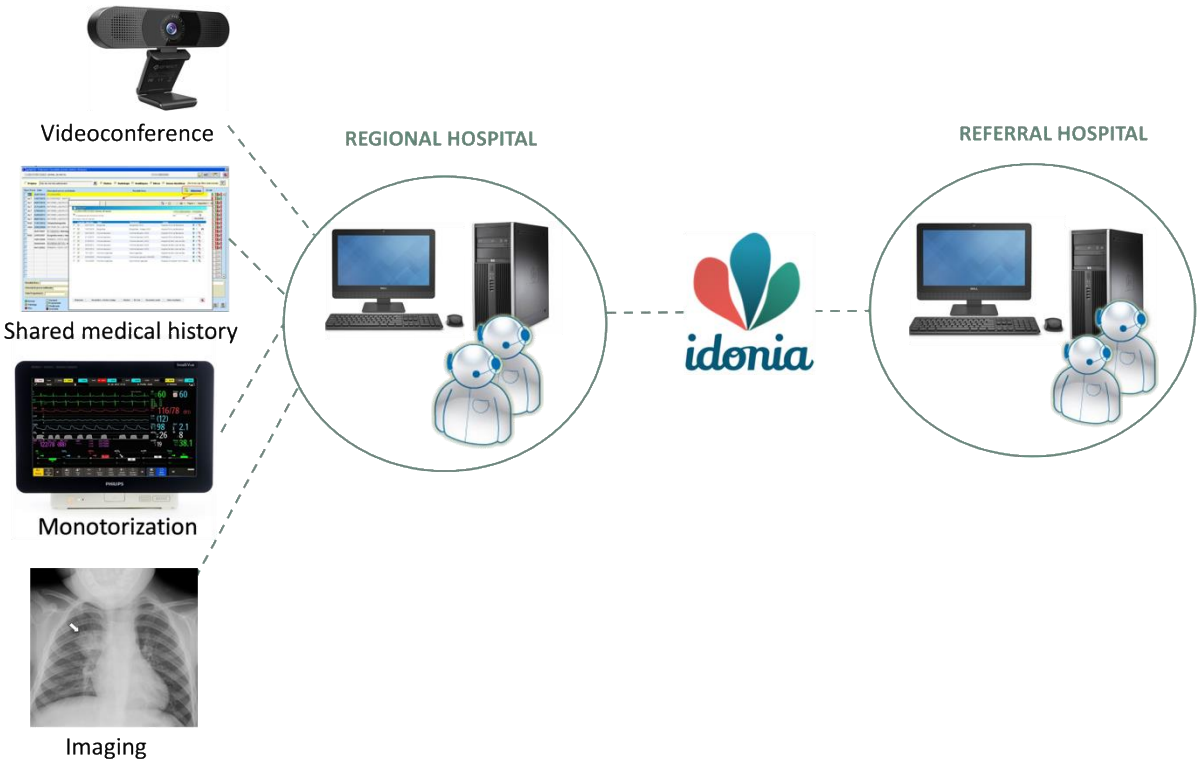

Figure 11. Intervention outline. Adapted form Cas Xarxa TeleIctus.

Using this design of Tele – ICU assistance, it will be necessary a 24 – hours attending **health professionals** who are on call, including the team of clinicians and nurses on the

regional center and two intensive physicians in the referral center. Therefore, there will be no need of more health professionals than the ones who are working on that moment.

All those professionals involved in the telemedicine assistance will receive a training before the clinical trial starts in order to acquire the abilities to manage the platform and handle with technology. However, each hospital's IT staff will be available for any problems that may arise when assisting patients with RSV bronchiolitis through telemedicine.

8.6.4. FOLLOWING – UP

8.6.4.1. TRANSFERRING WITH PEDIATRIC EMS

Two advanced pediatric specialized ambulances, one located at Hospital de la Vall d'Hebron and the other at the Hospital Sant Joan de Déu, are available 24 hours a day, 365 days a year. During the period of bronchiolitis (from December to March) a third ambulance is added. In periods of RSV highest incidence, it can take 24 - 48 hours for the pediatric EMS to do the transferring, as the system is at full capacity, and they are derived from Barcelona. Is during this time when we will carry out the intervention explained above to avoid delay in treatment.

Once the pediatric ambulance arrives at the regional hospital, the inter – transferring is very fast. All patients of both groups (**A** and **B**) will be taken by pediatric ambulance to the referral hospital of their region, as they have criteria to be assisted in a PICU for definitive treatment.

The stabilization of a child with severe bronchiolitis involves the work of a multidisciplinary team of healthcare professionals in the ambulance, including the pediatric medical transport technician, pediatric nurse, and pediatric intensivist. The ambulance cabin is equipped with specific material for this type of transport, for the monitoring, respiratory and hemodynamic support assistance.

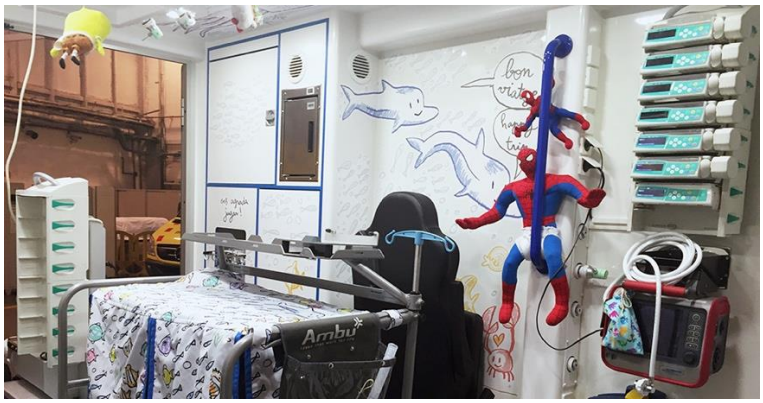

Figure 12. *Pediatric EMS equipation. Source: Hospital Sant Joan de Déu webpage*

8.6.4.2. TREATMENT AT REFERRING HOSPITAL ICU

At the moment the patient arrives at the referral hospital with the pediatric ambulance, he will be admitted to the pediatric ICU and treated according to the current protocol for acute bronchiolitis (*Annex 1*).

8.7. DATA COLLECTION

The elaboration of a database with the most relevant demographic, social and clinical variables will be a fundamental for evaluating the intervention and quantify its results later. All this information will be registered on the case report form (*Annex 5*) whether the patient who meets the inclusion criteria receive need – based telephone consultation or telemedicine assistance.

Professionals from the referral hospitals will be trained on how to fill in the case report form at the first meeting, so that there is no confusion on any aspect, and everyone do it equal.

The information needed to fill in the case report form meanwhile the patient is hospitalized is:

- Patient's affiliation: sex and age (months)
- Medical history: low birth weight, prematurity, chronic illness history.
- Complications once the patient is included on the study.
- Hour and day telemedicine or needed – based telephone consultation is started and the moment the patient arrives at the referral hospital.
- Number of days of hospitalization and ICU admission

A system will be set up to automatically upload the data collected by the coordinator of the research of each hospital on an excel every week for a later analysis.

Figure 13. *Summary of the data collection*

8.8. FLOW CHART

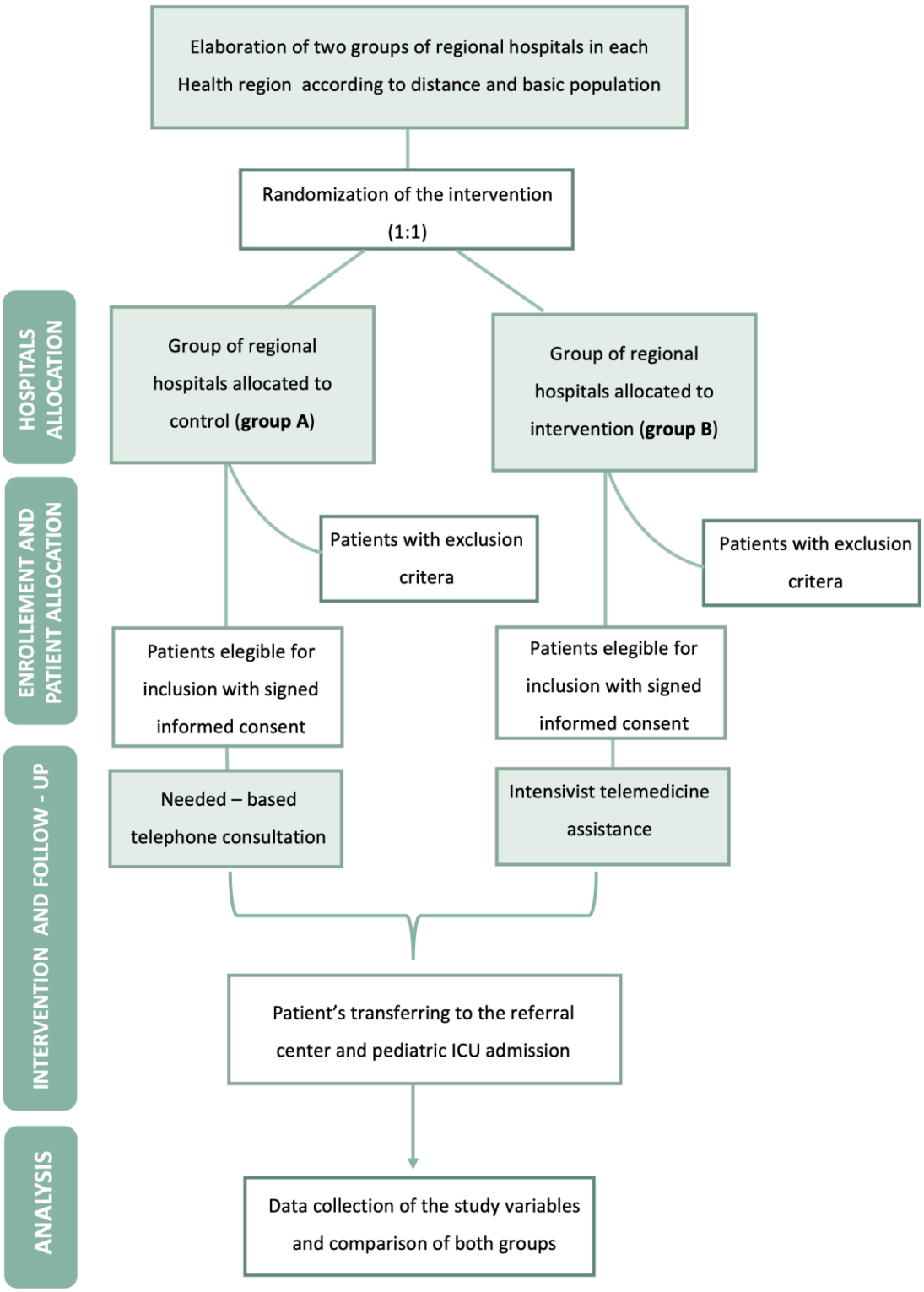

Figure 14. *Summary of the clinical trial process*

8.9. SAFETY

Telemedicine is a safe intervention, with no severe harmful effects for the patient. The main side effects are fears about decreased care quality, the exposition of medical data, the inability to examine patients, and poor providers experience.

Nevertheless, in our case, the application of telemedicine is an added support to regional hospital care, in order to complement those deficiencies that may appear when treating the critically ill patient with the assistance of intensivists who have more experience. Therefore, it is not a substitute for the human tract, but an addition.

The protection of medical data is guaranteed with the use of a private network and encrypted channels. The telemedicine software used for the information exchange in this clinical trial complies with all current regulations and it is already being used for attending patients with stroke in many hospitals in Catalunya, an aspect that provides us security guarantees.

Moreover, although the physical examination of the critically ill patient at distance is difficult, there will be health care professionals on the bedside of the infant that ensure it and assists the needs of the intensivist from the referral center.

In addition, to avoid problems with the functioning of the application, the training of the professionals who will work with it will be essential.

Although mortality rate among patients with RSV bronchiolitis is very low and we do not expect to find differences whether telemedicine is applied or not, we will document the deaths among patients with RSV bronchiolitis of both groups.

9. STATISTICAL ANALYSIS

The analysis of the data obtained will be done by a statistician, who will do the investigation blinded so that he does not know which group has received telemedicine assistance and it does not interfere with the final result.

The software used will be Statistical Package for Social Sciences (SPSS) software. A p-value <0.05 will be considered statistically significant.

9.1. DESCRIPTIVE ANALYSIS

In both groups, the statistician will describe the quantitative variables using mean and standard deviation for parametric distribution and median and interquartile range for non- parametric distribution. Qualitative variables will be described using proportions with a 95% confidence interval.

9.2. BIVARIATE ANALYSIS

The statistician will include all the significative variables in a bivariate analysis:

- We will use t-Student or Mann-Whitney tests to study if there are differences depending on whether telemedicine is used or not with quantitative variables (total ICU LOS, total LOS, complications, provide satisfaction, and economic cost), depending on if they follow or not a parametric distribution, respectively.
- We will use a chi-square contrast test for the association of using telemedicine or not using it with qualitative variables (assessment of individual complications).

9.3. MULTIVARIATE ANALYSIS

It will be necessary to do a multivariate analysis adjusting the independent variables with the dependent variable according to the covariates that can interfere in our results to avoid possible confusion.

A multiple linear regression model will be used for the association of the intervention with quantitative variables and a logistic regression model for the association of the intervention with the assessment of individual complications.

10. ETHICAL AND LEGAL CONSIDERATIONS

The clinical trial will be performed according to the fundamental ethical principles for medical research, collected in the **Declaration of Helsinki**, developed by the World Medical Association (WMA) in June 1964 and amended lately in October 2013. The clinical trial obeys the four fundamental ethical principles:

- The principle of **autonomy**: In this case, the study participants are minors and therefore, the autonomy lies to parents or legal guardians. They will be the ones who decide whether their child participates in the clinical trial or not through the informed consent after being informed about all the details of the clinical trial and read the information document.
- The principle of **beneficence**: All the patients with acute bronchiolitis will be treated according to the current protocol from *Sociedad Española de Neumología Pediátrica*, but one group of patients will receive an additional telemedicine support. All the procedures will be done in order to obtain the maxium benefit for the patient.
- The principle of **non – maleficence**: Studies demonstrate telemedicine has no harmful effects on patients. At most, some indicate that it makes no difference whether it is used or not. The study intervention does not involve an invasive procedure for the patient. The intervention will be always executed without causing prejudice to the patient.
- The principle of **justice**: All the patients from public regional hospitals from Girona, Tarragona and Terres de l'Ebre health regions who meet the inclusion criteria and do not have any exclusion criteria will have the possibility to enter in the clinical trial if their parents or guardians agree. The patients who are part of the basic population of the referral center and so they are attended there, will not be considered to the study but because they have directly access to the resources needed for the attention of critically ill patient.

Moreover, we will act following the current European Union and Spain **legislation** that empowers and protect the rights of the patients:

- The confidentiality and privacy of the patient is guaranteed through ***Ley Orgánica 3/2018****, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales* (LOPDD) and ***Regulation (EU) 2016/679 of the European Parliament and of the Council*** *of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.*
- The parents' decision whether or not their child participates in the clinical trial will be respected as it indicates ***Ley 41/2002****, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica.*
- The application of the telemedicine assistance will be done according to ***Real Decreto 1090/2015****, de 4 de diciembre, investigaciones clínicas con productos sanitarios.*

The software used for the telecommunication between hospitals in the clinical trial, *Idonia,* is a secure platform that uses an infrastructure certified by National Security Scheme as High Level and complies with all the security and privacy requirements of the European General Data Protection Regulation (GDPR) and LOPDD local regulations. The respect for the dignity of the patient will be always imposed over technology when using technology. Telehealth policies should be guided by general ethics, and the polices mentioned ensure the fundamental principles and requirements for data protection.

At hospital level, the clinical trial will be presented to **Comitè d'Ètica d'investigació Clínica** (CEIC) from Hospital Universtiari Doctor Josep Trueta and all the others centers involved. Its approval will be needed and all the suggestions from CEIC will be considered before starting the clinical trial.

All the members of the clinical trial will sign a document as they are agree with the ethical aspects of the clinical trial and that there is no conflict of interest.

The parents or guardians of all the patients who participate on the clinical trial must be informed about the clinical trial, the information document will be given to them *(Annex 3)* and informed consent must signed to authorize the participation of their son in the clinical trial (*Annex 4).* According to ***Artículo 156 del Código Civil,*** the informed consent document will be valid if it is signed by one parents with the express consent of the other.

The parents or legal guardian should be informed that they can abandon the study if they wish to do so at any time through the revocation of the informed consent.

11. WORK PLAN

The whole study will have an estimated duration of three years and 11 months. The personnel essential in the different stages of the clinical trial include:

- **Main investigator** (MI): Is the person leading the clinical trial, who is in contact with the coordinators of each hospital and makes sure that everything goes as it should. The MI will be an intensivist from HUDJT.
- **Hospital coordinators** (HC): In all the hospitals (both referral and regional centers) there will be a coordinator who collect the data and makes sure that the whole procedure is being done in the correct way in his center.
- **Health care professionals** (HCP): Include the intensivist, doctors and nurses from the referral hospital who are on call and carry out the intervention and collect the patients' data and the professionals fom the regional hospitals where the patient is located.
- **Other staff**: Include IT personnel needed in case of system problems and the statistician (Stat) who analyzes the data.

The stages and activities done on the clinical trial will succeed according the following order:

- **STAGE 1 – Elaboration of the protocol and study design**
    - Activity 1 (October - November 2021). Bibliographic research and protocol elaboration: It is necessary to look for information of the more recent telemedicine models and elaborate the protocol for executing the clinical trial.
    - Activity 2 (December 2021). Regional hospitals participating contact: The main investigator will propose to the hospitals selected in the clinical trial to participate in it.
    - Activity 3 (December 2021). Agreement with *Idonia*: It will be necessary to establish a contract with the software company used for telecommunication.

- Activity 4 (December 2021): Translation of the satisfaction questionnaire into Catalan and Spanish.

- **STAGE 2 – Ethical approval** (December 2021 - January 2022)
  - Activity 5. CEIC evaluation and approval: The main investigator will present the protocol to *Comité Ètic d'Investigació clinic* (CEIC), in Hospital Universtiari Doctor Josep Trueta, and subsequently, to all the centers participating in the clinical trial for the ethical approval. Any suggestion form CEIC will be considered and modified.
- **STAGE 3 – Coordination and health professionals training** (February – March 2022)
  - Activity 6 (February 2022). Research team of each hospital meeting and election of the hospital coordinator: The research team of each regional and referral hospitals included in the study will meet and decide who will be the hospital coordinator of each center.
  - Activity 7 (March 2022). Formation sessions: The training of all the members who will use telemedicine is essential before the intervention starts.
- **STAGE 4 – Sample recruitment, intervention, and data collection** (Apr 2022 – October 2024)
  - Activity 8. Randomization of the intervention: The two groups of hospitals from each health region will be randomly allocated to control or experimental group by a statistician.
  - Activity 9. Patient recruitment: The patients will be included in the study using a non-probabilistic consecutive method. It is important to highlight that RSV is a seasonal virus so between October and March we will have a significant proportion of patients.
  - Activity 10. Intervention and follow-up: The pediatrician from the regional hospitals and the intensivist from the referral center will be the ones in charge of applying the intervention. At the moment the patient is transferred to the referral center, the intensivist who firstly assisted the infant will do the follow – up during the hospitalized days.

- Activity 11. Data collection: The case report form will be filled in for every patient included in the clinical trial by the health professionals in charge. The coordinator of each hospital will collect the information and upload it.

- **STAGE 5 – Data analysis and interpretation** (November 2024 – February 2025)
  - Activity 12 (November – December 2024). Statistical analysis: Once we have all the data from the patients, a statistician will do a descriptive, bivariant and multivariant analysis and an interpretation of the data obtained.
  - Activity 13 (January - February 2025). Results and conclusions: The statistician will present the results to the research team, who will discuss the outcomes and draw conclusions.
- **STAGE 6 – Results publication and dissemination** (March - September 2025)
  - Activity 14 (Març - June 2025). Final Article publication: The main investigator will write the final article. It will be edited and supervised by English correctors and published afterwards.
  - Activity 15 (July - September 2025). Dissemination: We will present the article in *Societat Catalana de Pediatria* and *Associación Española de Pediatría* (AEP).

12. CHRONOGRAM

Table 6. Clinical trial chronogram. *MI, main investigator; HC, hospital coordinators; HCP, health care professionals; Stat, statistician.*

STAGES	STAFF	YEARS																																													
		2021			2022												2023												2024												2024								
		O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S
STAGE 1																																																	
A1. Protocol elaboration	MI																																																
A2. Participating hospitals contact																																																	
A3. Agreement with Idonia																																																	
A4. Questionnaire translation																																																	
STAGE 2																																																	
A5. CEIC evaluation and approval	CEIC																																																
STAGE 3																																																	
A6. Research team meeting	MI, HC																																																
A7. Formation sessions																																																	
STAGE 4																																																	
A8. Randomization of the intervention	HC, HCP																																																
A9. Patient recruitment	Stat.																																																
A10. Intervention and follow - up	HCP																																																
A11. Data collection	MI, HC																																																
STAGE 5																																																	
A12. Statistical analysis	Stat.																																																
A13. Results and conclusions	MI, HC																																																
STAGE 6																																																	
A14. Final article publication	MI, HC																																																
A15. Dissemination																																																	

13. BUDGET

When doing the budget, we will have to consider the following expenses, detailed in the table above (*Table 7*).

Personnel expenses

The health care professionals who will attend the patients are the ones that are on call every day and are part of the National Health System. We will not need more clinicians than the ones who are in the service working, so this will not suppose additional cost.

It will be necessary the support from the hospital's IT staff in case there is a problem with network connection.

We will hire a qualified statistician to analyze the data collected and draw conclusions. The salary will be 35 €/hour and approximately 100 hours of work will be necessary.

Coaching the professionals involved in the clinical trial on telemedicine by experts will be necessary in order all members have the ability to use technologies. In addition, instructions of how to fulfill the case report form will be done to unify criteria.

Contact research organization (CRO)

It will be necessary to contact with a CRO that supervises certain clinical trial aspects and coordinate the different centers involved on the project, as it is a multicentered clinical trial.

Liability insurance

We will have insurance covering for those cases where it may be necessary. As our intervention is non-invasive, it will not be very high.

Execution expenses

Although all hospitals have already the technological devices required, it will be necessary to purchase two equipment per center that are exclusively for telemedicine assistance. Each equipment includes a computer, screen, webcam and audio system. The referral center will have an accessory screen (one for videoconferencing and the

other for the patient's monitoring and medical history). Two ICU vital sign monitors will be homologated to the software in each regional hospital. We will also have to pay the licensing fees for the software *Idonia*.

In total there are 15 hospitals participating in the clinical trial, and only half of the regional centers will be telemedicine assisted by the referral center. So, it will be necessary to buy equipment for 7 regional hospitals and 2 referral centers.

There will be no extra financial costs for the treatment of the patient, as the transfer by pediatric ambulance will be done as usual and the admission to the ICU with all the necessary support and follow - up too.

Consumables

It will be necessary to print copies of the information document and informed consent to give to the families. Copies of case report form will be necessary for the researchers who are involved on the clinical trial for the documentation of the findings. We will also have to pay the license of SPSS statistics program.

Publication and diffusion costs

We will consider all the publication expenses (article revision and edition) and the costs for assisting to AEPED national congresses in order to disseminate the results.

Table 7. *Budget details*

Type of cost	Description	Unit cost	Hours or units	Total
Personnel expenses	On call intensivist and nurses	0€/h	-	0 €
	Hospital coordinators and main investigator	0€/h	-	0 €
	IT specialist	0€/h	-	0 €
	Statistician	35,00 €/h	100 hours	3.500 €
	Research assistance team training	-	-	2.000 €
Execution expenses	ICU vital sign monitor for homologation	487,00€ /unit	14 (2 monitors x 7 hospitals)	6.818 €
	Equipment set Screen Computer, keyboard and mouse Web cam	 109,00 € 349,00 € 23,00 €	18 (2 equipment set x 9 hospitals)	8.876 €
	Licensing fees *Idonia* software	1.000 €	9	9.000 €
Consumables	Printings	0,03€	160 copies x 3 documents	50 €
	SPSS license	-	-	200 €
CRO	-	-	-	20.000 €
Trial policy	-	30 €	168 patients	5.040 €
Study publication and dissemination expenses	Article publication	-	-	1.500 €
	National congress	1.500€	2	3.000 €
TOTAL				59.984 €

14. FEASIBILITY

As the study analyses the impact of telemedicine, the clinical trial has to be multicentered, including regional and referral hospitals, between which we will establish telecommunication.

The time of recruitment of the sample needed is two years and a half, a short – period that will not allow technology used become outdated.

The clinical trial will be executed by a group of experts with research experience. The members carrying out the intervention will be trained in technology and software used. In case they have any problem when using the program, they will have IT team from their hospital at his disposal.

Apart from the statistician, we will not hire additional personnel. The health care professionals who do the intervention will be the same doctors and nurses who are on call.

Regarding the technological equipment needed to carry out the intervention, two computers will be purchased for each hospital doing telemedicine. Although it is likely that hospitals already have such equipment, it is important that there are two for telemedicine patient care, so that no infant in the hospital is left without support just because there is no equipment available.

As it is mentioned before, the software contracted for telemedicine application is already used in some of the hospitals included in the clinical trial for other pathologies, such as stroke. This is a plus point as there is already knowledge of the program among professionals, especially computer scientists who install it.

15. LIMITATIONS OF THE STUDY

Although RSV infection is such a common pathology and there is a significant number of patients each year hospitalized because RSV bronchiolitis, the total number of patients admitted in the pediatric ICU of a referral hospital in a single health region is not enough for studying the impact of telemedicine. For this reason, we included hospitals from Girona, Tarragona and Terres de l'Ebre health region in the clinical trial.

The regional hospitals included in the study have different distances from the referral hospital, with a maximum ambulance transferring time difference between them of less than an hour, which is almost negligible. Moreover, the study is based on a pathology caused by a seasonal virus, so the number of patients affected by RSV depends on the incidence and geographical area. For this reason, the basic population of each hospital and the distance between the referral and regional hospitals has been considered for the elaboration of two comparable groups of hospitals in each health region. Thus, the allocation of which group is attended by need-based telephone consultation or intensivist telemedicine has been done randomly.

This clinical trial analyses the impact of telemedicine on the most severe cases of bronchiolitis, reason why the results cannot be extrapolated to the outpatient. However, among the patients admitted in pediatric ICU, the sample is heterogeneous, representing a diversified rang of infants under 12 months.

The time of the intervention is not homogeneous in all patients, as it depends on the time it takes for the ambulance to arrive at regional hospital and therefore on how saturated the system is. However, this factor has been considered as a co-variable and will also be analyzed in the multivariate study.

The clinical trial is open – label, as health care professionals as well as and patients and families are aware of the intervention. However, the statistician will do the analysis will be blinded.

16. CLINICAL AND HEALTHCARE IMPACT

Bronchiolitis is a common pathology that causes a significant number of hospitalizations among the pediatric patients and many admissions in the pediatric ICU. During the period of RSV highest incidence, hospital pediatric wards are about to reach maximum capacity because of this infection.

Therefore, a telemedicine intensivist support meanwhile the critically ill patient is not assisted in the referral center because pediatric EMS is oversaturated could have an important effect on the patients' health. In some cases, it can take up to 24 - 48 hours, a period necessary to stabilize the child and avoid a worsening of his condition.

It could have a great impact on the health system, reducing the length of stay and so, the economic cost. Consequently, it would improve the flow of patients and the hospitals will not run full of capacity during the period of high incidence.

In addition, the professionals of the regional hospitals, who are not used with the management of the critically ill patient would feel more comfortable as they will be supported with experts in the matter.

The telemedicine system, once implemented, could also be used in other pathologies in the pediatric service, as it is not implemented used in any pediatric subspeciality in the health region of Girona.

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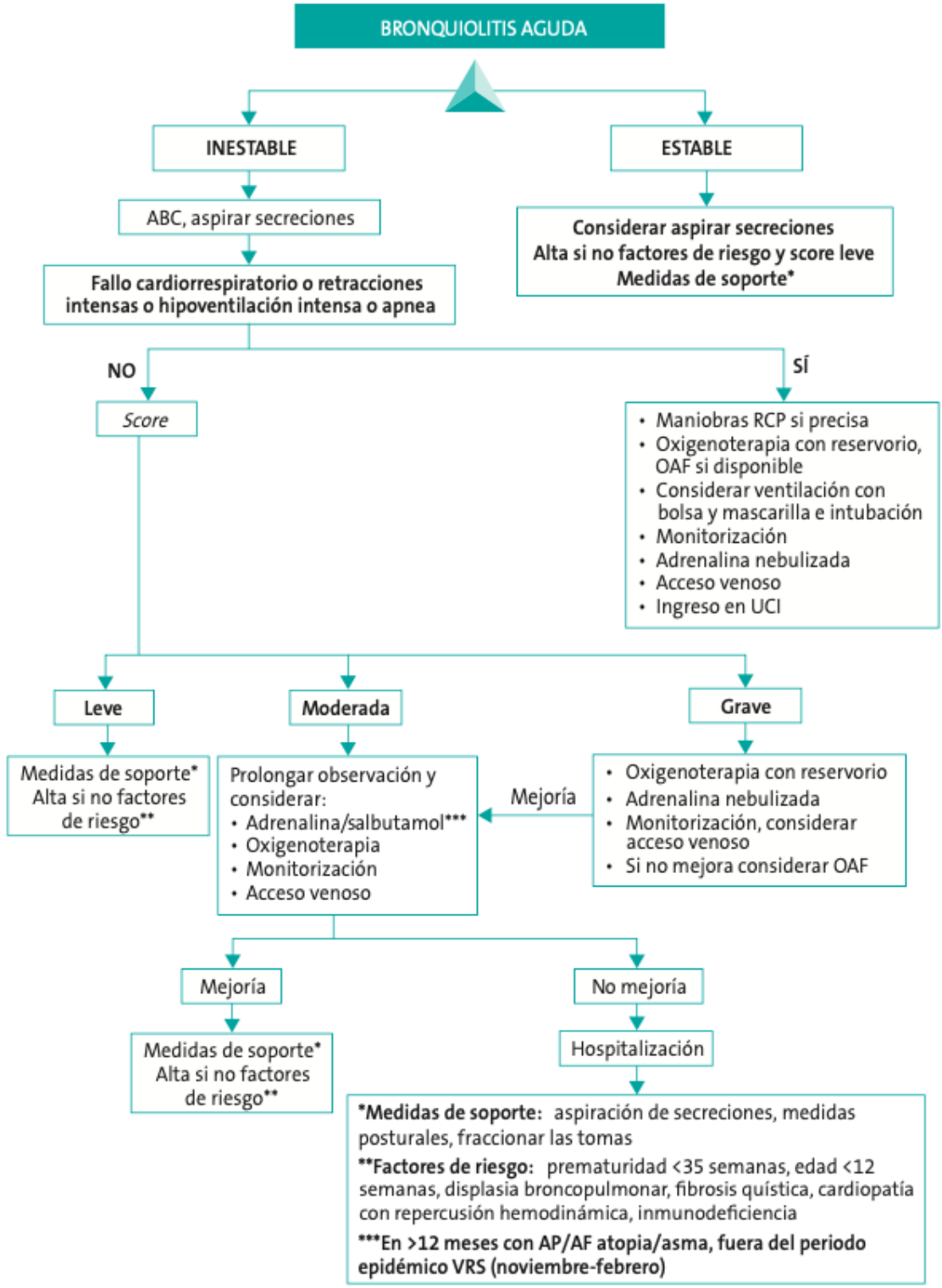
18. ANNEXES

Annex 1. Scheme of acute bronchiolitis management



***Source**: Sociedad Española de Urgencias de Pediatría*

Annex 2. Provider satisfaction questionnaire

TELEHEALTH USABILITY QUESTIONNAIRE (TUQ)

#	Statements	N/A	1 2 3 4 5 6 7
1.	Telehealth improves my access to healthcare services.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
2.	Telehealth saves me time traveling to a hospital or specialist clinic.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
3.	Telehealth provides for my healthcare need.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
4.	It was simple to use this system.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
5.	It was easy to learn to use the system.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
6.	I believe I could become productive quickly using this system	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
7.	The way I interact with this system is pleasant.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
8.	I like using the system.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
9.	The system is simple and easy to understand.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
10.	This system is able to do everything I would want it to be able to do.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
11.	I can easily talk to the clinician using the telehealth system.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
12.	I can hear the clinician clearly using the telehealth system.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
13.	I felt I was able to express myself effectively.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
14.	Using the telehealth system, I can see the clinician as well as if we met in person.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
15.	I think the visits provided over the telehealth system are the same as in-person visits.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
16.	Whenever I made a mistake using the system, I could recover easily and quickly.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
17.	The system gave error messages that clearly told me how to fix problems.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
18.	I feel comfortable communicating with the clinician using the telehealth system.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
19.	Telehealth is an acceptable way to receive healthcare services.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
20.	I would use telehealth services again.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE
21.	Overall, I am satisfied with this telehealth system.	☐	DISAGREE ☐ ☐ ☐ ☐ ☐ ☐ ☐ AGREE

In this questionnaire, 1 - strongly disagree, 2 – disagree, 3 – somewhat disagree, 4 – neither agree nor disagree, 5 – somewhat agree, 6 – agree, 7 – strongly agree

To determine the usability of the telehealth system, calculate the total and determine the average of the responses to all statements. The higher the overall average, the higher the usability of the telehealth system.

Annex 3. Information document

DOCUMENT D'INFORMACIÓ AL FAMILIAR RESPONSABLE O REPRESENTANT LEGAL

Nom de l'estudi: Telemedicina intensiva versus trucades telefòniques a demanda en el pacient pediàtric amb bronquiolitis per virus respiratori sincitial.

Centre assistencial:

Investigador/a principal:

Benvingut/da,

Ens dirigim a vostè, com a pare/mare/tutor legal del pacient per informar-li sobre un estudi d'investigació en el que se l'invita a participar degut al diagnòstic de bronquiolitis aguda del seu fill/a.

El projecte es durà a terme pel Servei de Pediatria i la Unitat de Cures Intensives Pediàtrica de diferents hospitals comarcals i de referència de Catalunya.

Aquest projecte té com a objectiu millorar la qualitat assistencial dels pacients amb bronquiolitis per VRS dels hospitals comarcals mitjançant un sistema de telemedicina amb l'hospital de referència. Aquest estudi ha sigut aprovat pel Comitè d'Ètica i de la Investigació de l'Hospital Universitari Doctor Josep Trueta.

La nostra intenció és que vostè rebi tota la informació correcte i suficient perquè pugui decidir si accepta o no que el seu fill/a participi en aquest estudi. Per això és necessari que llegeixi aquest full informatiu amb atenció i nosaltres li aclarirem tots els dubtes que li puguin sorgir. Ho pot consultar també amb les persones que vostè consideri oportú.

Participació voluntària

Cal que sàpiga que la participació en aquest estudi és voluntària i que pot decidir no participar. Si decideix participar, pot canviar la seva decisió i retirar el consentiment en qualsevol moment, sense que per aquest motiu s'alteri la seva relació amb el metge/metgessa ni es produeixi cap perjudici en la seva atenció sanitària.

Objectiu de l'estudi

La bronquiolitis aguda causada pel virus respiratori sincitial (VRS) és la infecció de les vies aèries inferiors més freqüent en els infants de menys de 12 mesos, representant així la primera causa d'hospitalització en l'edat pediàtrica. En alguns casos, el pacient requereix ingrés a la Unitat de Cures Intensives Pediàtrica (UCIP). No obstant això, només els centres de referència disposen dels recursos necessaris per l'assistència al pacient pediàtric crític.

És per aquest motiu que els pacients en estat crític dels hospitals comarcals que requereixen ingrés a la UCI pediàtrica necessiten el trasllat mitjançant una ambulància pediàtrica per ser atesos a l'hospital de referència. El servei d'emergències mèdic pediàtric, centralitzat a Barcelona, no és immediat i el trasllat tarda en fer-se efectiu, sobretot durant els mesos en que el virus té més incidència entre la població.

Aquest període de temps, des de que es demana el trasllat al centre de referència fins que aquest s'efectua, és molt important per l'estat del pacient.

En la última dècada, la telemedicina ha anat guanyant importància per millorar la qualitat de l'assistència al pacient. Aquest sistema consisteix en l'intercanvi d'informació mèdica del pacient des de punts geogràfics diferents entre els professionals sanitaris per tal de poder rebre el suport i el consell d'altres metges de centres més especialitzats.

L'objectiu d'aquest assaig clínic és estudiar l'impacte que tindria la implantació d'un sistema de telemedicina en l'estat del pacient i els dies d'hospitalització posteriors a aquests, durant aquest interval de temps en que el pacient crític no pot ser traslladat a l'hospital de referència perquè no hi ha servei d'ambulància pediàtric disponible.

Descripció de l'estudi

Per estudiar el nostre objectiu, s'ha dissenyat un assaig clínic en les regions sanitàries de Girona, Tarragona i Terres de l'Ebre.

L'hospital Universitari Doctor Josep Trueta és el centre de referència dels hospitals comarcals de la regió sanitària de Girona, mentre que l'hospital Universitari Joan XXIII

de Tarragona ho és de la regió sanitària de Tarragona i de Terres de l'Ebre. Així doncs, per cada hospital de referència, s'han elaborat dos grups d'hospitals comarcals, homogenis entre ells pel que fa a població bàsica i distància.

De forma aleatòria, cada grup d'hospitals de la seva regió sanitària rebrà una assistència del pacient crític diferent:

- Trucades telefòniques a demanda amb l'hospital de referència, que és el sistema de comunicació que s'ha utilitzat fins ara.
- Assistència amb telemedicina, basada en un seguiment continuat del pacient per part del centre de referència, mitjançant un sistema de videoconferència per observar el pacient, la monitorització de les seves constants vitals de forma continuada i també la transferència de totes les imatges radiològiques i història clínica, útil perquè els professionals del centre de referència puguin participar també en el maneig del pacient crític mentre aquest es troba a l'hospital regional.

La intervenció s'iniciarà quan el pacient de l'hospital comarcal amb bronquiolitis per VRS presenti criteris de derivació a l'hospital de referència. En el moment en que l'infant sigui traslladat amb l'ambulància, la telecomunicació finalitzarà, però es seguirà el pacient fins que rebi l'alta hospitalària.

Participants en el projecte

L'assaig cínic necessita la participació d'un total de 168 pacients dels hospitals comarcals diagnosticats de bronquiolitis aguda per VRS amb criteris de derivació a l'hospital de referència.

Riscs derivats de la participació a l'estudi

Els efectes colaterals de l'assistència amb telemedicina són derivats de preocupació per la seguretat en l'exposició de la informació mèdica i la falta de formació en l'ús de les noves tecnologies.

No obstant això, el programa que s'utilitzarà per la telecomunicació entre l'hospital comarcal i l'hospital de referència, anomenat *Idonia,* ja s'utilitza en molts dels hospitals que participen en aquest assaig clínic en maneig d'altres patologies en pacient crític, com és el cas de l'ictus, aspecte que aporta garanties de seguretat.

La plataforma compleix amb els requisits de seguretat exigits per la LOPDD i RGPD i està certificada per l'Esquema Nacional de Seguretat en el Nivell Alt.

Per altra banda, tots els professionals ofereixen el servei de telemedicina estaran formats prèviament amb la plataforma i tot l'equipament tecnològic.

A més a més, cal tenir en compte que la telemedicina no substitueix la relació cara a cara metge – pacient si no que és un suport a aquesta.

Possibles beneficis derivats de la participació a l'estudi

L'assistència amb telemedicina des de l'hospital de referència, amb professionals experts en el tractament de la bronquiolitis pot aconseguir un millor maneig del pacient des d'un principi, evitant possibles complicacions i disminuint així la durada de l'ingrés.

També és possible que no s'obtingui cap benefici per la salut pel fet de participar en aquest assaig clínic.

Confidencialitat

Tant el promotor com el centre s'asseguraran que es compleixin els principis contemplats en la normativa de protecció de dades, tant nacional com europea.

Si accepta la participació a l'estudi, permet que les dades del seu fill/a s'utilitzin segons el que està planejat en aquest estudi i en les activitats d'investigació relacionades necessàries. El seu accés només estarà disponible pels investigadors.

Les seves dades del seu fill/a seran identificades com a un número i sempre seran tractades des de l'anonimat, respectant la Llei de Protecció de Dades 3/2018.

Difusió dels resultats

Un cop s'hagi finalitzat l'estudi, s'extrauran els resultats i s'elaboraran conclusions. Es preveu la publicació dels resultats a revistes científiques, tant si el resultat és positiu com si es negatiu.

Tot aquest procés es farà sempre respectant l'anonimat del pacient.

D'aquesta manera, altres centres assistencials se'n podran beneficiar i podran implementar la telemedicina si es demostra que aquesta té beneficis pel pacient.

Participació i compensació econòmica

Els investigadors que participen en l'assaig clínic no reben cap tipus de benefici econòmic.

La participació del seu fill/a en l'assaig clínic és voluntària i per tant, no serà remunerada. Tampoc li comportarà cap cost econòmic addicional a la pràctica clínica habitual.

Si decideix que el seu fill/a participi, haurà de firmar el full de consentiment informat conforme ho aprova. En cas que en algun moment vulgui que el seu fill/a deixi de participar en l'estudi clínic, podrà firmar la revocació del consentiment informat sense haver de donar cap tipus de justificació ni que es vegi afectada la seva assistència mèdica.

Responsabilitat i assegurança

El promotor de l'estudi disposa d'una pòlissa d'assegurança que s'ajusta a la legislació vigent (Real decret 1090/2015) i que proporcionarà compensació o indemnització en cas necessari, sempre que no sigui conseqüència de la pròpia malaltia que s'estudia o de l'evolució pròpia de la seva malaltia.

Contacte en cas de dubte

Si durant la participació té algun dubte o necessita obtenir més informació, cal que es posi en contacte amb _____ mitjançant el següent telèfon de contacte _____,

Annex 4. Informed consent

CONSENTIMENT INFORMAT

Nom de l'estudi: Telemedicina intensiva versus trucades telefòniques a demanda en el pacient pediàtric amb bronquiolitis per virus respiratori sincitial.

Centre assistencial:

Investigador/a principal:

Jo, _____, amb document d'identificació personal (DNI/NIE) _____, com a pare/mare/ tutor legal de _____, afirmo que:

☐ He llegit el full d'informació que se m'ha entregat sobre l'estudi.

☐ He pogut fer preguntes sobre l'estudi.

☐ He rebut suficient informació sobre l'estudi.

☐ He parlat amb <<*nom de l'investigador*>>

☐ Comprenc que la participació en l'estudi és voluntària i no remunerada.

☐ Comprenc que puc retirar el meu fill/a de l'estudi:

- Quan vulgui
- Sense haver de donar explicacions
- Sense que això repercuteixi en la seva assistència mèdica.

☐ Dono accés i utilització de les dades en les condicions detallades en el full d'informació, sempre tractades des de l'anonimat i confidencialitat.

Rebré una copia firmada del full d'informació i consentiment informat.

Confirmo que he llegit el document d'informació i estic conforme amb el seu contingut. Presento lliurement la meva conformitat perquè _____ participi en l'estudi.

Firma dels progenitors o tutor legal	**Firma de l'investigador**
Data: ___/___/____	Data: ___/___/____

En el supòsit de que només ho autoritzi un dels progenitors, el progenitor que autoritza declara que:

- ☐ Confirmo amb la present que l'altra progenitor no s'oposa a la participació del nostre fill/a a l'estudi
- ☐ El firmant és l'únic tutor legal.

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo, _____, amb document d'identificació personal (DNI/NIE) _____, com a pare/mare/ tutor legal de _____, revoco el consentiment informat prestat en data _____ i declaro, que després de la informació rebuda no autoritzo que el meu fill participi en l'assaig clínic.

Annex 5. Case report form

QUADERN DE RECOLLIDA DE DADES

Projecte: Telemedicina intensiva versus trucades telefòniques a demanda en el pacient pediàtric amb bronquiolitis per virus respiratori sincitial.

Full de recollida de dades dels pacients que participen a l'estudi. Cal marcar amb una creu la opció més adient.

Hospital regional d'on procedeix el pacient: _____

Hospital de referència del pacient: _____

Persona que recull les dades: _____

Data i hora: _____/_____/_____

Número d'identificació del pacient: _____

Data de naixement: _____/_____ /____

Sexe:

☐ Masculí ☐ Femení

Història de prematuritat:

☐ Sí ☐ No

Baix pes al néixer (<2.500):

☐ Sí ☐ No

Malaltia pulmonar crònica (displàsia broncopulmonar o fibrosis quística)**:**

☐ Sí ☐ No

Complicacions (inclourem aquelles desenvolupades a partir del moment en que es demana la derivació a l'hospital de referència):

☐ Apnees

☐ Coinfecció bacteriana

☐ Hiponatrèmia

☐ Complicacions cardiovasculars (taquicàrdia ventricular, fibril·lació ventricular, miocarditis o envasament pericàrdic)

☐ Deshidratació

☐ Fracàs respiratori

☐ Hepatitis

☐ Alteracions neurològiques (apnea central, letargia, anormalitat del to)

Número de complicacions total : __ / 8

Registre d'horari de l'hospitalització del pacient:

Data d'ingrés a l'hospital regional: ____/____/____

Dia i hora d'avís al SEM pediàtric: ____/____/____ a l'hora ___:___

Dia i hora d'arribada a l'hospital de referència: ____/____/____ a l'hora ___:___

Dia d'ingrés a la UCI pediàtrica: ____/____/____

Dia d'alta a la UCI pediàtrica: ____/____/____

Dia d'alta d'hospitalització: ____/____/____

Enquesta de satisfacció:
Resultat de l'enquesta de satisfacció del professional de l'hospital regional: _____