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PARIS – Study Specifics

High Flow Nasal Cannula therapy in infants with bronchiolitis, a randomised controlled trial

PARIS (Paediatric Acute Respiratory Intervention Studies)

PREDICT and PCCRG NHMRC sponsored Study

PARIS
Paediatric Acute Respiratory Intervention Study
High Flow Trial

Study Coordinator – Donna Franklin

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Paediatric Critical Care Research Group
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PARIS Discussion points

- Ethics
- Governance
- Adverse events
- Pilot Trial -> Multicentre International RCT
- Practical logistic set ups of 17 centres
- Educational components
- Database & Data collection
- Papers

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PARIS Ethics

- NEAF
- Children's Health Qld HREC (Pilot/larger RCT)
- Individual hospital HREC/HDEC
  - NZ HDEC in person (delayed consent)
- Amendments throughout RCT

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PARIS Ethics

- Amendments (CHQ and locally)
  - Adding additional sites
  - Parent Flyer
  - Delayed Consent rules surrounding date collection
  - Delayed Consent use of telephone consents
  - Feeding question
- Serious Adverse Events
  - Prompt reporting DSMB and Ethics

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PARIS Governance

17 centres with varied processes

* 4 Australian States
* 2 countries

Requirements each centre:

1. **Site Specific Application** (SSA) (include in-kind costs) – provide relevant docs (HREC's, CRF's, Consents, Protocol – track changed for specific hospital)
2. **Clinical Trials Research Agreement** (CTRA) – individual centres (DoV – Schedule 2)
3. **Public Health Act** (PHA) + Victorian Specific Module (equipment & consented/non-consented patients)

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PARIS Governance Challenges

- Qld – varied with same overarching guideline for 11 centres (SSA requirements)
- SSA – Section 18 (Funding) clarity
- CTRA (Medicines Australia template) – some centres very specific about equipment/consumables
- Advantageous for same consistent team with CTRA and MIA (funding details)
- PHA for Qld – timeframe with Director-General

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Governance with NHMRC funding

Multi-institutional agreement (MIA)

- Is a multiparty collaborative agreement
- Governs conduct of the grant and disbursement of grant funds to CI sites
- NHMRC CI centres receive additional secondary gain as NHMRC institution behind it.
- CTRA (funding) – for non MIA parties (other PI's)

Lessons learned

- **Get started early! (Legal sign off locally) Four sites for PARIS**

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PARIS Serious Adverse events

- Timely manner (within 24-72hrs) to:
  - Report to DSMB (2 independent members)
  - Report to governance/HREC (local & central - CHQ HREC)
  - Feedback to relevant team involved
  - Action changes required if outlined

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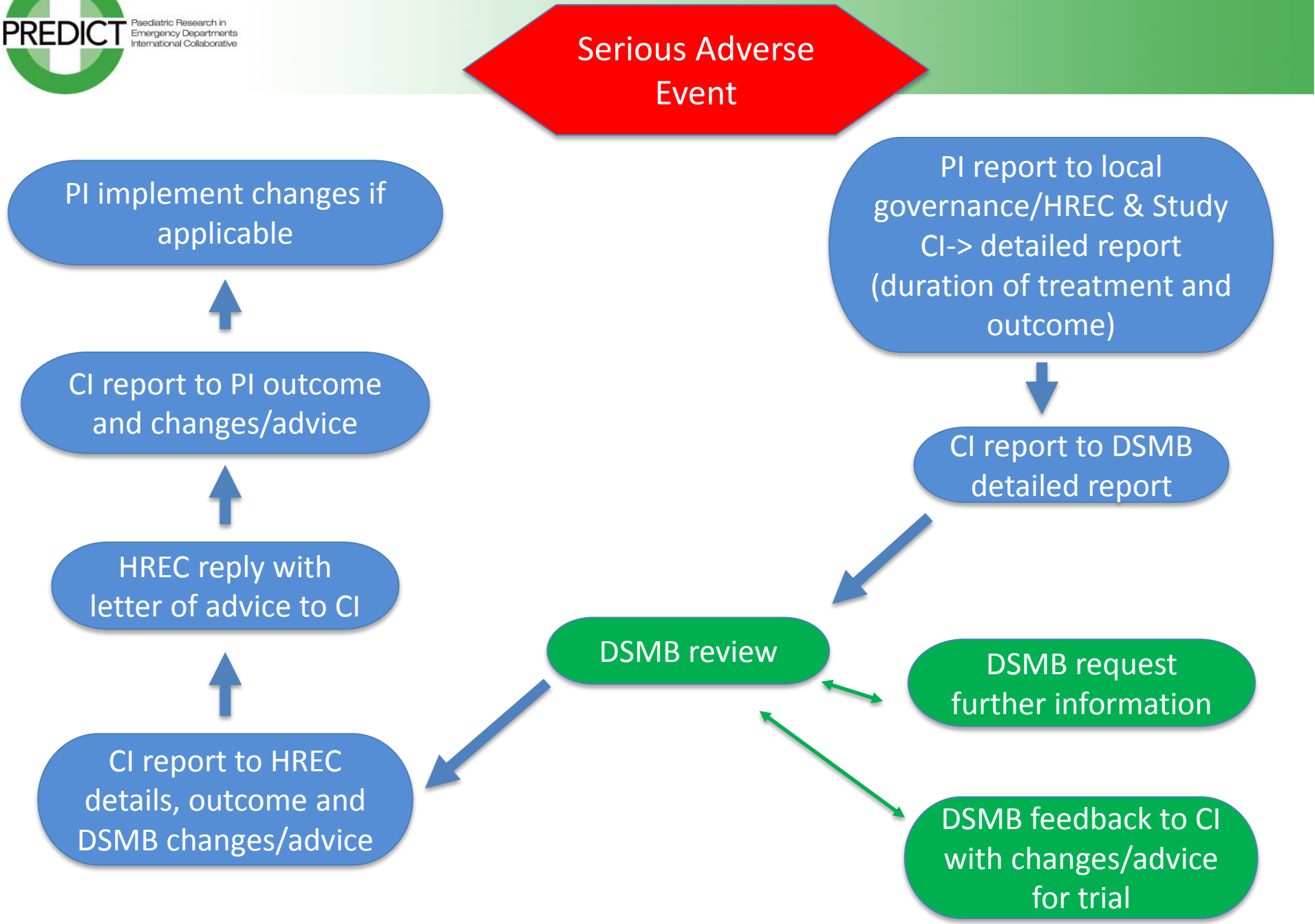

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PARIS Serious Adverse Events

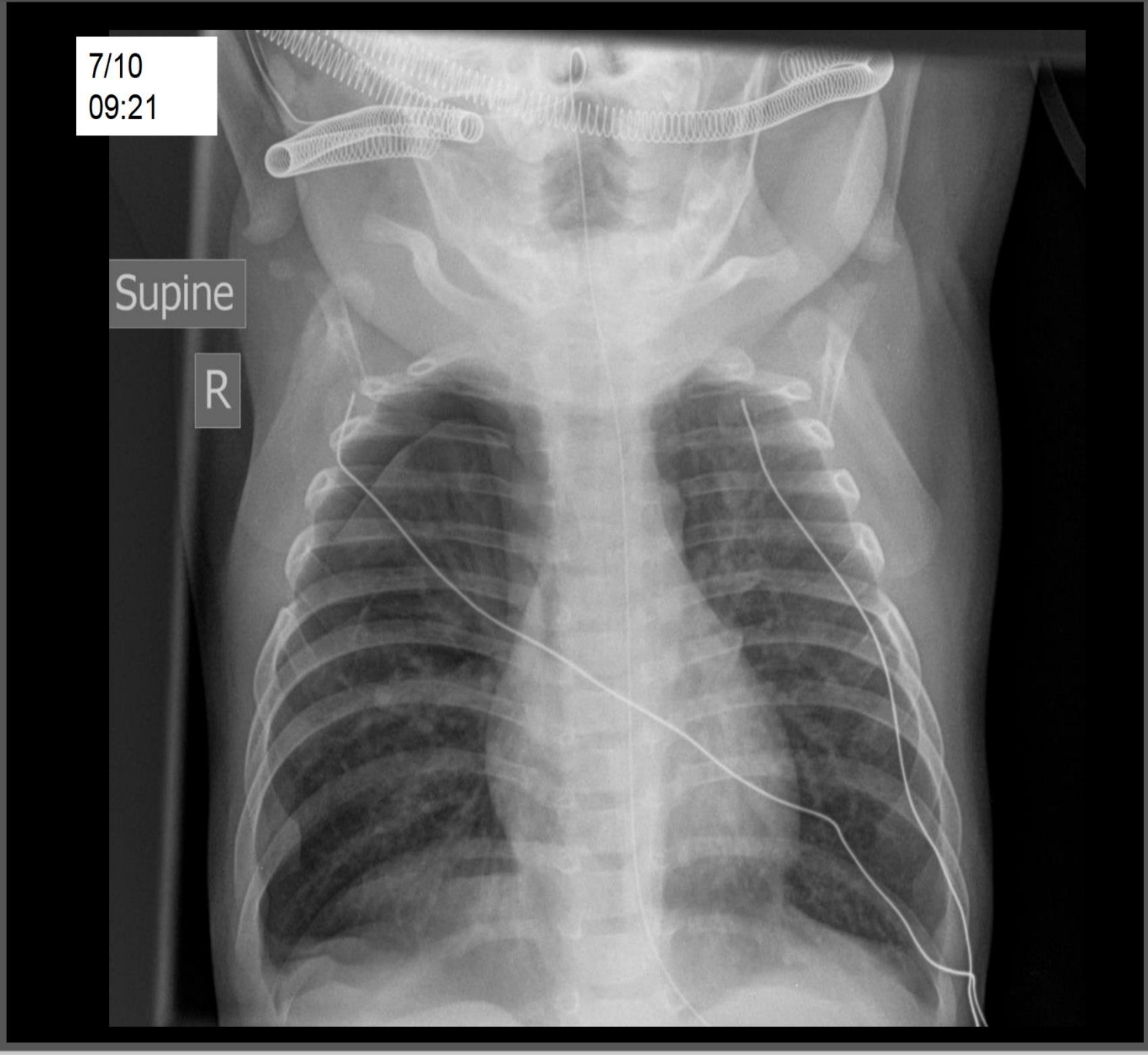
- 2 serious adverse events reported to date (July and Oct 2015) – pneumothorax – Control & High Flow
- Reporting – one prompt and one late as central team picked up

Event 1 description

Event 2 description

Lessons learned with late reporting -

- Failed to educate local team to report in a timely manner.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Supposed adverse event -> improved study outcome

- Suspension of Trial 5 days in Qld affecting 5 centres
- Inaccurate reporting to the Patient Safety Unit (PSU)
- 5 days to clarify with QH/CHQ Exec
- Good outcome as improved reporting from PSU and improved EWT's

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Pilot Trial -> Multicentre International RCT

- Pilot trial essential – included elements of final trial to test intervention
- Iron out problems
- Commenced with one centre (Nov 2013 start)
- NHMRC funded -> 17 centres within 10 months
- Lessons learned from pilot trial
  - Revised Protocol – treatment failure (40% FiO2)
  - Champion Booklet
  - Key leaders established (nursing in regional centres)
  - Improved documentation

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Practical logistic set ups of centres – differences

- Randomisation from ED and ward in some centres
- ED not involved in one centre
- Site visits **VITAL** – establish understanding of baseline (staff, EWT's, pt flow, use of HF and current guideline/where used, mixed ED's and paediatric training, ICU on-site)
- SSU – include or not include (effects screening log data).

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Educational resources PARIS

- Face to face nursing and medical education – with/without presentations (voiceover)
- Educational package for PREDICT centre Research Nurses
- Locally funded RA's
- Refresher presentations
- Patient Booklet – step-by-step guide
- Champion Booklets
- Early Warning Tools (EWT) x 9 versions (ED & Ward)
- Signage – Champions names & badges/flowcharts
- Lanyards
- Troubleshooting Guide
- FAQ's
- Airvo2 app and signage

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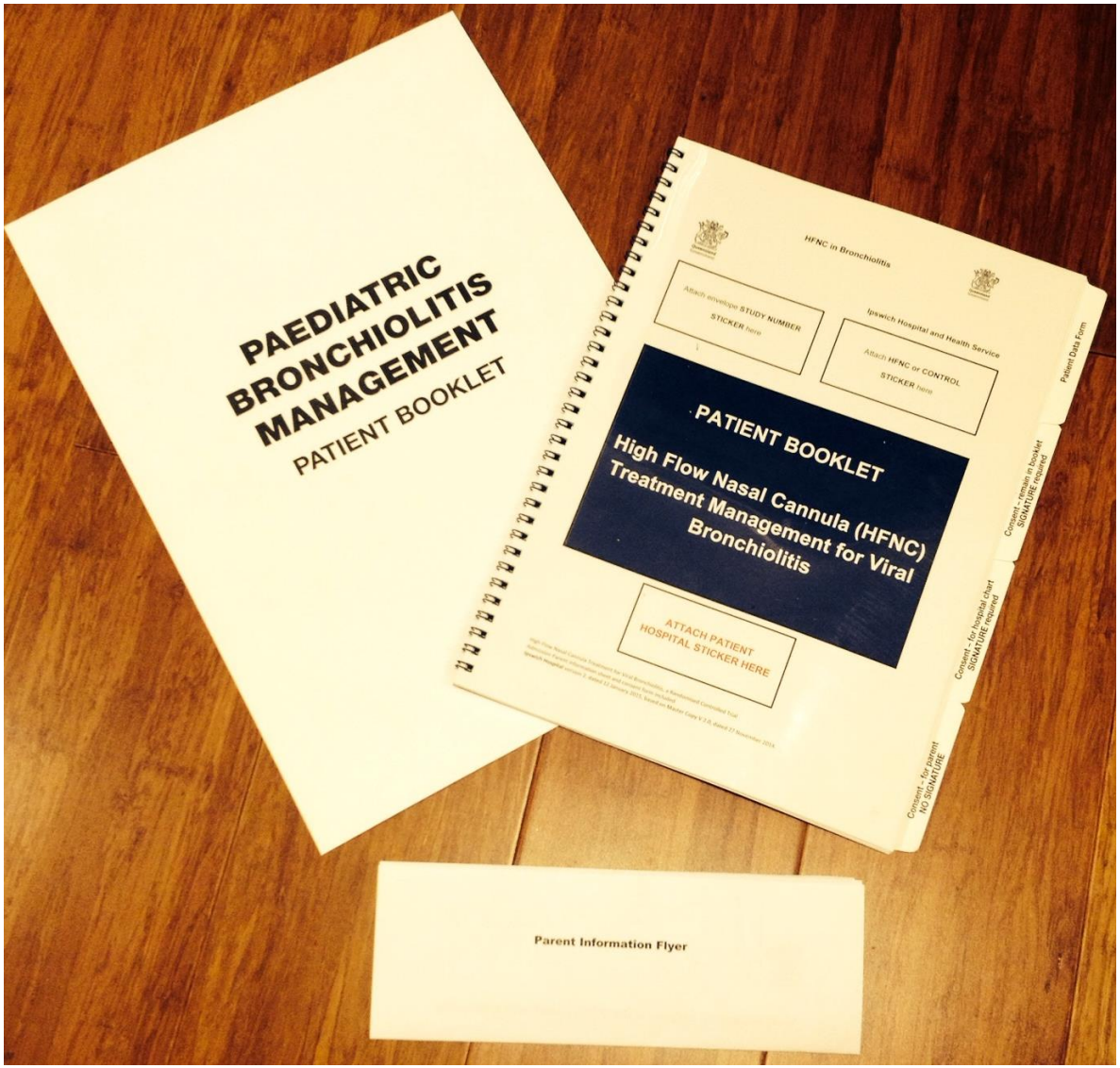
Educational resources
PARIS
Patient Booklet



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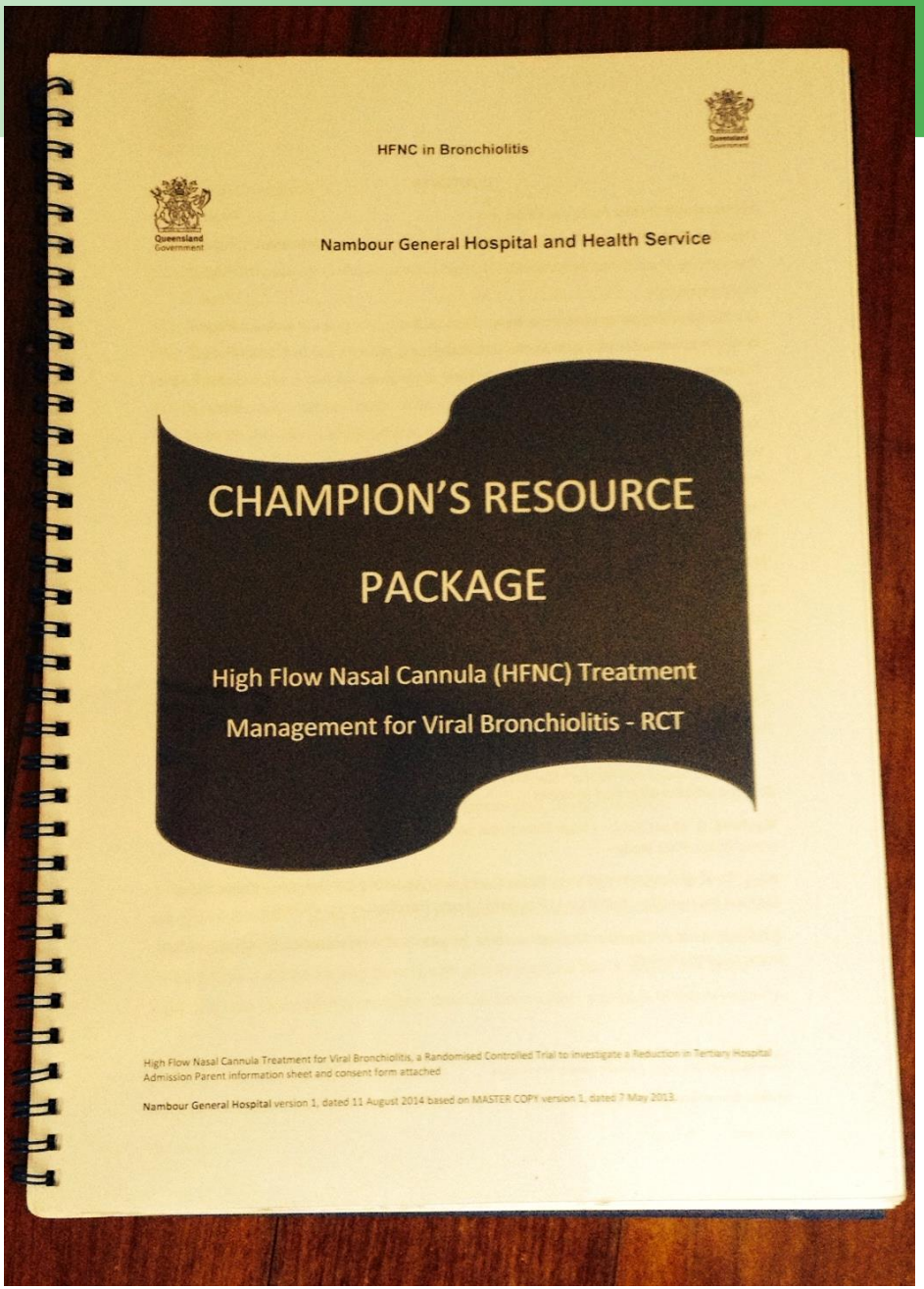
Educational resources
PARIS
Champion Booklet



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Educational resources
PARIS
EWT's

9 versions of CONTROL

9 versions of HIGH FLOW

9 versions of ESCALATION

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Educational resources
PARIS
Signage

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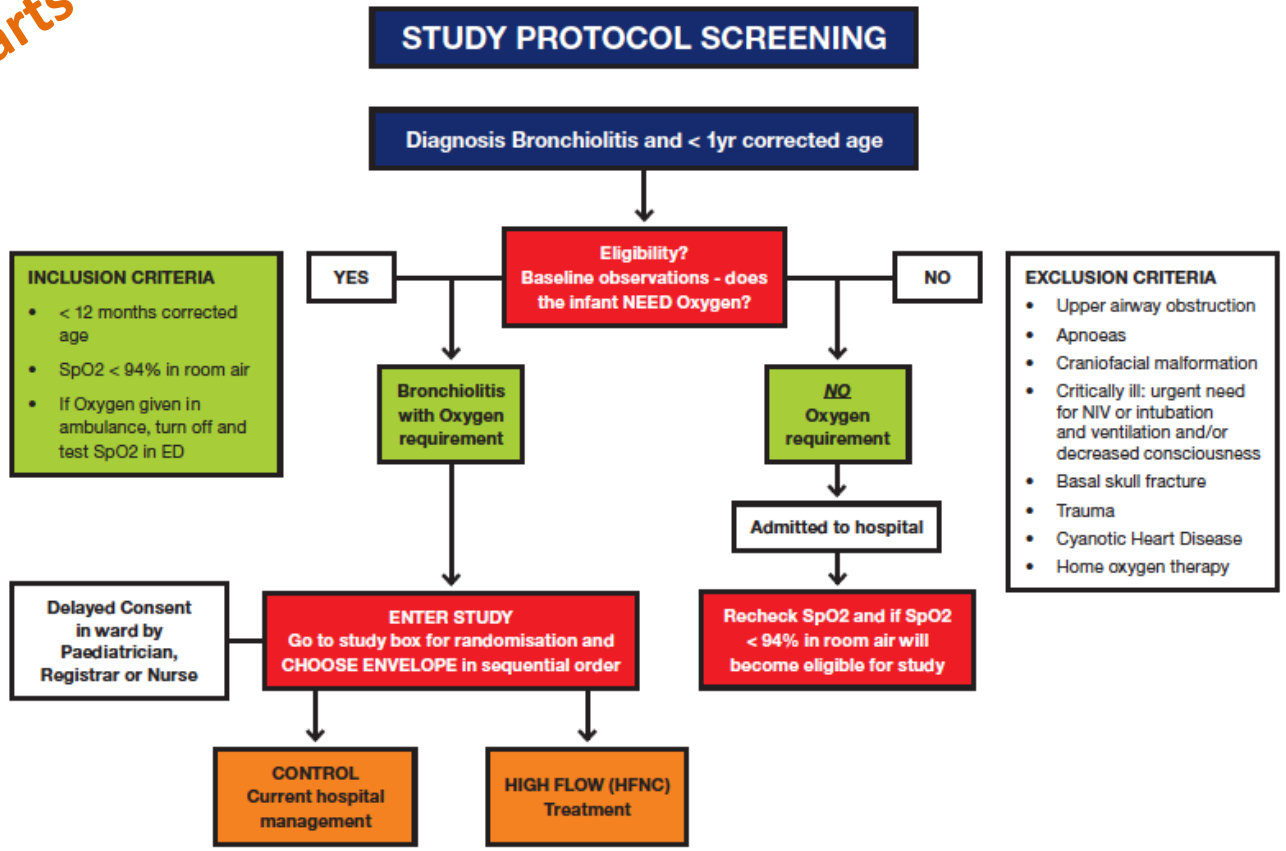
9 VERSIONS

Educational resources
PARIS
Flowcharts



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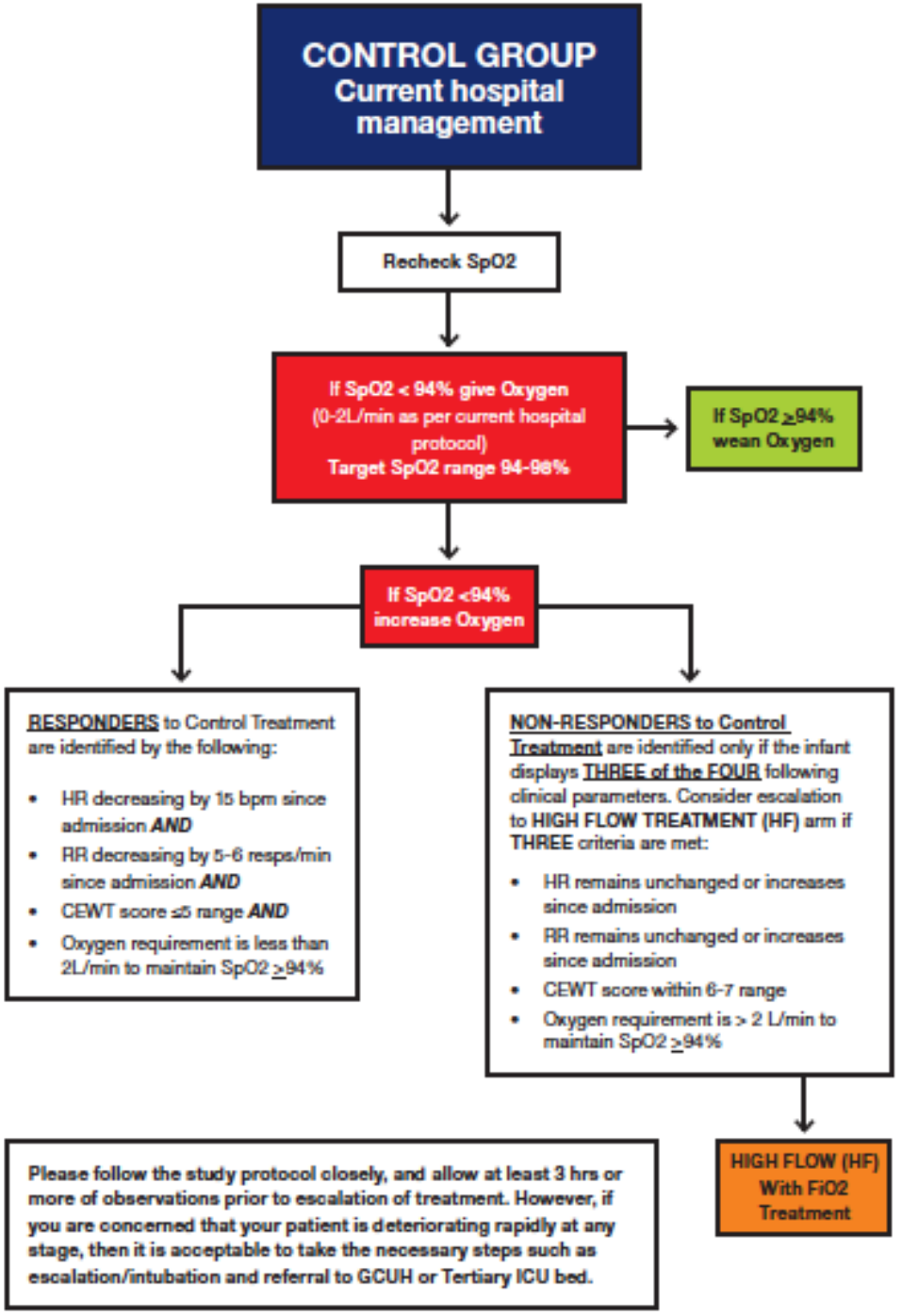
Educational resources
PARIS
Flowcharts



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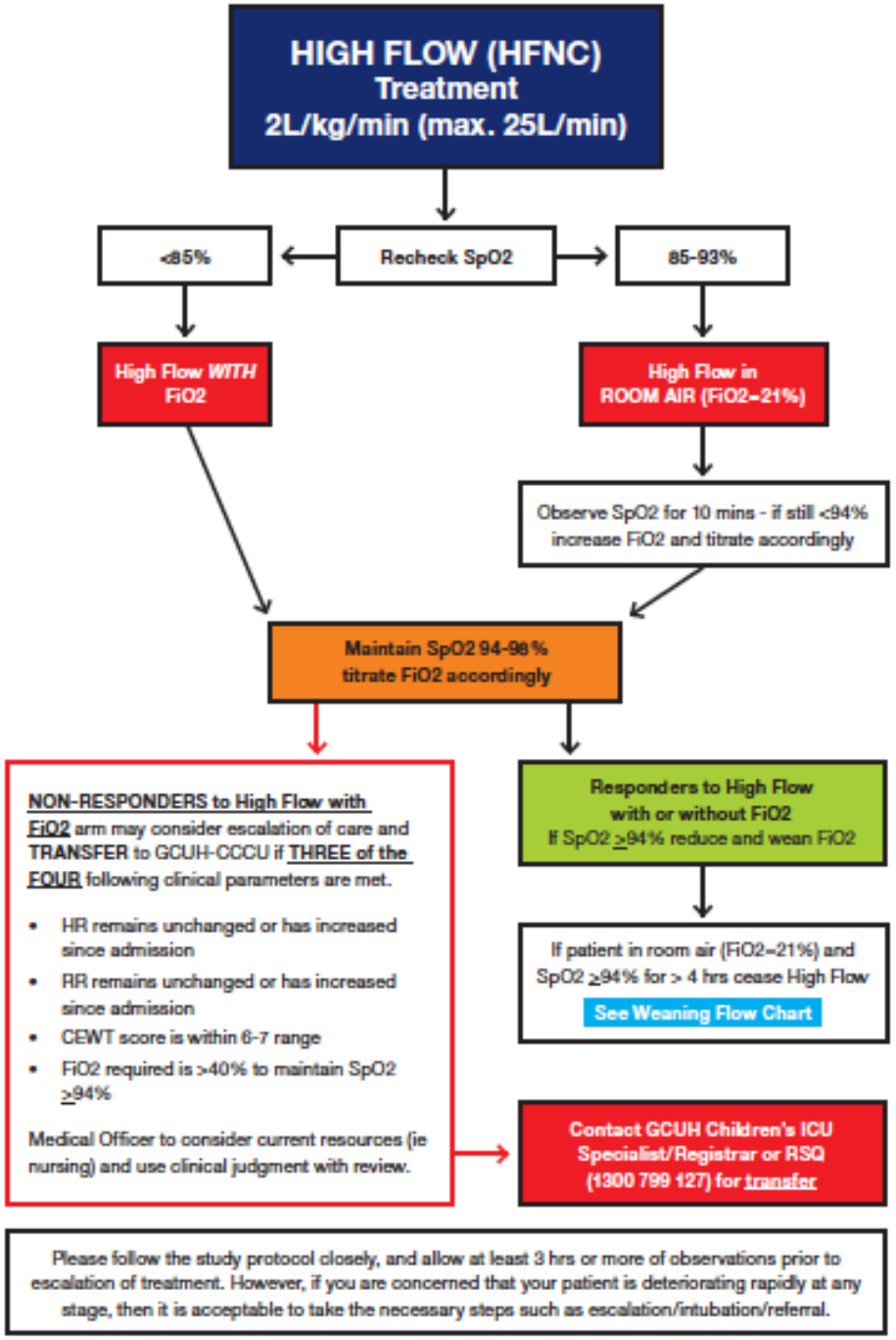
Educational resources
PARIS
Flowcharts



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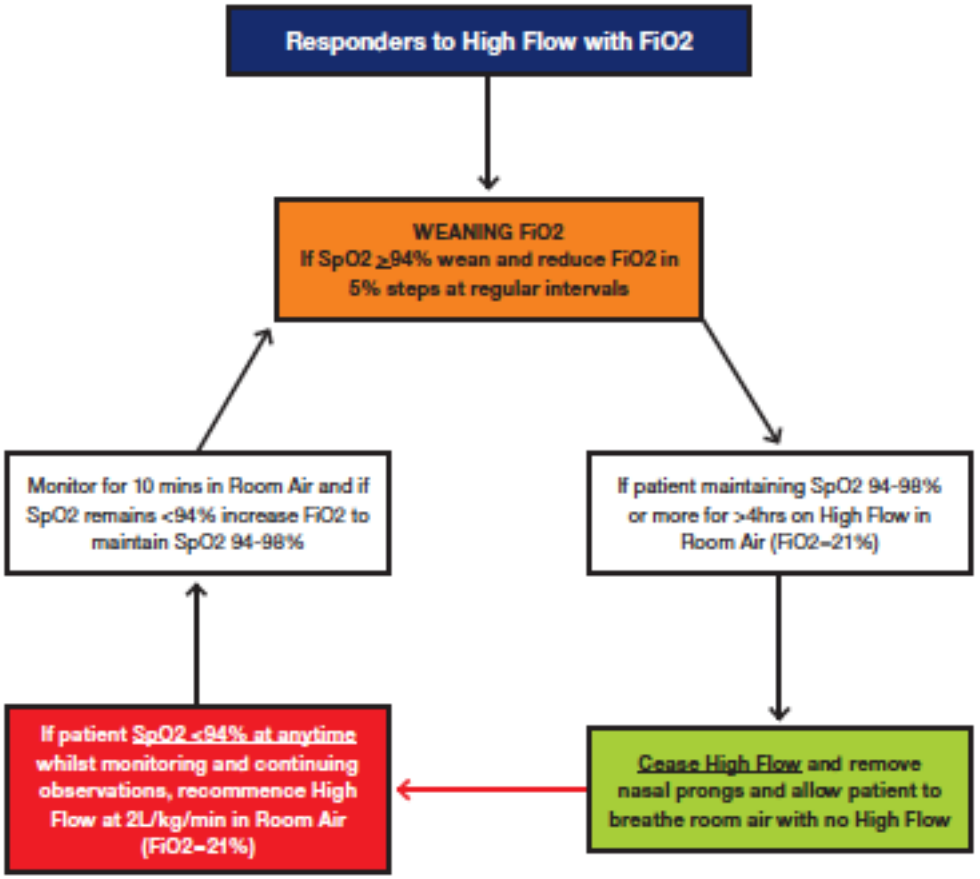
Educational resources
PARIS
Flowcharts

TITRATING AND WEANING patients on HIGH FLOW with FiO2



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Educational resources
PARIS
Lanyards

Control Therapy
(Standard Oxygen Therapy)

- Document patients room air baseline vitals on hospital early warning tool chart
- If SpO2 <92% give Oxygen
- Apply standard hospital nasal prongs
- Give 0-2L/min as per current hospital protocol
- Aim for SpO2 92-98%
- If SpO2 stable and ≥92% wean Oxygen

High Flow Treatment
(HFNC)

Document patients room air baseline vitals on hospital early warning tool chart

Collect equipment

- AIRVO2, Circuit, Green Optiflow Nasal Cannula, water bag
- Turn AIRVO2 on and ensure paediatric mode (bird and butterfly on screen)
- Attach circuit and water bag
- Apply green optiflow nasal prongs
- Set HFNC flow at 2L/kg/min at all times (Max 25L/min for >12.5 kg)
- If SpO2 85-91% give HFNC in room air (FiO2=21%) for 10 mins
- If SpO2 <85% give HFNC with FiO2
- Aim for SpO2 92-98% and titrate FiO2 accordingly
- Refer to Weaning Flow Chart

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Educational resources
PARIS
Troubleshooting Guide

TROUBLESHOOTING GUIDE WITH AIRVO2

PROBLEM	SOLUTION
Incorrect L/minute on display screen for weight.	• Work out correct L/kg/minute for specific patient weight (eg. 8 kg infant = 16 L/kg/min of flow with AIRVO2) • Press the 'MODE' button (side arrow button) twice (as the first press will give you humidification and the second press will give you L/minute). • Press the up and down arrows together for 5 seconds to release the lock. • Then increase or decrease the L/minute displayed using up and down arrows. • Once reached correct L/minute, press the 'MODE' button again once for 1 second to lock.
Unable to increase Oxygen	• Check correct position of nasal prongs to ensure no occlusion exists, which includes secretions and/or positioning at nares. • Oxygen is manually increased using Oxygen flow meter at wall (needs to be a 15L/min flow meter). • Actual Oxygen being delivered to the patient is shown on the display screen (eg. FiO2 of 30 % may be 2 L/minute of flow at wall for a particular size of infant). • It's important to observe the display screen FiO2 when increasing the Oxygen at the wall flow meter to achieve the FiO2 required to maintain SpO2.
Unable to decrease Oxygen	• Check correct position of nasal prongs to ensure no occlusion exists, which includes secretions and/or positioning at nares. • Decrease Oxygen at wall flow meter whilst observing the display screen FiO2. With each small decrease on the wall you will see the FiO2 decrease on the display screen. • **ROOM AIR = 21 % FIO2** • **FIO2 is Fraction of Inspired Oxygen**
Machine alarming 'Occlusion' or 'Blockage'	• Check correct size of nasal prongs. Only green Optiflow nasal prongs for the High Flow study patients are to be used. • Check there are no kinks in the nasal cannula or the circuit. • Check that the display screen shows a bird and butterfly which represents 'Junior Mode' and if not, then AIRVO2 is in 'Adult Mode' and needs to be changed. To change to 'Junior Mode' hold the 'Mode' button (side arrow) down for 5 seconds until you see the bird and butterfly back on the screen..
Humidifier water level below maximum level (line allocated on chamber).	• Water is only required to cover the plate and does not have to reach the maximum line level allocated on the chamber. • There is a sensor floating ball in the chamber which prevents the humidifier from going dry (so long as there is a water bag with water in it).
Where does the AIRVO2 go once finished with its use?	• Return cleaned (wipe down with antibacterial wipes) and disinfected to **INSERT DEPT/AREA.**
Machine displays 'Amber' traffic light when switched on. Unsure if it can be used	• If 'Amber' traffic light is shown this means that the disinfection cycle has **not** been completed and needs to be done prior to using on a new patient. • A 'Green' traffic light indicates a disinfected and clean machine ready for new patient.
How to disinfect AIRVO2 after use with a patient?	• Remove all consumables using PPE from AIRVO2 and discard appropriately. • Attach red disinfection tubing (attached to the AIRVO2 pole) to machine. • Switch machine on • Machine will sense disinfection tubing and will automatically disinfect over a 55 minute period. • The display screen will show the time in minutes until completion. Once complete it will show a 'tick' symbol. • MUST switch machine off at on/off button prior to unplugging from wall. Otherwise it will alarm.

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1	A baby recruited to the trial has a secondary diagnosis of gastroenteritis - can the baby be recruited or stay on the trial if the gastro started after admission?

YES

As the baby has a diagnosis of bronchiolitis, regardless of it being secondary to the gastroenteritis diagnosis.

2	A baby being recruited to the trial has also got Tracheomalacia - is the baby still eligible to be recruited?

YES

In the Exclusion Criteria "Upper Airway Obstruction" refers to babies with Croup and Anatomical upper airway malformations. An example of this exclusion criteria is Laryngomalacia. However, babies with Tracheomalacia and Bronchomalacia can be recruited to the Trial.

3	Bronchiolitis Vs Asthma in babies less than 12 months, should we include them into the trial?

YES

Differentiating bronchiolitis and early onset of asthma in the first year of life is difficult and some experts call any presentation similar to it a "reactive airway disease", mainly defined by a response to a salbutamol trial, and rarely with a lung function test (except if this is available).

Bronchiolitis and asthma is blurred in the first year of life, therefore again some experts state "do not diagnose asthma", but experienced clinicians may detect already the first signs of a real asthma in the patient.

In principle asthma as a pure diagnosis should not have an oxygen requirement in mild to moderate stage. This is somewhat a weak argument but never-the-less true.

In all bronchiolitis trials there have been a good percentage of "reactive airways' patients included and this is generally accepted as there is no clinical test to exclude them.

A positive NPA will confirm to some extent the diagnosis of bronchiolitis.

4	How do I give a Nebulizer to a baby on High Flow with the AIRVO2 machine?

For the duration of the nebulizer reduce the flow from the 2L/kg/min (i.e if a baby is 10kgs the baby will be on a flow of 20L/min) down to LOW FLOW at 2L/min. Do this by decreasing flow using AIRVO2 up and down arrows. Then increase the oxygen to 100% FIO2 by slowly increasing the wall flow meter and observing the AIRVO2 machine monitor screen for the FiO2 percentage increasing number to 100%. After the nebulizer is finished restart AIRVO2 at previous settings, changing both the L/min flow (ie. back to 20L/min for a 10 kg baby) and decreasing the flow meter on the wall to meet the required FIO2 on the machine screen.

5	What colour nasal prongs can I use on the paediatric circuit?

The Paediatric Circuit is suitable for two sizes of nasal cannula on the AIRVO2, however for the purpose of the study you will use mostly Green and on rare occasions with smaller infants, the Purple nasal cannula. If you use purple nasal cannula then please document on the early warning tool (observation chart) that you used the PURPLE cannula. Purple cannulas are used from the hospital stock presently until it is noted that there is a large volume used and a need for these cannulas in this study and for this population of infants.

6	Do I use corrected age or chronological age as 12 months?

Use only corrected age of infant when establishing if the patient meets inclusion criteria of less than 12 months of age. This means that if a baby is born at 32 weeks gestation (ie. 8 weeks earlier than 'planned' birthdate), their corrected age is 8 weeks post their 'actual' birthdate.

7	How many times can the same patient be enrolled in the study?

A patient can have one enrolment per admission – if they are on the trial and weaned off CONTROL or HIGH FLOW but require further therapy, be that CONTROL or HIGH FLOW, always document the last time they came off CONTROL or HIGH FLOW in the data form.

If the patient represents to the hospital again (and again) then they can be placed on the trial if they meet the inclusion criteria. New admissions require a new patient booklet and a new consent form to be completed.

8	If the infant is weaned off FiO2 and then weaned off High Flow and maintains SpO2 ≥92% when awake but desaturates when asleep; do we return the infant to High Flow only when asleep?

The infant needs to go back on High Flow immediately as per weaning protocol. This means the infant is on High Flow at both sleep and awake times. The infant may only required a flow of 2L/Kg/Min in room air (FiO2 21%). Aiming for saturations between 92-98% if maintained for >4hrs then turn High Flow off.

9	When High Flow is weaned and stopped, can we stop Nasogastric feeds and allow mum to breastfeed?

Yes.

10	When can I wean the infant's FiO2 ((High Flow patient) or standard wall Oxygen (Control patient)?

When the infants SpO2 is stable between 92-98% you can then wean the patient's oxygen. You do not need to wait until the SpO2 are at 98% - you can start to wean when the SpO2 are stable and above 92%.

11	The baby has increased work of breathing however the saturations remain ≥92%? Can I commence on High Flow for the work of breathing?

No you cannot if you want to recruit this patient to the study. It is recognised that this is difficult for the medical and nursing staff to observe and not apply High Flow however this is the reason for the study taking place – to prove or disprove the effect and usefulness of High Flow against standard Oxygen therapy. The infant will have been working hard prior to presenting to the hospital whilst at home, and the infants will declare themselves by dropping their saturations at some point if this is going to occur. Admit the patient to the ward if you think this is what is needed and continue to observe and monitor SpO2.

Educational resources
PARIS
FAQ's x 2 versions

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Educational resources
PARIS
Airvo2 resources

- Smart phone APP
- Youtube link for set up
- Signage with Airvo2's

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Education Challenges PARIS

- Creep in effect –> HF already in use
- Flow rates adjustments initially
- Adherence to protocol

  WOB -> understanding Oxygen vs Flow
- Change of Dx to treat with HF
- Sometimes escalation criteria
- Oxygen toxicity
- NGT (mixed ED's with more adult trained)

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Educational benefits PARIS

- Standardised protocol (control or high flow)

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Education
(Knowledge translation into practice)

- Collecting education numbers/times
- National Bronchiolitis Guidelines
- Statewide guidelines
- Measuring bronchiolitis management one year post PARIS I
- Grant submission

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Educational future - High Flow

3 x Video Documentaries - mid 2016

- Physiology
- Current evidence and practice of HF in Emergency, General Paediatrics and ICU (guidelines in place)
- Process of implementation, research that has been influential

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Database - WebSpirit

- Plan ahead well as cannot change database (can add but not remove)
- Layout is poor
- Costs involved – per site/per form
- Export cumbersome
- WebSpirit number vs Study ID
- Sites can review own data (Visit Status)
- FAQ for data entry users

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PARIS Papers to be published

- Many ideas
- Main paper – outcomes analysis
- Physiology (EWT's)
- Quality & Safety aspect (adverse events)
- Feeding
- Delayed Consent

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CONSORT Statement
(Consolidated Standards of Reporting Trials)

- An evidence-based, minimum set of recommendations for reporting randomized trials.
- Standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation.
- **25-item checklist** - focus on reporting how the trial was designed, analysed, and interpreted
- **Flow diagram** - displays the progress of all participants through the trial.
- Endorsed by prominent general medical journals

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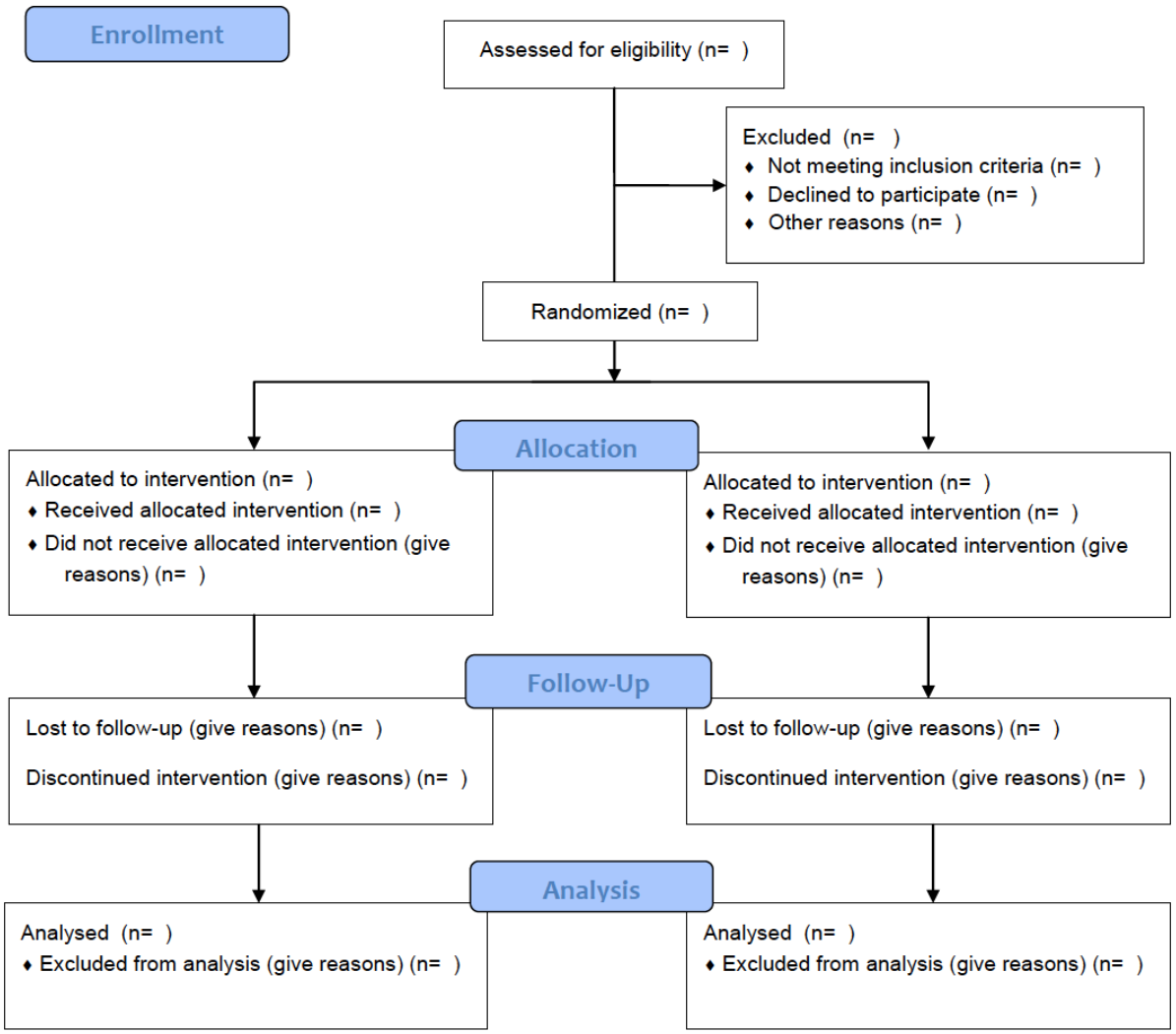
CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT template

CONSORT 2010 Flow Diagram



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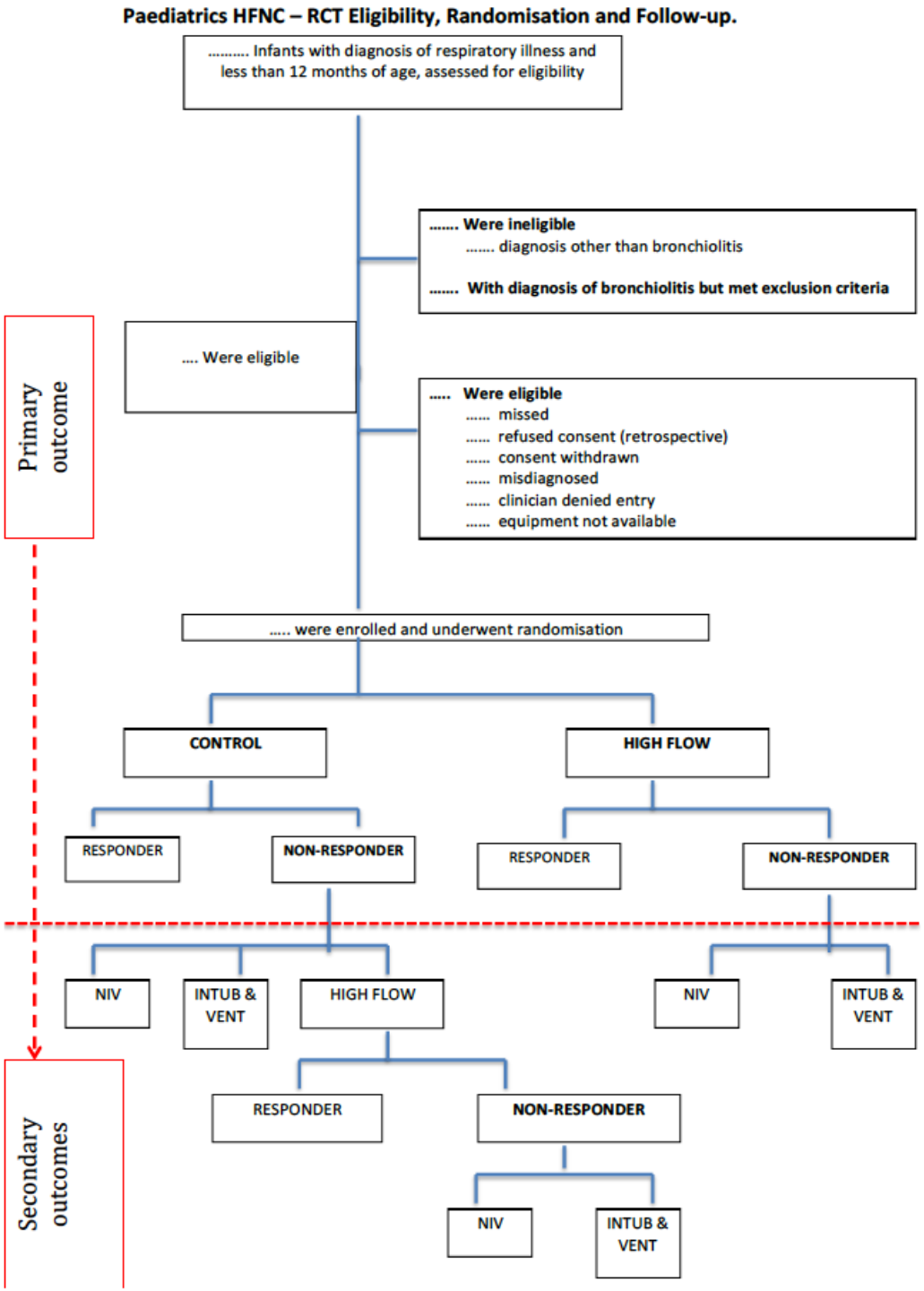
CONSORT PARIS …



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