Are Intermittent Inhaled Steroids an Effective Option to Treat Asthma in Children?

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Disclosure

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Population Health Program

Evolving Patterns in Asthma Management

Period	Goal of Management	Medications
1960s	Relieve bronchospasm	Short-acting ß-agonists
1970s	Prevent bronchospasm	Albuterol, theophylline
1980s	Prevent allergen-induced bronchospasm	Cromolyn
1990s	Prevent and resolve inflammation	ICS, LT modifiers, LABA, ICS/LABA
2000s	Asthma control	Anti IgE
2010s	Personalized medicine; Early intervention; Exacerbation prevention	Patient characteristics, biomarkers, genetics; Immunomodulators
2020s	Population Health Management	Individualized Treatment Strategies

Primary Goal of Therapy: Achieving and Maintaining Asthma Control

- Primary goal of asthma therapy is to enable a patient to *achieve and maintain control* over their asthma
  - *Eliminate impairments* including symptoms, functional limitations, poor quality of life, and other manifestations of asthma
  - *Reduce risk* of exacerbations, ED visits, and hospitalizations
- Treatment goals are identical for all levels of asthma severity

NHLBI. National Asthma Education and Prevention Program. Full report of the Expert Panel: Guidelines for the Diagnosis and Management of Asthma (EPR-3). Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed August 31, 2007.

Considerations in Intermittent Strategies

- Age of patient

- Type of strategy

- Body of evidence

- Education

- Guidelines discussion

Approaches to stepping up and stepping down care in asthmatic patients

Alex Thomas, MD,[a] Robert F. Lemanske, Jr, MD,[a,b] and Daniel J. Jackson, MD[a]   *Madison, Wis*

Various Intermittent Strategies

- Maintenance and prn ICS/LABA [SMART]

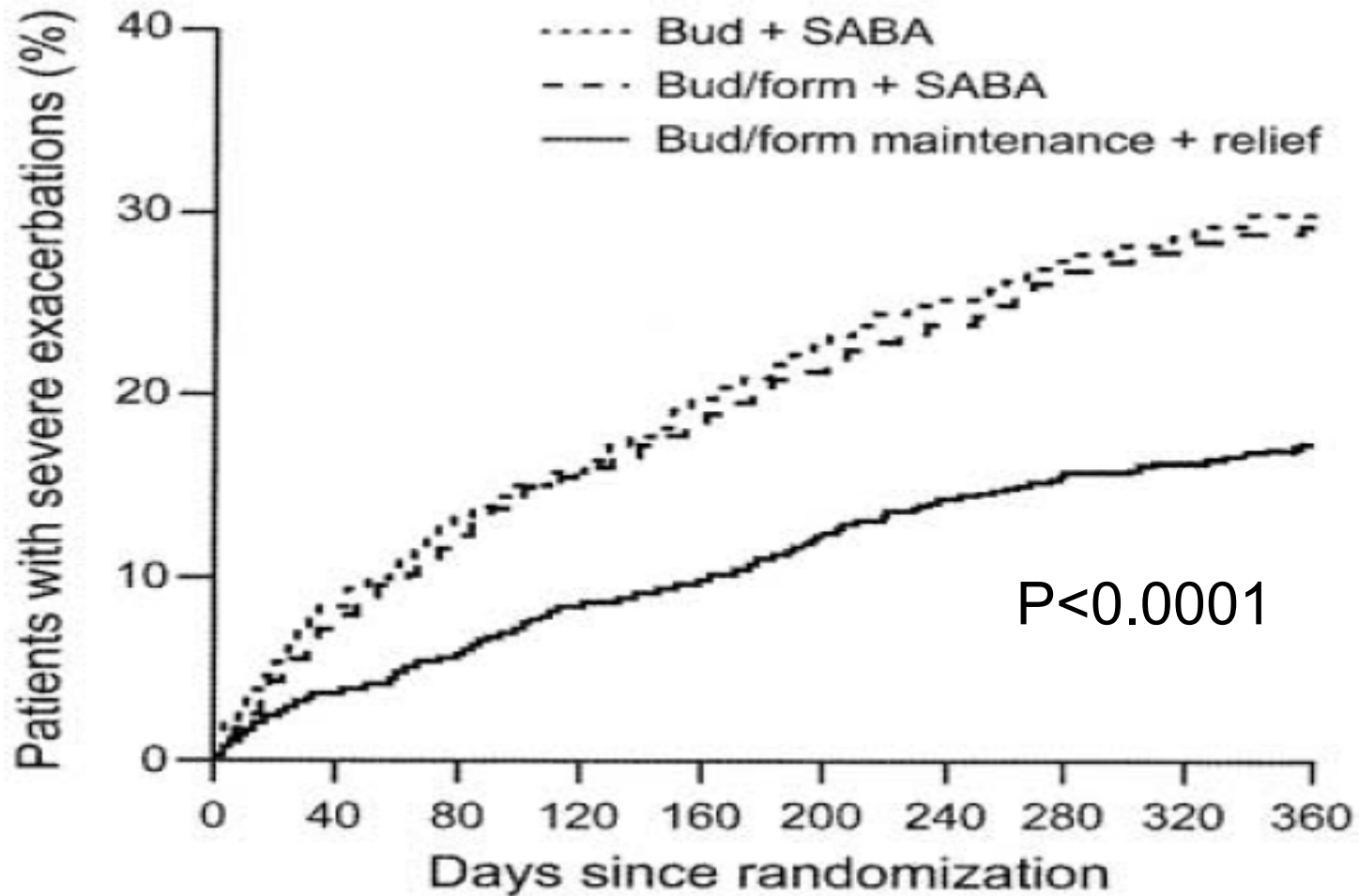- Prn ICS/SABA – rescue therapy [TREXA]

- ICS short course [MIST]

- Seasonal [PROSE]

Terminology

- Step-Up long term – for lack of control

- Step-Up short term – temporary loss of control

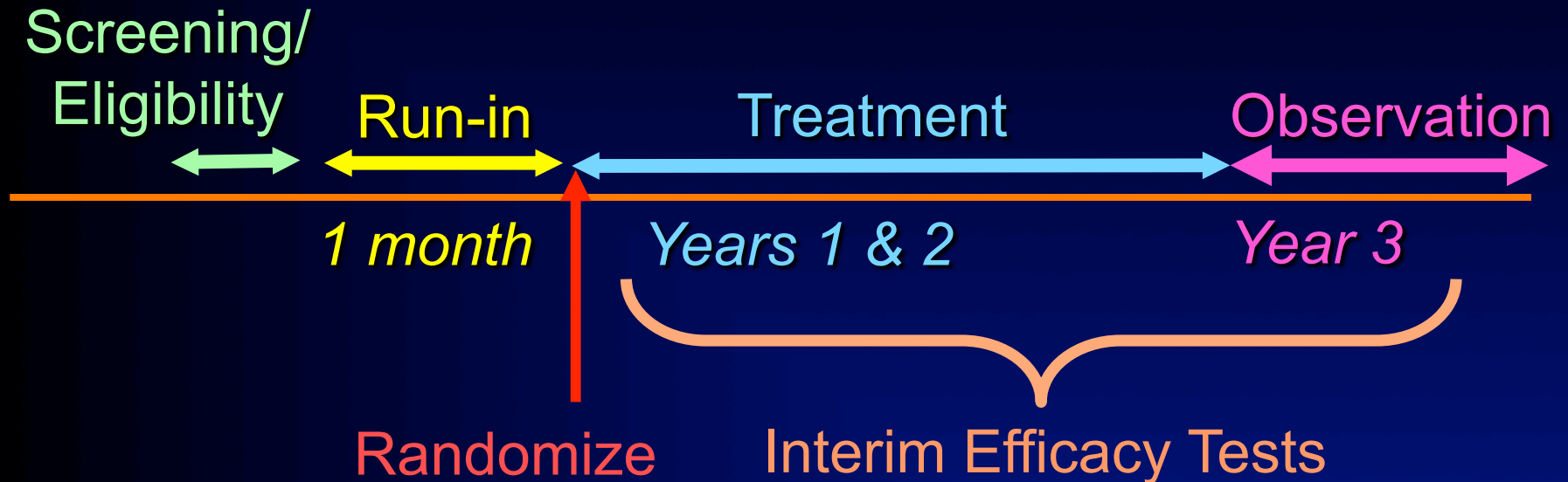- Step-Up intermittent – treating symptoms related to variability of disease

Other strategies:

- Seasonal intervention – for prevention of anticipated exacerbations

SMART Reduces Exacerbations

O'Byrne et al., AJRCCM 2005

PEAK: Study Design

Screening/
Eligibility | Run-in | Treatment | Observation

1 month | Years 1 & 2 | Year 3

Randomize | Interim Efficacy Tests

- Randomized, multicenter, double-blind, parallel group, placebo-controlled trial
- 285 two and three year olds at high-risk for asthma
- Fluticasone 44 μg/puff or placebo (2 puffs b.i.d.)

Asthma Predictive Index

- Identify high risk children (ages 2 & 3):

  - $\geq$ 4 wheezing episodes in the past year
    (at least one must be MD diagnosed)

    PLUS

  - <u>One major criteria</u> *OR* - <u>Two minor criteria</u>

    - Parent with asthma
    - Atopic dermatitis
      eosinophilia
          ($\geq$4%)
    - Aero-allergen sensitivity
      to

    - Food sensitivity
    - Peripheral
   - Wheezing not related
      infection

PEAK Study: Episode-free Days
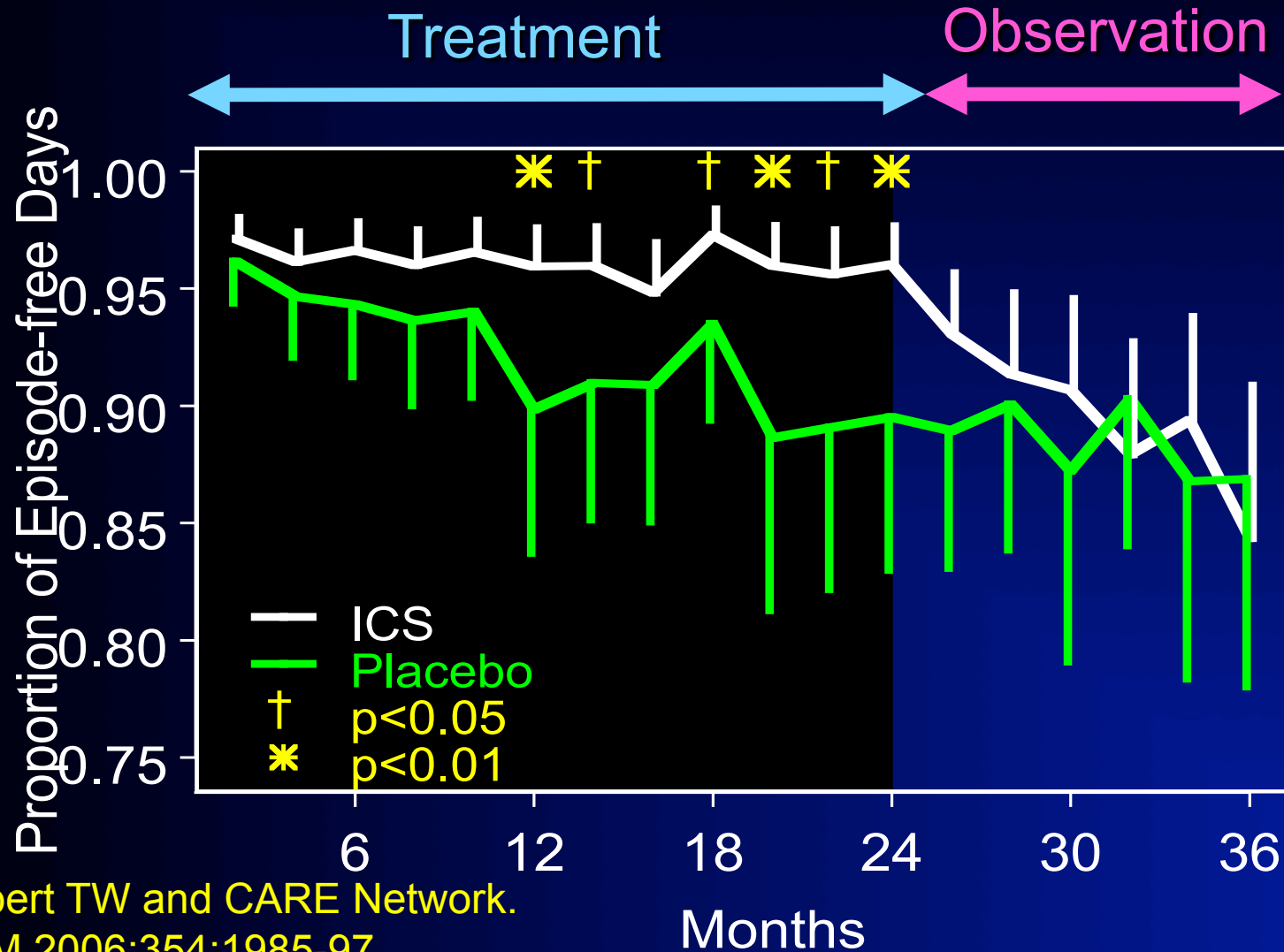
Guilbert TW and CARE Network.
NEJM 2006;354:1985-97.
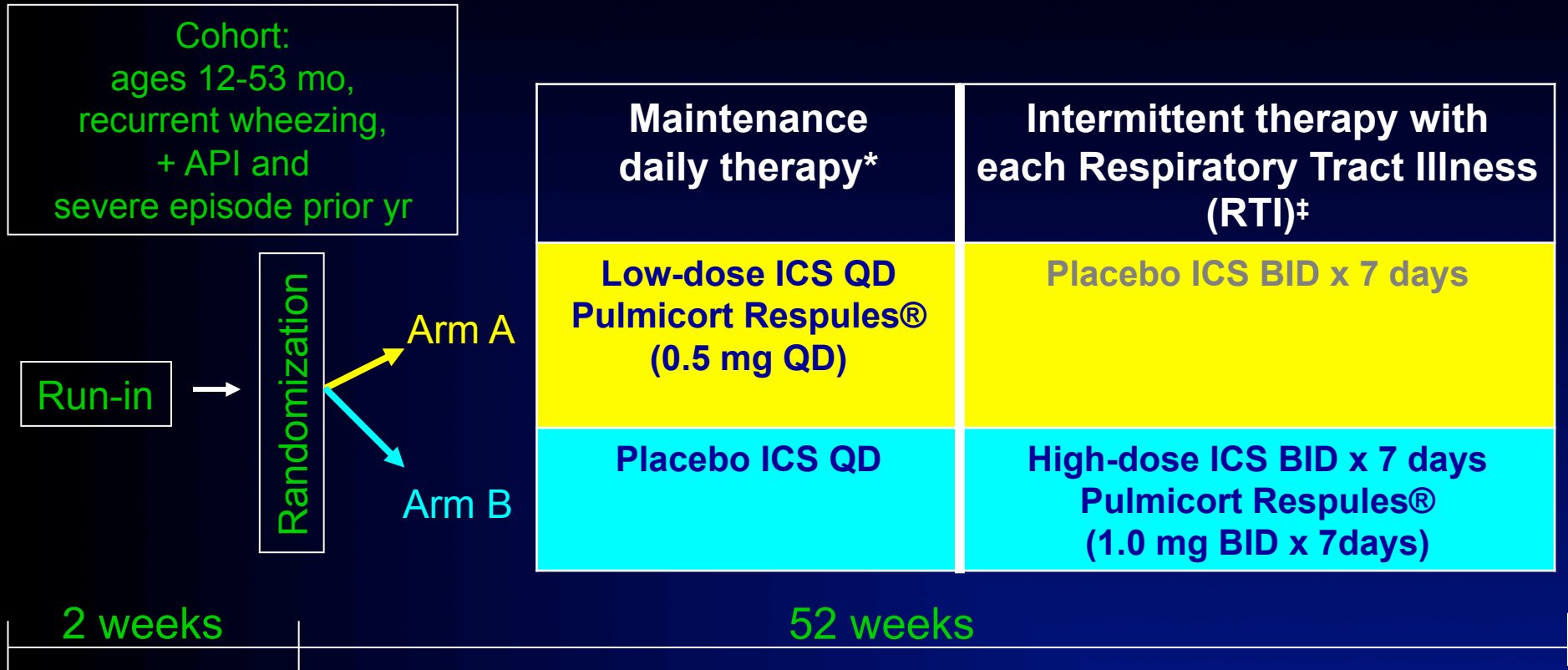
Characteristics Associated with EFD Response

Stratifying Variable	Percentage of EFDs			P-value (ICS vs Placebo)
	ICS Mean (95% CI)	Placebo Mean (95% CI)	Difference (95% CI)	
Male	93 (92, 95)	86 (83, 89)	7.3 (3.9, 11.1)	0.0005
Female	92 (89, 94)	92 (89, 94)	0.1 (-3.4, 3.5)	0.9
Caucasian	93 (91, 95)	84 (80, 88)	9.1 (4.8, 13.9)	0.0001
Non-Caucasian	92 (89, 94)	93 (91, 94)	-1.0 (-3.9, 1.7)	0.6
Run-In EFD <80%	92 (90, 94)	84 (79, 87)	8.6 (4.2, 13.2)	0.0009
Run-In EFD >=80%	93 (91, 95)	93 (91, 95)	0.0 (-2.5, 2.5)	0.9
ED/Hospitalization History	95 (93, 96)	87 (83, 90)	7.7 (3.9, 11.6	0.0004
No ED/Hospitalization History	90 (87, 92)	91 (89, 93)	-1.1 (-4.4, 2.1)	0.6
≥1 Positive Aeroallergen Skin Test	93 (91, 94)	86 (83, 89)	6.5 (3.2, 10.0)	0.0027
Negative Aeroallergen Skin Test	93 (90, 95)	92 (89, 94)	0.9 (-2.5, 4.4)	0.6

Bacharier LB et al. J Allergy Clin Immunol 2009
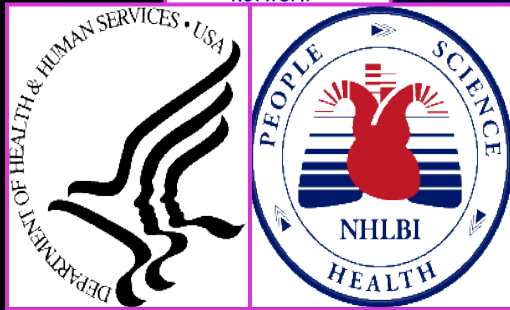
Maintenance vs **I**ntermittent Inhaled **S**teroids In Wheezing **T**oddlers (MIST) Trial

A trial in preschool children with recurrent wheezing, positive asthma predictive index and prior year severe wheezing exacerbation that compares the effect of maintenance low-dose ICS versus intermittent high-dose ICS at the onset of respiratory tract illnesses on the rate of exacerbations requiring systemic corticosteroids

MIST Design

Cohort:
ages 12-53 mo,
recurrent wheezing,
+ API and
severe episode prior yr

Run-in → Randomization

Arm A

Arm B

	Maintenance daily therapy*	Intermittent therapy with each Respiratory Tract Illness (RTI)‡
Arm A	Low-dose ICS QD Pulmicort Respules® (0.5 mg QD)	Placebo ICS BID x 7 days
Arm B	Placebo ICS QD	High-dose ICS BID x 7 days Pulmicort Respules® (1.0 mg BID x 7days)

2 weeks

52 weeks

Randomized, DBPC parallel multicenter trial comparing maintenance low-dose ICS vs intermittent high-dose ICS x 7days with every RTI on rate of exacerbations requiring systemic corticosteroids.

* Maintenance therapy continued during every respiratory tract illness
‡ Conventional episodic therapy: albuterol qid x 2 days, then prn and, if indicated, oral steroid rescue

Primary Efficacy Outcome

- Rate of severe exacerbations requiring systemic corticosteroids.
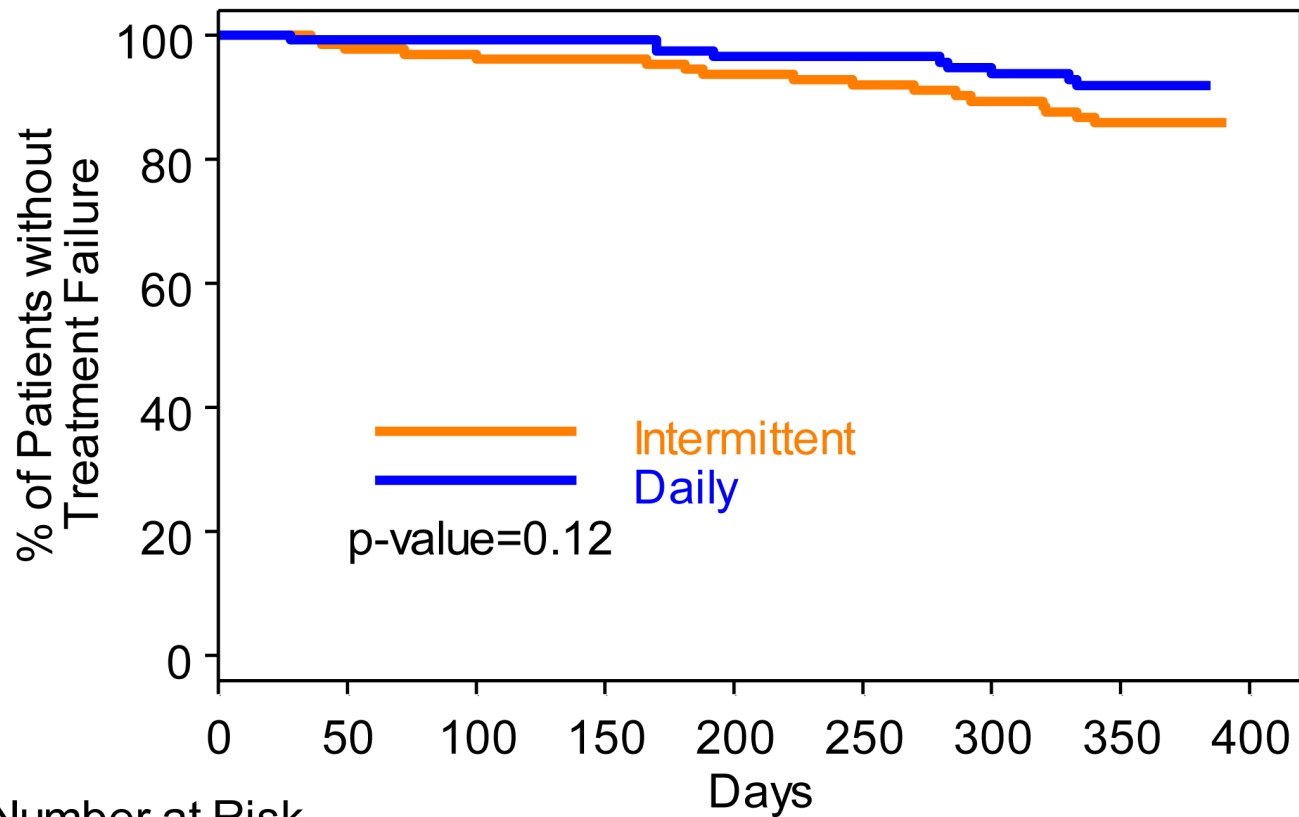
Frequency of Exacerbations
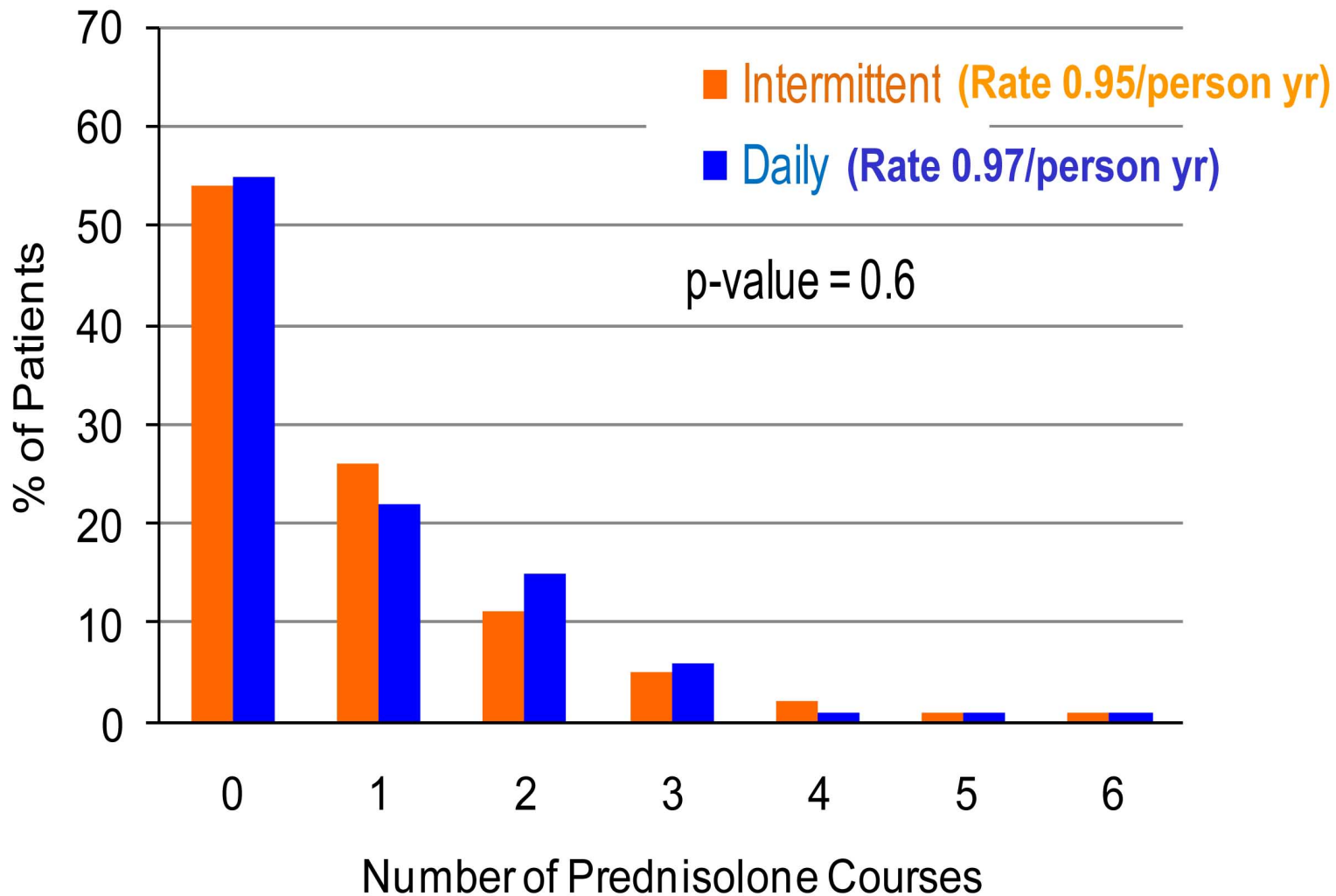
Time to 1st Exacerbation
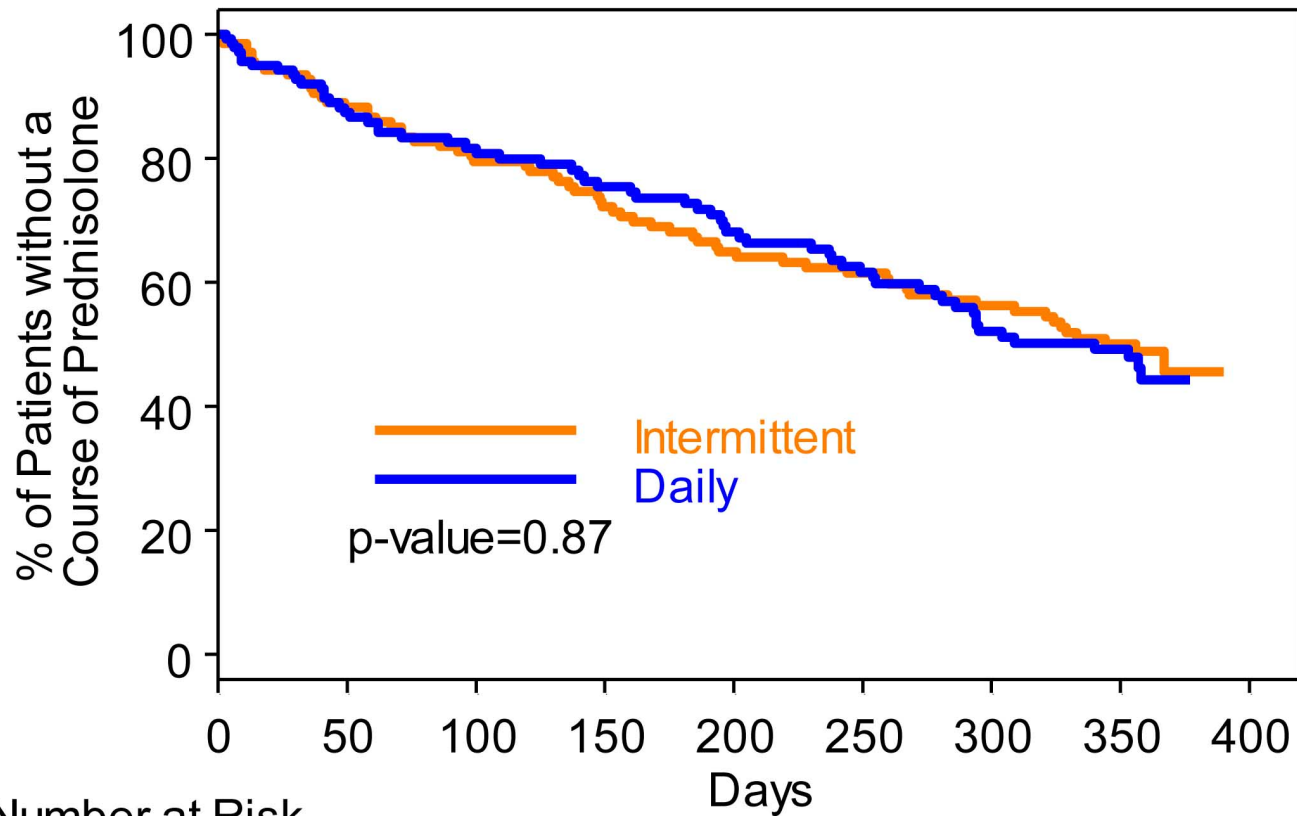
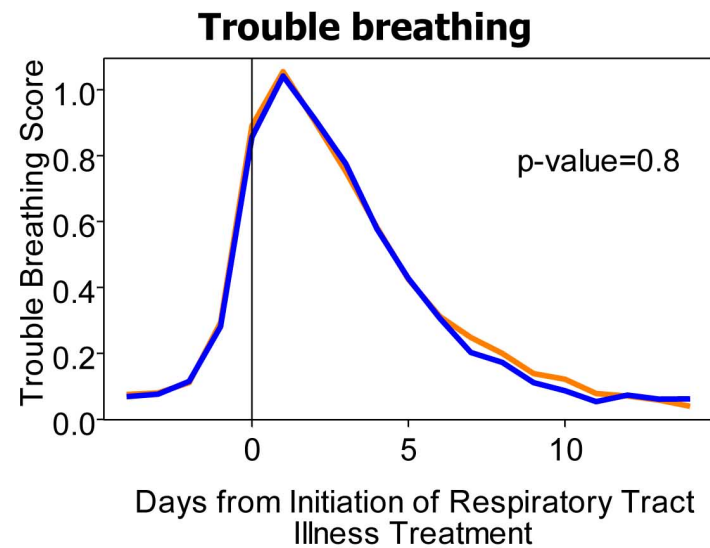# Time to Treatment Failure
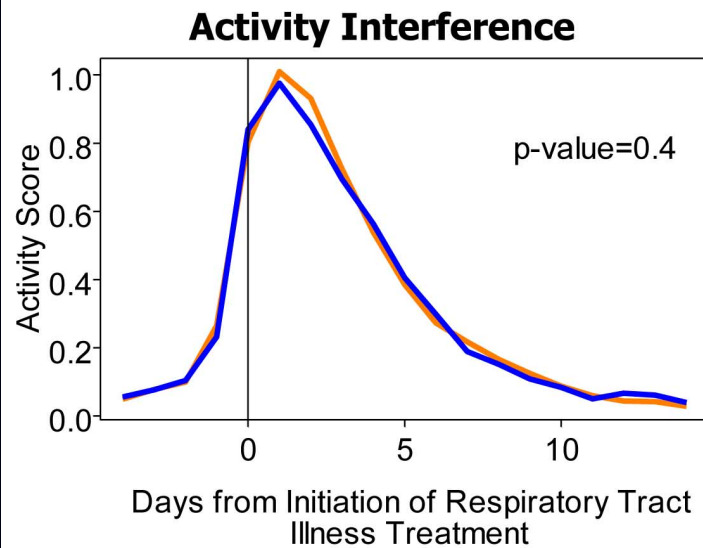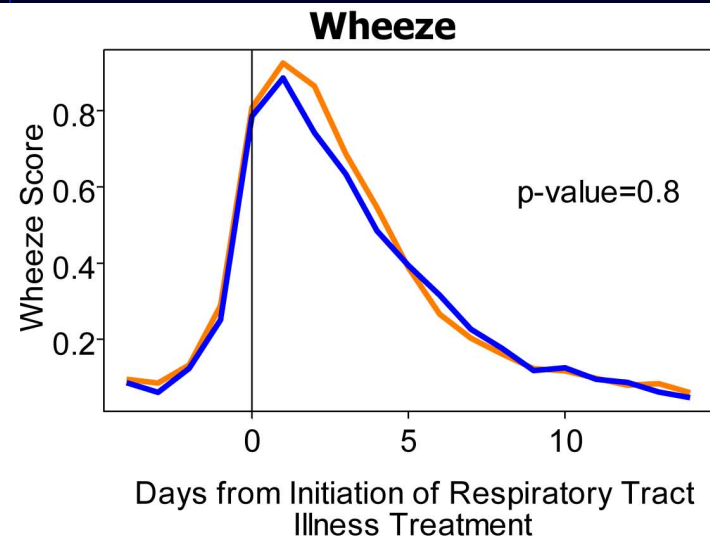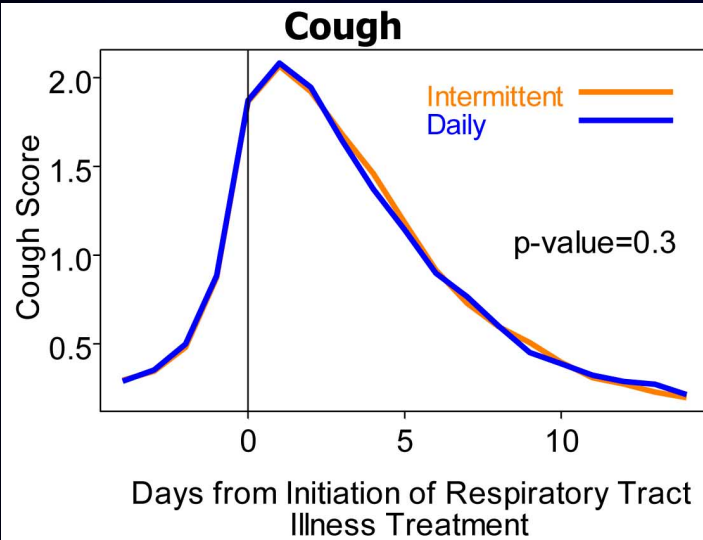
MIST Results

Secondary Outcomes

Frequency of Respiratory Tract Illnesses (RTI)
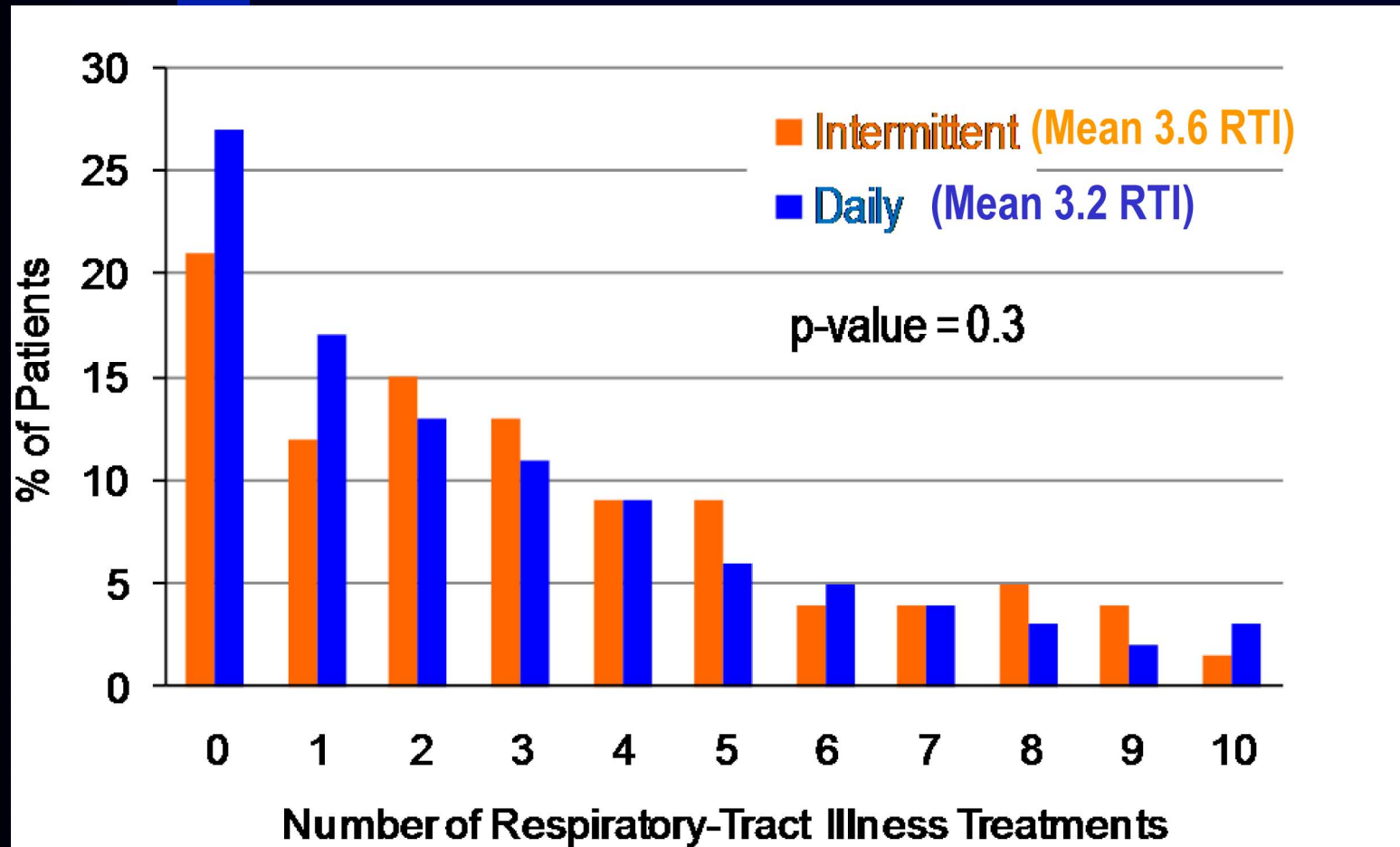
- Approximately 25% of RTI required oral prednisolone in both groups.
- Viruses detected in 83% of nasal samples during RTI in both groups.

22

Severity of RTI

Acute Visits and EFD*

Results	Intermittent (N=139)	Daily (N=139)	Treatment Effect
	Treatment Group Event Rates (per person-year)		Relative Rate
# of urgent/emergent care visits due to asthma	2.37 (1.89, 2.97)	2.40 (1.91, 3.02)	0.99 (0.72, 1.35)
	Treatment Group Averages		Average Difference
% episode-free days/year	78 (75, 80)	78 (76, 81)	-0.7 (-4, 2)
% episode-free days/year (excluding RTIs)	85 (82, 87)	84 (82, 86)	0.5 (-3, 4)

*No significant group differences.

No significant differences between groups in changes from baseline in
1. Infant Toddler Quality of Life and
2. % days with albuterol use (about 5%)

24

Individualized Therapy for Asthma in Toddlers *(INFANT)*

Anne M. Fitzpatrick, Ph.D.
Daniel J. Jackson, M.D.
Stanley J. Szefler, M.D.

And the INFANT Working Group

INFANT Innovation –
Addressing the problem in a new way

- **INFANT will be the first study to:**

    - Address the efficacy of three asthma treatment strategies head-on in preschool children.

    - Test as-needed ICS/SABA therapy in young children.

    - Predict the differential response to asthma therapies in preschool children using a combination of clinical and molecular biomarkers.

INFANT Primary Null Hypothesis

- In preschool children 12-59 months of age with persistent asthma, the following Step 2 asthma therapies will provide similar degrees of asthma control:

    – Daily inhaled corticosteroids (ICS)
    – Daily leukotriene receptor antagonists (LTRA)
    – As-needed ICS plus SABA (rescue treatment)

Study Design – *INFANT/AVICA*
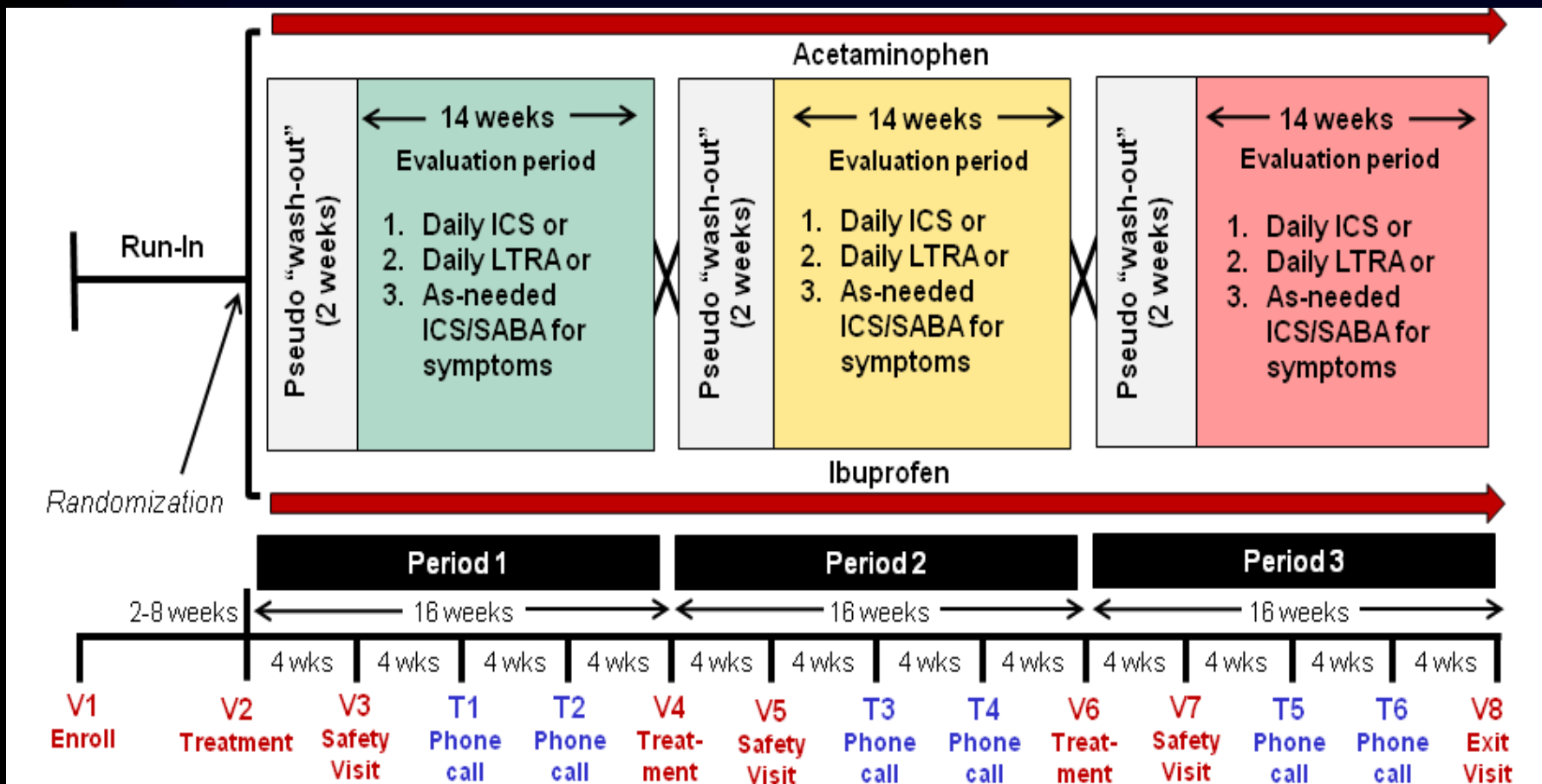
Primary Outcome

- **<u>Composite variable</u>** of asthma control encompassing domains of asthma risk and impairment, with two levels of assessment:

  - Time from the start of the treatment period to an asthma exacerbation that requires systemic corticosteroids
    - **Indicator of asthma "risk"**

  - Annualized number of asthma control days within that treatment period
    - **Indicator of asthma "impairment"**

Conclusions

- **Intermittent ICS therapy is a potential option in young children with emerging asthma**

- **Response should be monitored carefully and stepped up to continuous therapy, if**
  - **3 or more exacerbations in one year, or**
  - **symptoms occur 2 or more times per week, or**
  - **nocturnal symptoms develop**