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# Presentation Overview

- This presentation was made by Dr. Salapatek at a Cliantha Research symposium on Respiratory Drug Development in Mumbai, India in November 2018.
- It highlights the requirements for generic inhaled product development, the potential pitfalls and how cost and time efficiencies can be gained by conducting trials in both North America and India.
- This symposium was attended by Inhalation product developers from  across India.
- Dr. Salapatek is the Chief Scientific Officer for Cliantha Research and has over 20 years experience and expertise in respiratory drug development.

# Pharmacodynamic Studies for Inhaled Products : The North American Experience & a Hybrid Approach

Dr Anne Marie Salapatek MSc, PhD
Executive Vice President & Chief Scientific Officer

# Presentation Agenda

- Introduction/Background
- Inflamax experience: Pharma, Generic
- Development of Inhaled products: PK through to PD
  - PK Studies for Inhaled Products in HNV
  - Overall PD Design
- Study Design Considerations
  - Crossover vs Parallel
  - Run-In
  - Blinding
  - Quality Outcomes: Training & Standardization
- Experience:  PD studies in North America, Case Studies
- The Hybrid Approach:  PD studies in India & North America

# Nasal Sprays: Allergic & Non-Allergic Rhinitis

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## Nasal Allergy – Drugs in the Class

| Generic name | Trade Name | Manufacturer | Patent expiration |
|---|---|---|---|
| **Nasal Corticosteroids** | | | |
| Fluticasone propionate | Flonase | Glaxo SmithKline, generics | -- |
| Mometasone | Nasonex | Merck & Co | 2014-2018 |
| Flunisolide | -- | Generics | -- |
| Beclomethasone | Beconase AQ | GlaxoSmithKline | -- |
| Budesonide | Rhinocort Aqua | AstraZeneca | 2017 |
| Ciclesonide | Omnaris | Sunovion | 2017- 2020 |
| Fluticasone furoate | Veramyst | GlaxoSmithKline | 2021 |
| Triamcinolone | Nasacort AQ | Sanofi-Aventis | 2016 |
| **Nasal Anticholinergic & Antihistamines** | | | |
| Azelastine 0.1% | Astelin | MEDA Pharma, generic | -- |
| Azelastine 0.15% with sucrose | Astepro | MEDA Pharma | Excl to Aug 2012 |
| Ipratropium bromide | Atrovent nasal spray | Boehringer-Ingelheim, generics | -- |
| Olopatadine HCL | Patanase | Alcon | Jun 2011, Excl to 2013 |

**Corticosteroids:**
Allergic Rhinitis (AR)
Non-Allergic Rhinitis (NAR)


Flonase, Fluticasone proprionate


Rhinocort, budesonide


Veramyst, fluticasone furoate

**Antihistaminess:**
Allergic Rhinitis (AR)
**Anticholinergics**


Patanase, Olopatadine HCl


Astelin, Azelastine

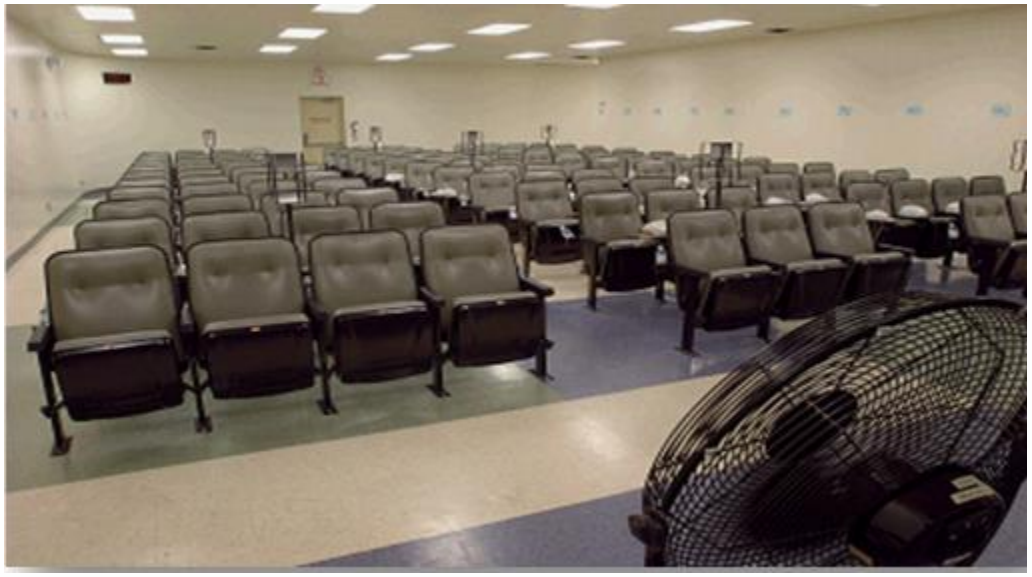

Afrin, oxymetazoline

# Developing Generic Or New FDC Nasal Sprays

## Case Study: New Fixed Dose Combination – A 505b2 Approach

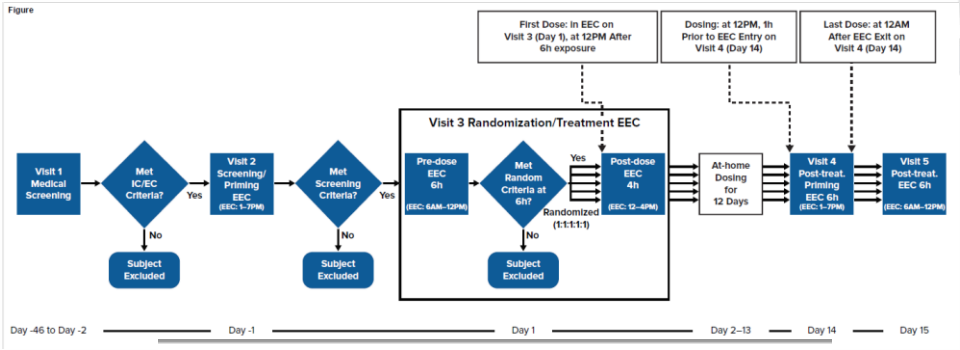
# Case Study: Nasal Spray 505b2 Approach

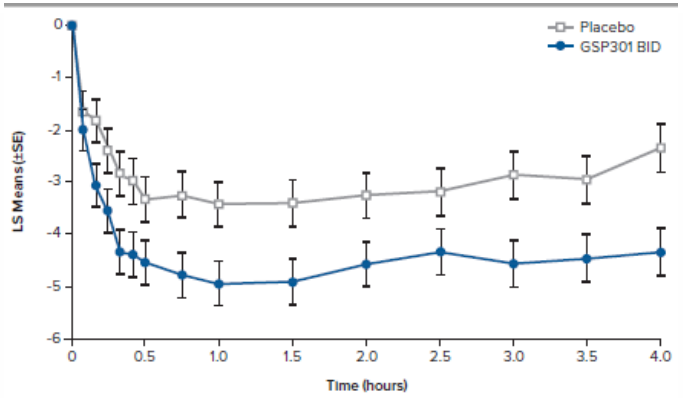
- New Fixed Dose Combination: Mometasone + Olopatadine (MOLO)
- Efficacy: MCFB Total Nasal Symptom Score (TNSS); Dose-ranging; Onset & Duration of Action
- Population:  Allergic Rhinitis – Ragweed Allergy
- Blinding – Masking
- Utilizing Environmental Exposure Chamber (EEC)
- MCFB Total Nasal Symptom Score (TNSS)

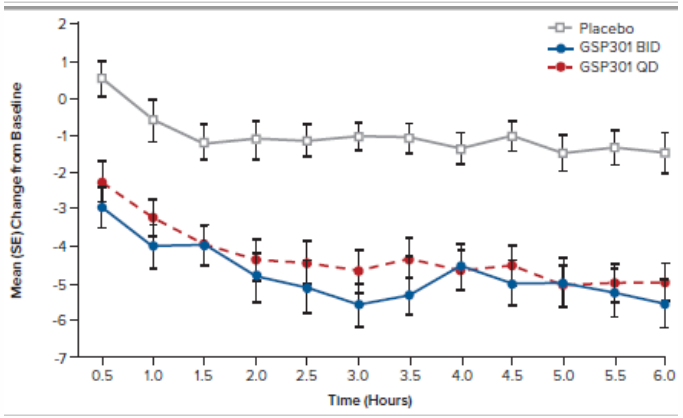



# Results

- Hybrid design of dosing in house and EEC onset of action and efficacy after one dose.
- Dosing at-home for 2 weeks and return to the EEC.
- Showed benefit over comparators.
- NDA approval




Press Release – For Immediate Release

**Glenmark Pharmaceuticals Announces FDA Acceptance of the Company's First New Drug Application for Ryaltris™ for Patients with Seasonal Allergic Rhinitis**

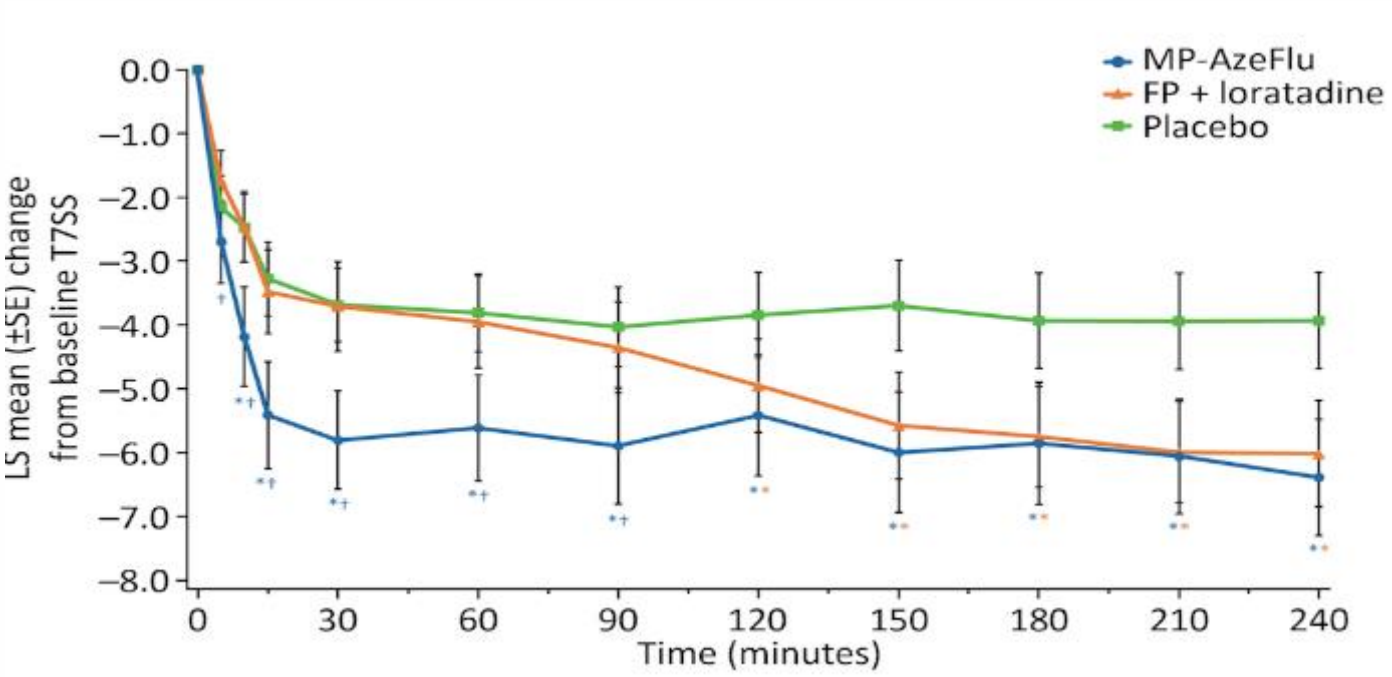
*The Prescription Drug User Fee Act (PDUFA) target action date for completion of the FDA review is March 21, 2019*

*Ryaltris (olopatadine hydrochloride [665 mcg] and mometasone furoate [25 mcg]), formerly GSP 301 Nasal Spray, is the company's leading respiratory pipeline asset*

**Mahwah, NJ; August 7, 2018** – Glenmark Pharmaceuticals, a global pharmaceutical company, today announced that the U.S. Food & Drug Administration (FDA) has accepted for review the company's New Drug Application for its leading respiratory pipeline candidate Ryaltris™ (rye - al' - tris), an investigational fixed-dose combination nasal spray of an antihistamine and a steroid, as a treatment for seasonal allergic rhinitis (SAR) in patients 12 years of age and older. Ryaltris (olopatadine hydrochloride [665 mcg] and mometasone furoate [25 mcg]), formerly GSP 301 Nasal Spray, has been conditionally accepted by the FDA as the brand name.

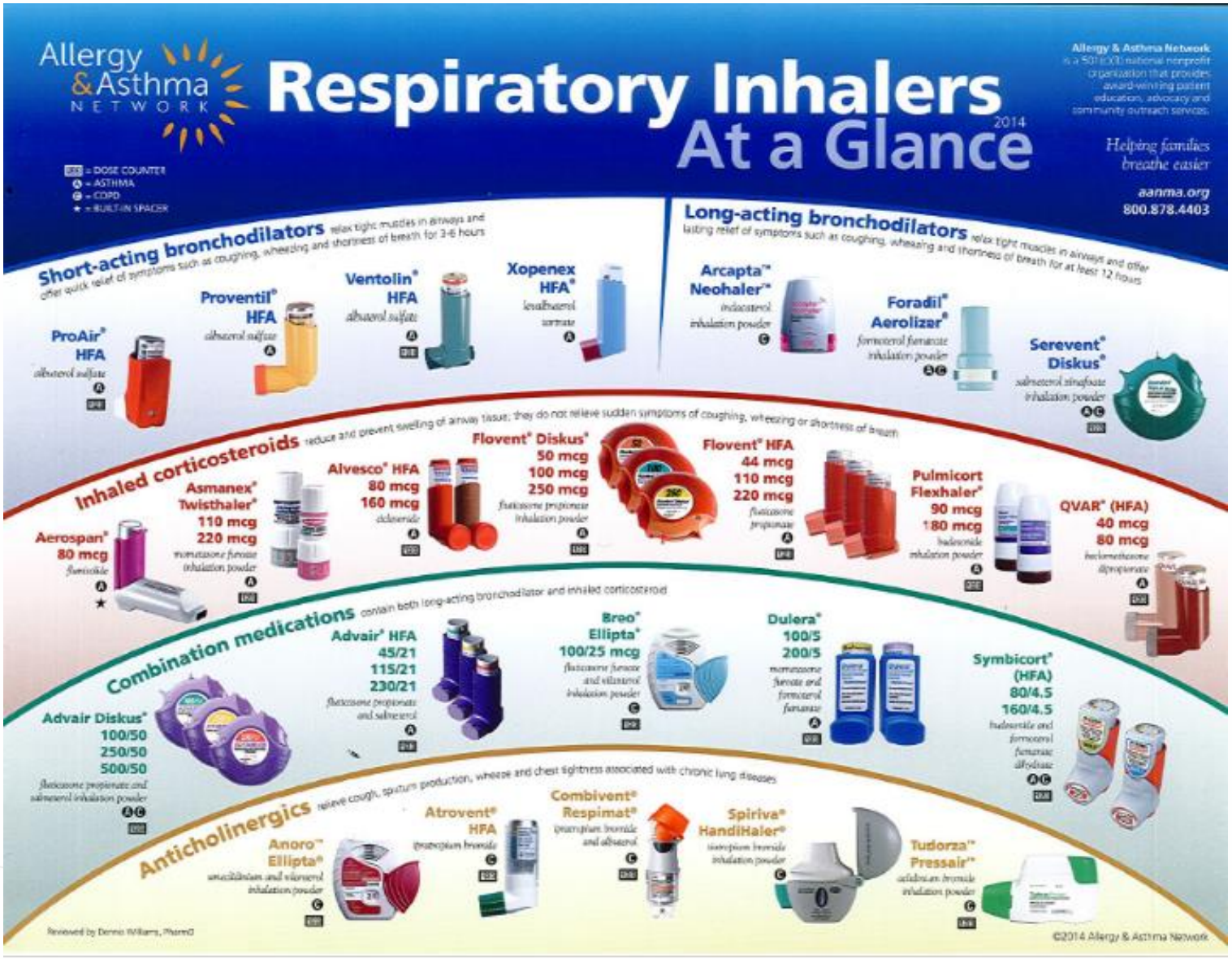
# Fast Onset of Action: Dymysta


- Dymista – Fluticasone + Azelastine n.s.
- 3-way crossover, placebo controlled trial conducted in the EEC
- Showed the fastest OOA: 5min with ePRO



# Developing Generic Inhaled Products

# Inhalers: Asthma & COPD



# FDA Guidance for Generic Anticholinergics

| Product | Class of Drug | Population | 1º Endpoint | Study Design | 1º Analysis | Duration of Dosing |
|---|---|---|---|---|---|---|
| **Tiotropium Bromide (DPI)** | Anticholinergics | COPD | FEV1 (T/R Ratio) | Parallel/ Crossover | Serial FEV1 (AUC0-24h) after treatment. | Single Dose (2 inhalations) |
| **Ipratropium Bromide (MDI)** | Anticholinergics | COPD | FEV1 (T/R Ratio) | Parallel/ Crossover | Serial FEV1 (AUC0-6h) after treatment. | Single Dose (2 inhalations) |
| **Aclidinium Bromide (DPI)** | Anticholinergics | COPD | FEV1 (T/R Ratio) | Parallel/ Crossover | Serial FEV1 (AUC0-6h) after treatment. | Single Dose (1 inhalation) |
| **Ipratropium Bromide & Albuterol Sulfate (MDI)** | Anticholinergics & SABA | COPD | FEV1 | Parallel (Test/Ipratropium/ Albuterol) | Serial FEV1 (AUC0-8h) after treatment. | Single Dose- 12 weeks |

# FDA Guidance for: Inhaled Short & Long Acting Bronchodilators (β agonists)

| Product | Drug Class | Popula -tion | 1º End point | Study Design | 1º Analysis | Duration of Dosing |
|---|---|---|---|---|---|---|
| **Albuterol Sulfate (MDI)** | SABA | Asthmatics | FEV1 | Crossover Bronchoprovocation or Bronchodilatation Study | Post-dose PC20 or PD20 (Provoactive conc or dose) | Single Dose – 24hr washout period |
| **Salmeterol Xinafoate (DPI)** | LABA | Asthmatics | FEV1 (T/R Ratio) | Parallel/ Crossover | Serial FEV1 (AUC0-12h) after treatment. | Single Dose (1 inhalation) |
| **Formoterol Fumarate (DPI)** | LABA | Asthmatics | FEV1 (T/R Ratio) | Parallel/ Crossover | Serial FEV1 (AUC0-12h) after treatment. | Single Dose (1 inhalation) |
| **Levalbuterol Tartrate (MDI)** | SABA | Asthmatics | FEV1 | Crossover Bronchoprovocation Study | Post-dose PC20 or PD20 (Provoactive conc or dose) | Single Dose – 24hr washout period |
| **Indacaterol maleate (DPI)** | LABA | COPD | FEV1 (T/R Ratio) | Parallel/ Crossover | Serial FEV1 (AUC0-24h) after treatment. | Single Dose (1 inhalation) |

# FDA Guidance for: Inhaled Corticosteroids/ Combo Medications Inhalers

| Product | Class of Drug | Population | 1ry Endpoint | Study Design | 1ry Analysis | Duration of Dosing |
|---|---|---|---|---|---|---|
| Fluticasone propionate (nasal spray) | ICS | SAR | TNSS | Parallel (multicenter recommended) | MCFB through the treatment period | Dose: once daily for 14-days |
| Budesonide (DPI) | ICS | Asthmatics | FEV1 (T/R Ratio) | Parallel | FEV1 prior to dosing on the last day | Dose: 4-inhalations twice daily for 4-weeks |
| Beclomethasone dipropionate | ICS | Asthmatics | FEV1 | Parallel | FEV1<br>AM PEF<br>Asthma symptoms | Dose: twice daily |
| Mometasone furoate (DPI) | ICS | Asthmatics | FEV1 (T/R Ratio) | Parallel | FEV1 prior to dosing on the last day | Dose: 2-inhalations once daily for 4-weeks twice daily for 4-weeks |
| Fluticasone Propionate & Salmeterol (DPI) | ICS & LABA | Asthmatics | FEV1 | Parallel | a) serial FEV1 (AUC0-24h) after first dose to assess salmeterol component and b) FEV1 prior to dosing on the last day to assess fluticasone | Dose: twice daily for 4-weeks |
| Fluticasone Furoate & Vilanterol (DPI) | ICS & SABA | Asthmatics | FEV1 | Parallel | a) serial FEV1 (AUC0-24h) after first dose to assess salmeterol component and b) FEV1 prior to dosing on the last day to assess fluticasone | Dose: 1-inhalation once daily for 4-weeks |
| Mometasone furoate & Formoterol fumarate (MDI) | ICS & LABA | Asthmatics | FEV1 | Parallel | a) serial FEV1 (AUC0-12h) after first dose to assess salmeterol component and b) FEV1 prior to dosing on the last day to assess fluticasone | Dose: 2-inhalations twice daily for 4-weeks |
| Budesonide & Formoterol Fumarate dehydrate (MDI) | ICS & LABA | Asthmatics | FEV1 | Parallel | a) serial FEV1 (AUC0-12h) after first dose to assess salmeterol component and b) FEV1 prior to dosing on the last day to assess fluticasone | Dose: 2-inhalations twice daily for 6-weeks |

# Considerations:
# Pharmacokinetic Studies for Inhaled Products

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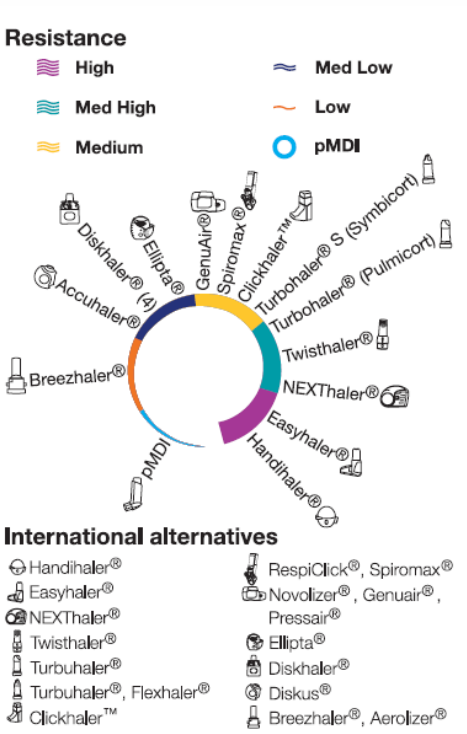
- Healthy Normal Volunteers (HNV)
  - By definition are not used to using inhalers or performing any lung function testing.
  - Require training to achieve the following:
    - Adequate dosing e.g. use In-check Dial G16 trainer
    - Consistent dosing – in 'green' good, 'red' failed
    - Clients come to retest their products in our experienced clinic
- Important for good results also require:
  - Experienced Staff for patient coaching/training
  - Experienced Staff for fast and quality blood draws and sample handling and preparation → laboratory analysis.
  - Good chain of custody for samples

# Training

- For pMDI
  - Attachments can be added to simulate the appropriate resistances

HOW TO USE ADAPTERS

## Setting '0' pMDI

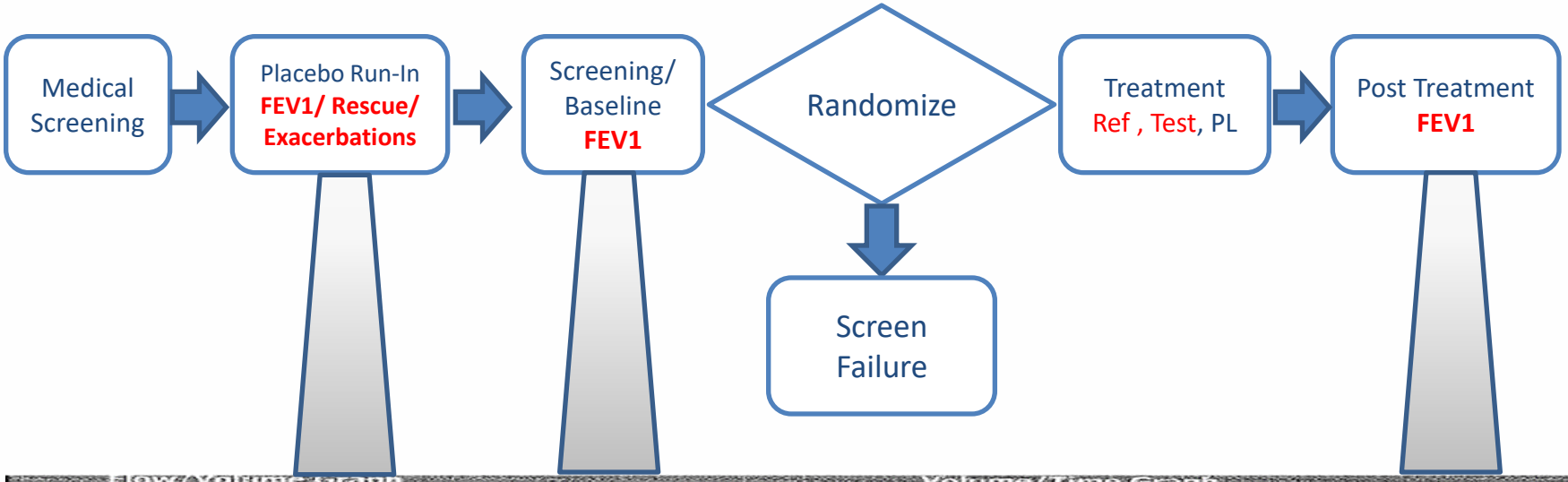
Specific adapters are available for the following devices:-

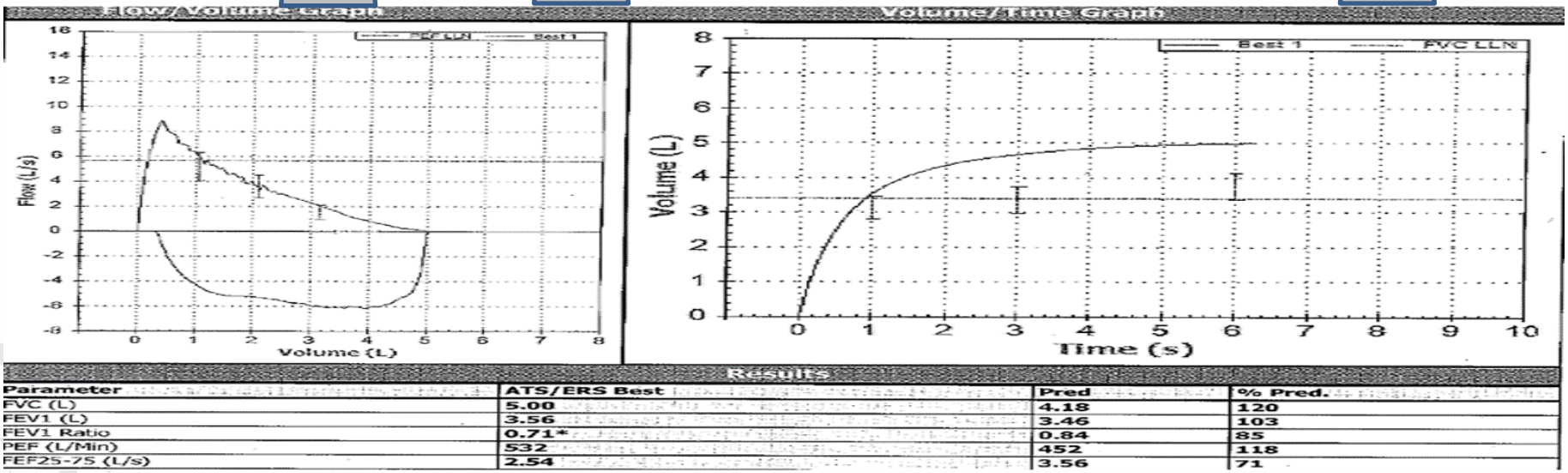
- Turbohaler
- Promedica
- HandiHaler
- Diskhaler 4 Blister
- Clickhaler
- Easyhaler
- Autohaler/Accuhaler/Discus
- Easybreath
- Foradil
- Accuhaler/Discus
- Easybreath- Breezhaler/Foradil
- Grenuair
- Evohaler - freeflow setting

# Design Considerations: FEV1 Measures & Profiles

- ICS
  - ≥4 week treatment
- SABA
  - After bronchodilation – Serial FEV1s after 1 dose
  - Bronchoprotection/broncoprovocation – FEV1 after Tx with SABA and looking at the PC20
- Anticholinergics: Tiotropium
  - Crossover or Parallel:  Serial FEV1 after 1 dose
- Combination Products:  Advair©, Symbicort©
  - Fast Acting Component (β agonist) measured after 1 dose: Serial FEV1s – Area Under the Curve (AUC)
  - Slow Acting Component (ICS) measured after a long term dose, 4 or 6 weeks, FEV1 at clinic

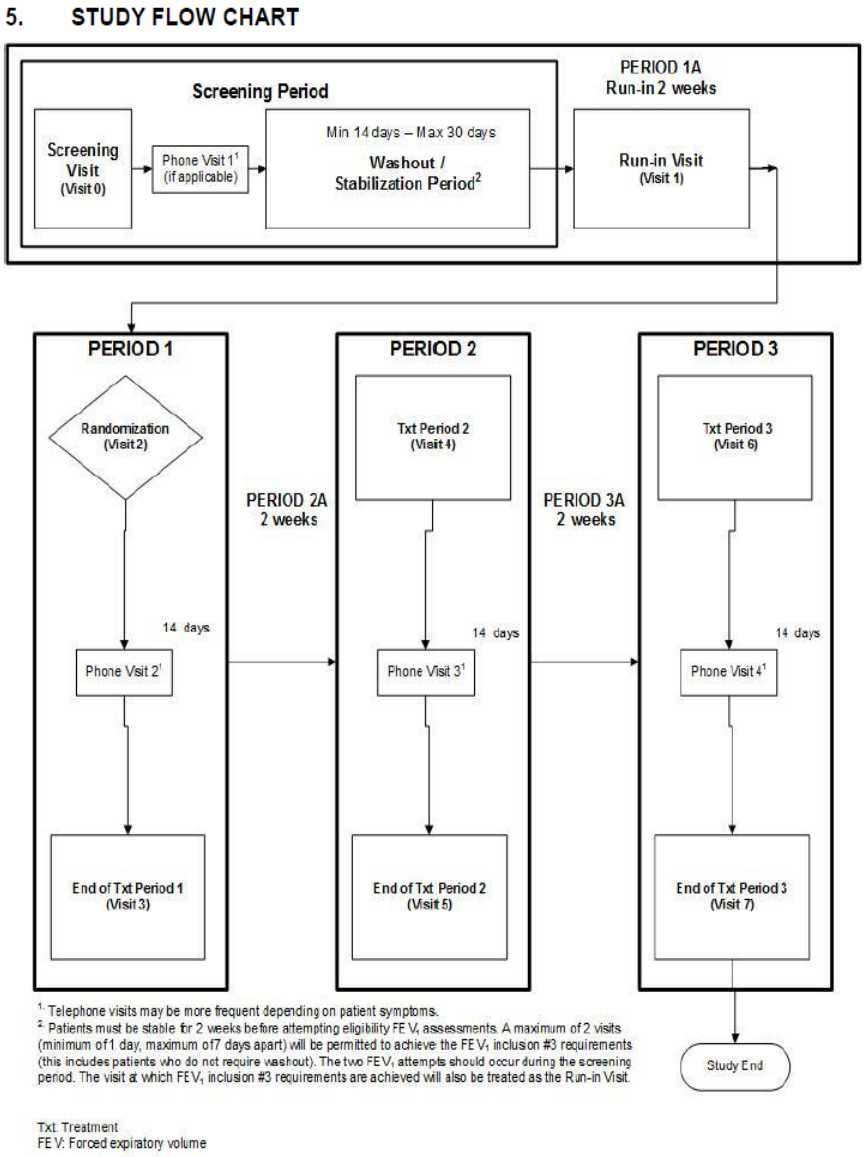
# Overall Study Design: Inhaled Products



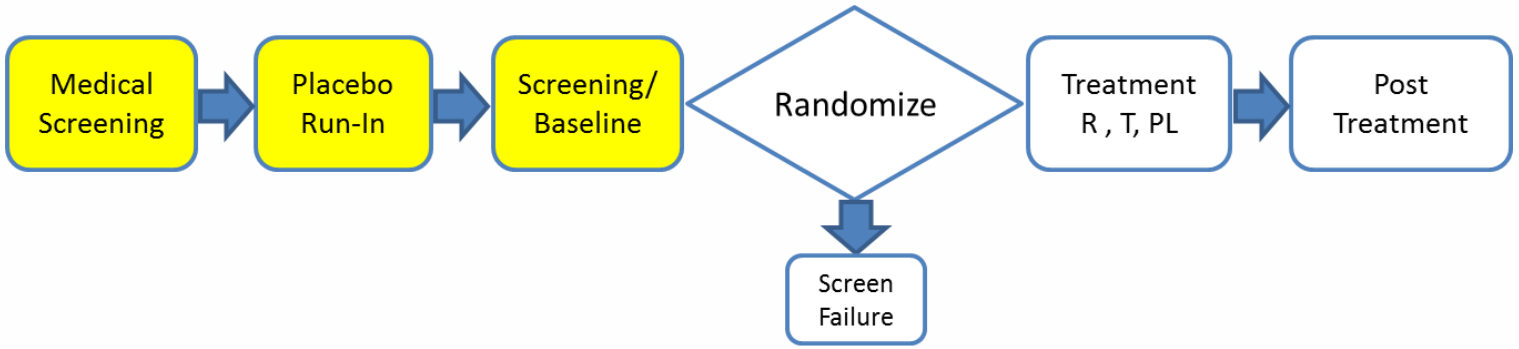



# Design Considerations: Crossover vs Parallel

- General: SABA, LABA & Anticholinergics allow X-over
- Fluticasone + Albuterol
- FDA permission though not in guidance
- Safety cover – ePDAT, monitoring
- PROS:
  - Fewer patients
  - Overall faster
- CONS:
  - Longer duration for each patient need to assure safety
  - Risk of patient withdrawal greater



# Considerations: Screening & Placebo Run-In



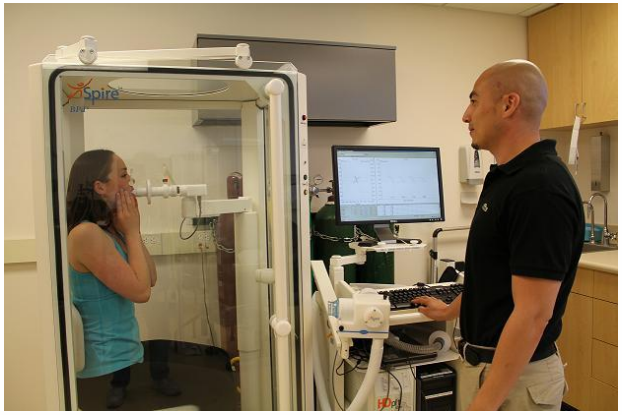

- **Population – Asthmatics, COPD: Severity, Current Tx → Recruitment**
  - **Screening:** Medical History, Pulmonary Function Testing including reversibility to confirm diagnosis and demonstrate that there can be improvement potential for Test drug testing. E.g. Tiotropium Study – need patient to show reversibility
- **Placebo Run-In:**
  - **Washout** of current medications that would interfere with testing of Reference vs Test vs Placebo
  - Need to demonstrate **Stability and Safety** to be studied throughout the course of the trial even when or if on placebo, i.e. during crossover period or randomly assigned in a parallel design.

# Considerations: Product Blinding

- **Products must be identical in dosage and performance**
  - Devices that are not identical in appearance leads to unblinding of patient and Investigator.
  - Dry Powder Inhalers (DPIs) particularly difficult:
    - Patents on DPIs
    - Jurisdictional differences in DPIs
- **Approaches:**
  - Over-masking where possible – e.g. foils, clam shells for nasal sprays
  - Partial Double Dummy Designs, a part solution:
    - Only partially blinded: e.g. Test product DPI has active and placebo but Reference product still identifiable even if Reference with Active and Placebo are both tested.
    - Evaluator, Investigator and other analysis staff to remain blinded and patient to have limited access to products (single dose studies).

# Considerations: Respiratory Measures

- Experienced & Trained Staff are vital
- Experienced Respiratory Technicians
- PFT Capabilities for clinical research with extensive experience in:
  - Full PFT, DLCO, Volumes including body box
  - FeNO
  - Challenge procedures: Methacholine, Histamine, Ozone, Adenosine, Exercise, Cold Air
  - Biomarker measurement including Induced Sputum, Exhaled breath condensate and BAL procedures
  - Though not required endpoints demonstrate ability to well characterize or phenotype patients



# Spirometry

- For example:
  - Team of Registered Respiratory Therapists to perform Pulmonary Function Testing (PFT)
  - The College of Respiratory Therapists of Ontario (CRTO) is the governing body that regulates Respiratory Therapy in Ontario
- Able to have patients to perform reproducible Spirometry according to American Thoracic Society and the European Respiratory Society (ATS/ERS) Guidelines.
- Consistent evaluators
- Full lung function including lung volumes and transfer factors, as well as differential exhaled nitric oxide
- Spiroair – the 'Gold Standard' PFT testing

# Training & Standardization

# Considerations: Standardization

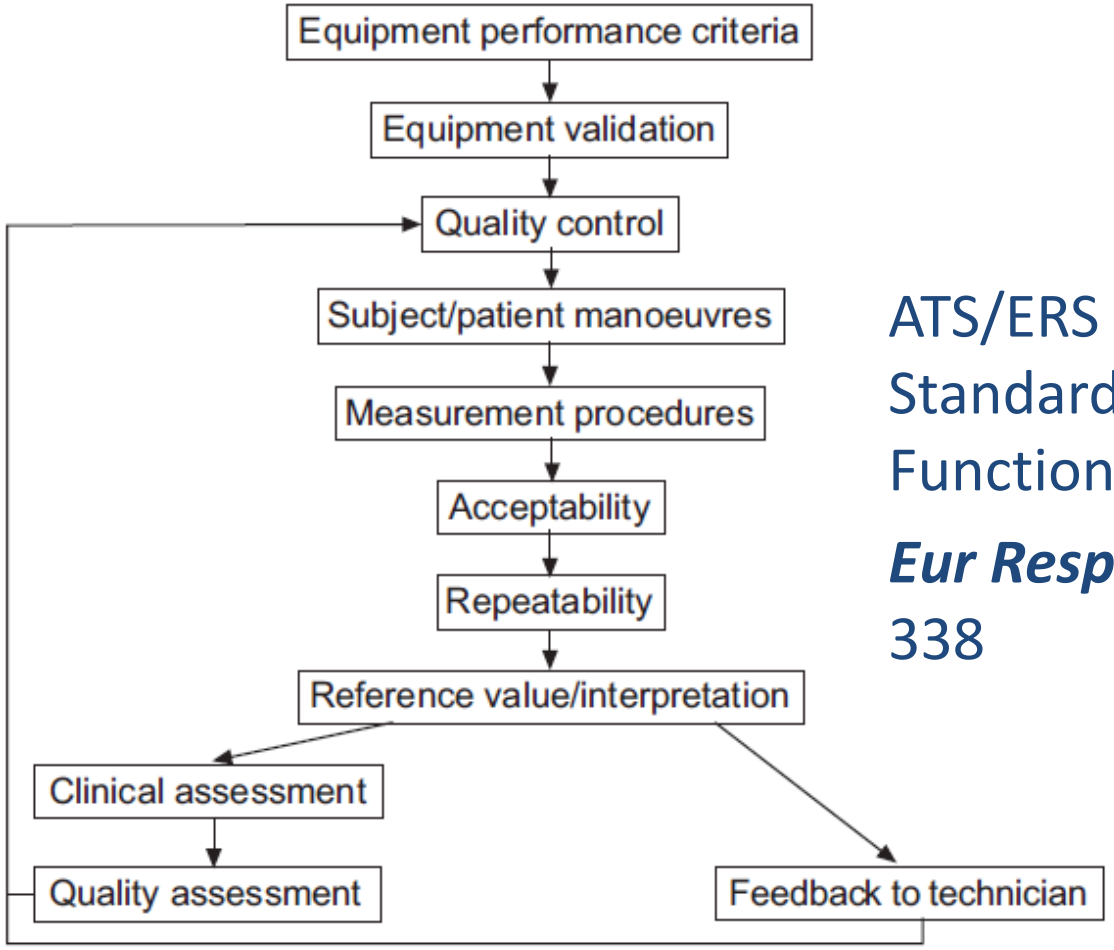



**FIGURE 1.** Spirometry standardisation steps.

ATS/ERS Task Force: Standardization of Lung Function Testing

***Eur Respir J*** 2005; 26:319-338

# Considerations: Training

- Experience
- Coaching
- Interpretation
  - No testing into compliance
  - Within-manoeuvre criteria of acceptability
  - Between-manoeuvre criteria of acceptability
  - Reference values & interpretation
- ATS: Recommendations for Standardized Pulmonary Function Report 2017: Recommend Global Lung Function Initiative (GLI)-2012 multiethnic spirometry reference values for NA and elsewhere

**TABLE 5** Summary of within- and between-manoeuvre acceptability criteria

**Within-manoeuvre criteria**

Individual spirograms are "acceptable" if

They are free from artefacts [3]

Cough during the first second of exhalation

Glottis closure that influences the measurement

Early termination or cut-off

Effort that is not maximal throughout

Leak

Obstructed mouthpiece

They have good starts

Extrapolated volume <5% of FVC or 0.15 L, whichever is greater

They show satisfactory exhalation

Duration of ⩾6 s (3 s for children) or a plateau in the volume–time curve or

If the subject cannot or should not continue to exhale

**Between-manoeuvre criteria**

After three acceptable spirograms have been obtained, apply the following tests

The two largest values of FVC must be within 0.150 L of each other

The two largest values of $FEV_1$ must be within 0.150 L of each other

If both of these criteria are met, the test session may be concluded

If both of these criteria are not met, continue testing until

Both of the criteria are met with analysis of additional acceptable spirograms

or

A total of eight tests have been performed (optional) or

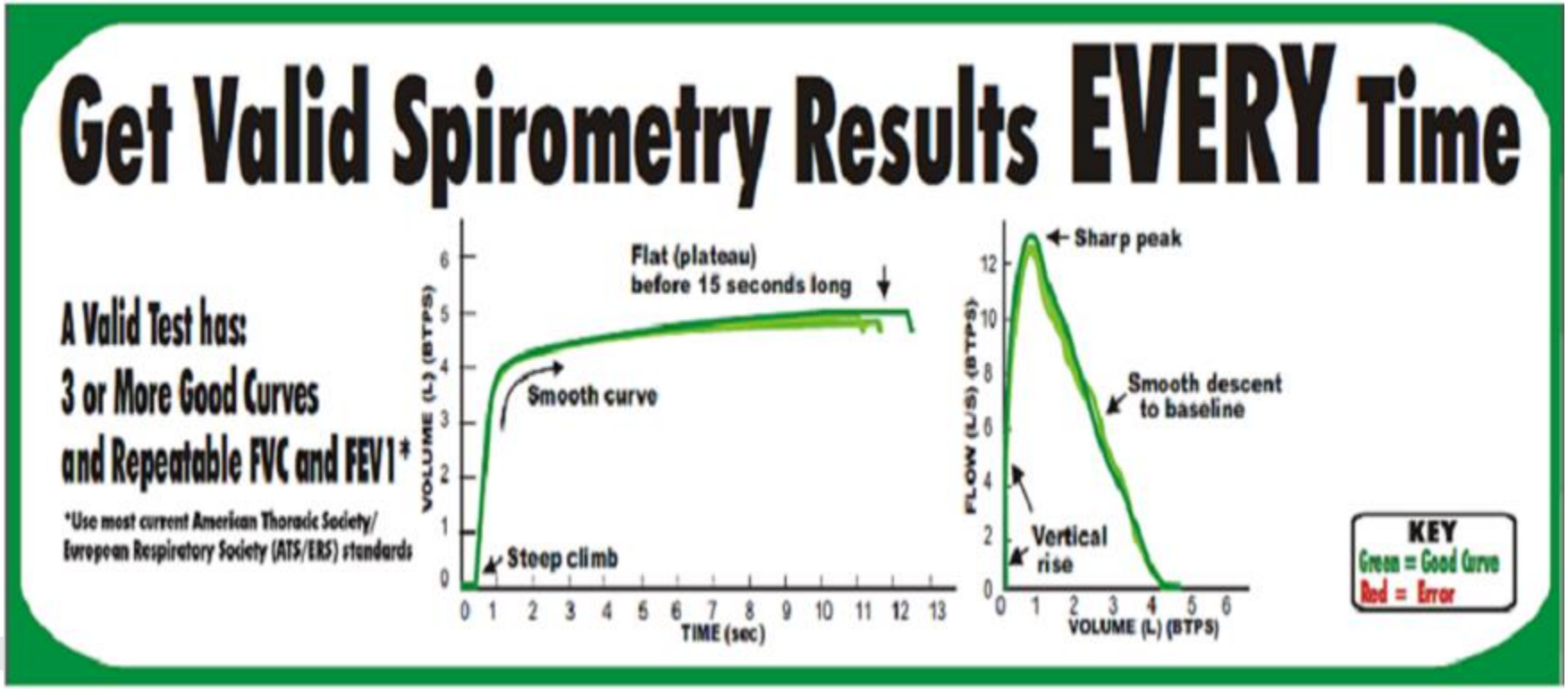
The patient/subject cannot or should not continue

Save, as a minimum, the three satisfactory manoeuvres

FVC: forced vital capacity; $FEV_1$: forced expiratory volume in one second.

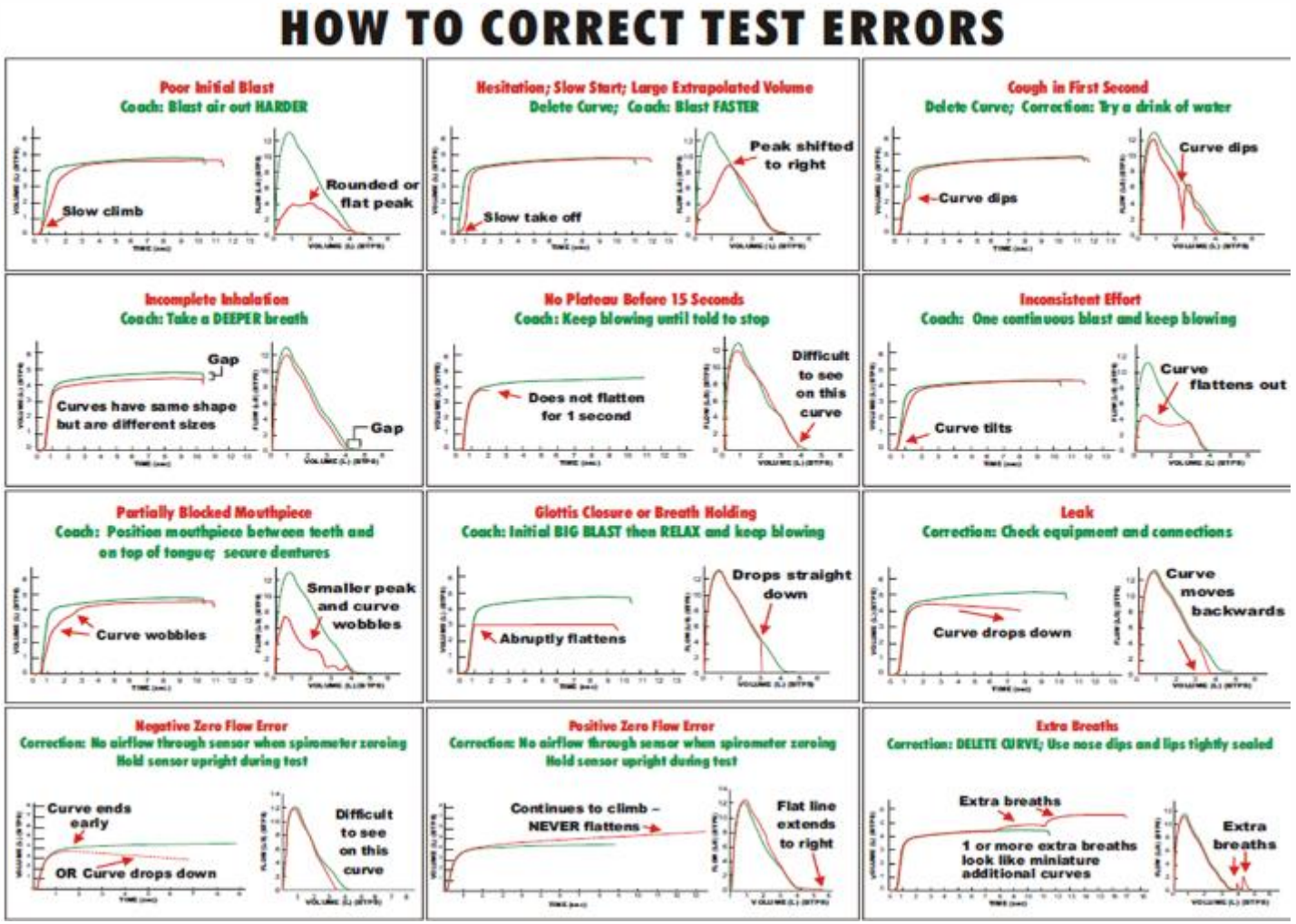
# Coaching

## Its All in the Coaching!!!



# An Introduction to Spirometry

- Spirometry Performance Issues



# Respiratory Service Providers

- Provide equipment
  - Allows for consistency of measures
- Provide Training
  - Overview if lung function testing
  - Lung function testing guidelines and considerations
  - How to identify good/bad test sessions
  - Online video training
- Over-reading
  - Over-readers review the test results, confirm that the tests have been performed correctly and that they meet relevant guidelines to help ensure quality data is submitted.

# PD Studies in North America and india

# Pharma & Generics Experience

## Innovator Products

- Schering Plough: Mometasone nasal and inhaled
  - Dose ranging study of nasal mometasone
  - Phase II study with Mometasone inhaled
- Meda now Mylan
  - Dymista nasal spray
- Genentech: Xolair
  - Pivotal studies with Severe adult asthma
  - Cat room challenge study with Xolair in severe asthma
- GSK
  - Veramyst – Fluticasone furoate
  - Advair
- Alcon: Olopatadine
  - Multiple EEC studies

## Generic or 505B2 Products

- Olopatadine + Mometasone – nasal spray
- Fluticasone + Salmeterol - inhaled
- Budesonide + Formoterol - inhaled
- Mometasone Furoate, nasal spray
- Albuterol – inhaled
- Tiotropium
- Other new formulations or devices for steroids – 505b2 approach

# Challenges of NA Only

- Recruitment
  - Slow and require many Investigators – Allergy & Asthma Foundation of America
    - Advisory Board – only CRO member, recruit through this membership over 50,000 online members patients and caregivers
  - Treatment level of patients is high → Washout of treatment requires time and good patient management
  - Costs are high, cost over-runs
- Monitoring
  - Ensure patient population's safety and is appropriate, remote monitoring
  - Knowledgeable in the subject matter area

# Case Study: Albuterol Bronchoprovocation Study Advantage to NA – Canada only

**Pharmacodynamic (PD) BE Study** *Recommended Apr 2013; Revised Jun 2013; Dec 2016* 4

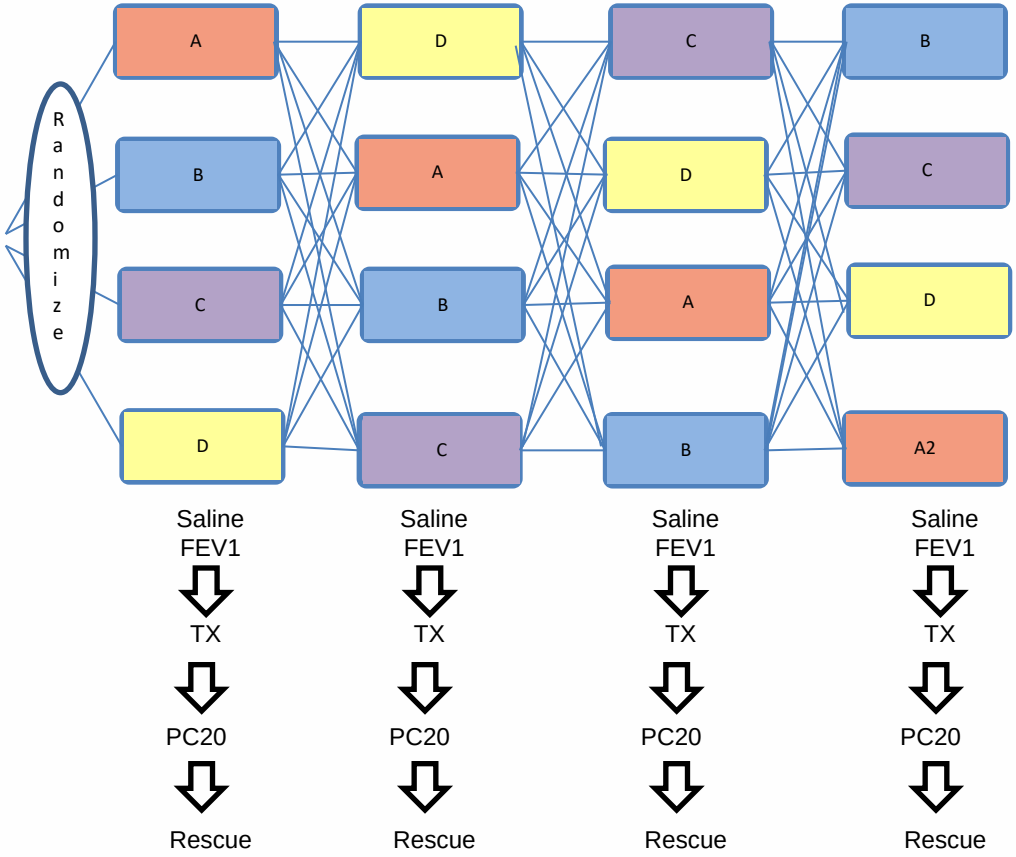
7a. Type of Study: Bronchoprovocation study

- Design: Single-dose, double-blind, double dummy, randomized, crossover study that is recommended at minimum to consist of:
- Zero dose: One actuation each from two different placebo R inhalation aerosols and one actuation each from two different placebo T inhalation aerosols
- 0.09 mg of R: One actuation each from the R inhalation aerosol and the placebo R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols
- 0.18 mg of R: One actuation each from two different R inhalation aerosol and one actuation each from two different placebo T inhalation aerosols
- 0.09 mg of T: One actuation each from the T inhalation aerosol and the placebo T inhalation aerosol and one actuation each from two different placebo R inhalation aerosols
- No less than a 24 hour washout period should be allotted between treatments.

# Study Design

Screening

FEV1
Baseline PC
20




V1
D-1

V2
D0
(D-1+1)-13d

V3
D1
(DO+48h)+3d

V4
D2
(D1+48h)+3d

V5
D3
(D2+48h)+3d

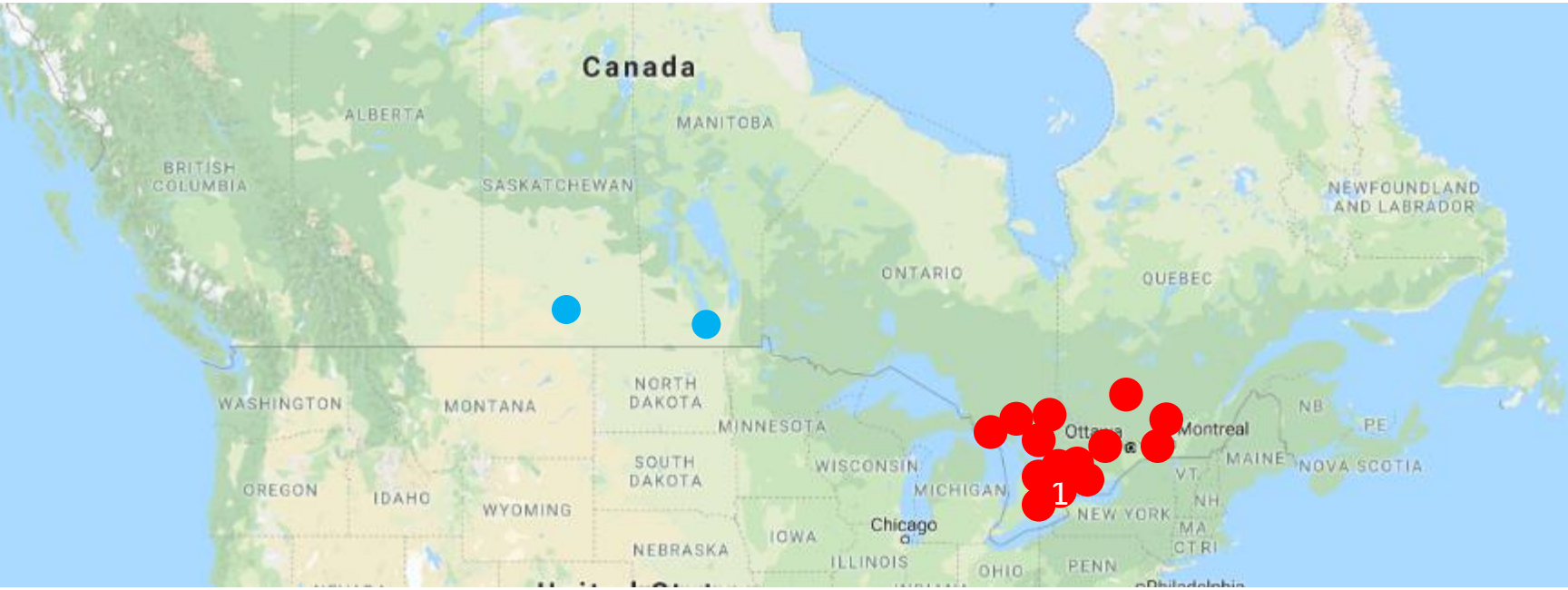
# Study Design contd.

- **PD endpoint(s):** Post-dose PC20 or PD20, which are the provocative concentration or dose, respectively, of the methacholine challenge agent required to reduce the forced expiratory volume in one second (FEV1) by 20% following administration of differing doses of albuterol (or placebo) by inhalation. The 20% reduction in FEV1 is determined relative to the saline FEV1 measured before the placebo or albuterol administration.
- **Equivalence based on:** Dose-scale analysis of the PD data. The 90% confidence intervals for the relative bioavailability (F) should fall within 67.00-150.00% to establish equivalence in the PD study.

# Albuterol PD

- Bronchoprovocation Approach
- Experience MCh challenge, RRT, Respirologists
- Dr. Patel publications to develop this model
  - Newhouse MT, Patel P, Parry-Billings M. Protection against methacholine-induced bronchospasm: salbutamol pMDI versus Clickhaler DPI. *Eur Respir J* 2003;21:816-820.
- BIO-IND not needed in Canada – MCh provider reach doses required
- Team experienced to standardize training of sites
- Standardize equipment and procedures
- Ventilated facilities for MCh studies

# Jurisdiction: Canada




## 18 sites All in Canada

One jurisdiction – One regulatory filing – 30d

Conducted by In-House Regulatory team

Experienced sites

Standardize sites with training

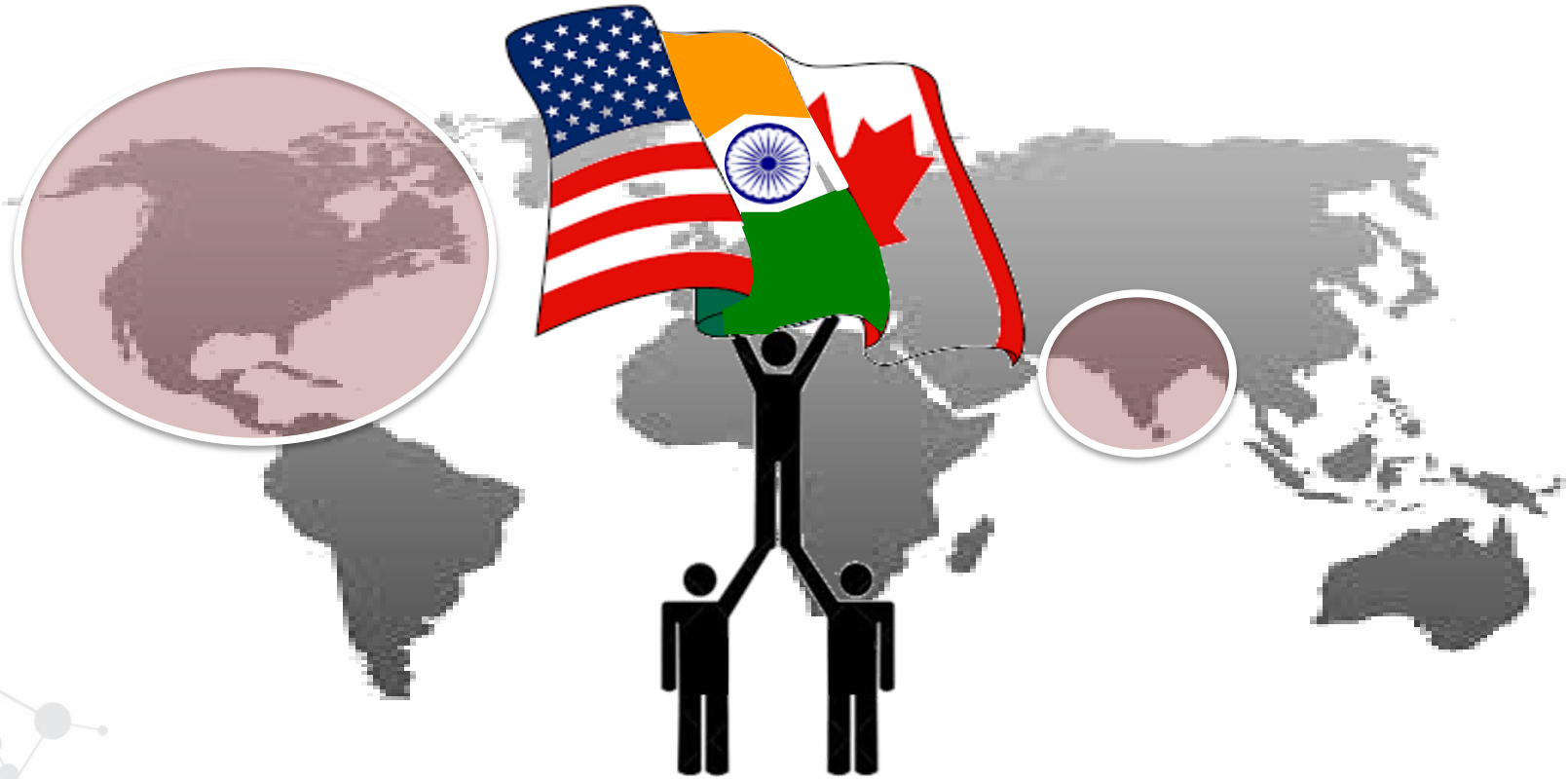
- Equipment – nebulizers
- Methacholine preparation
- MCh Challenge

# Sources of Variability

- MCh challenge studies are difficult to standardize
- Dependent on Respiratory Therapist – interpretation variability
  - Keep the same evaluator for each patient
- MCh induction – tidal breathing vs dosimeter – keep the same for all sites.

# PD Study Design in North America & India

- FDA open to multi-jurisdiction studies with NA
- Cliantha unique capability across one organization to provide CRO and clinic services in both NA & India.



# Potential Concerns To Overcome

- Patient populations in NA and India similar?
- Poor quality of measures and inability to standardize measures
- Regulatory landscape
- Global trials are difficult to coordinate due to the following:
  - Working across different organizations with different practices and SOPs
  - Time differences
- Right sized CRO

# Organization of Services

**CRO Services:**

- Global Project Director with Scientific and Medical Oversight
- Project Manager in India
- Project Manager in North America
- Each Jurisdiction PM has a full team to support activities including Project Associates, Start-Up team specialists
- Lead Monitor in North America
- Lead Monitor in India
- Monitors provided according to the number of sites and locations
- Investigator site ratio: 50% India & 50% in North America

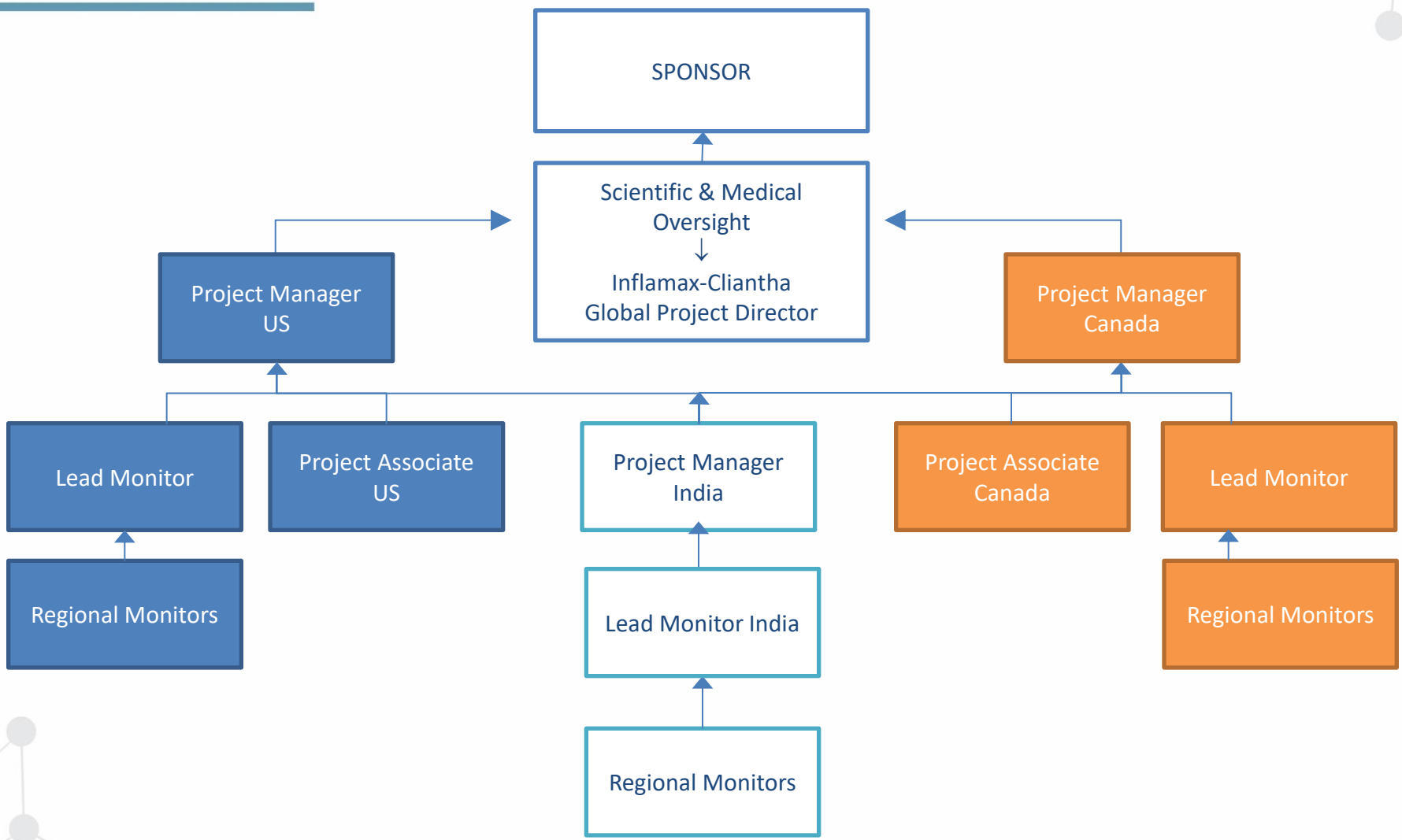
**Clinical Sites:**

- Include 'Super Clinic Site' – Outpatient Clinics with experience in respiratory clinical research
  - Act as a site like any other and for this reason are behind a 'fire wall'

# Case Study: Inhaled Product 505B2-

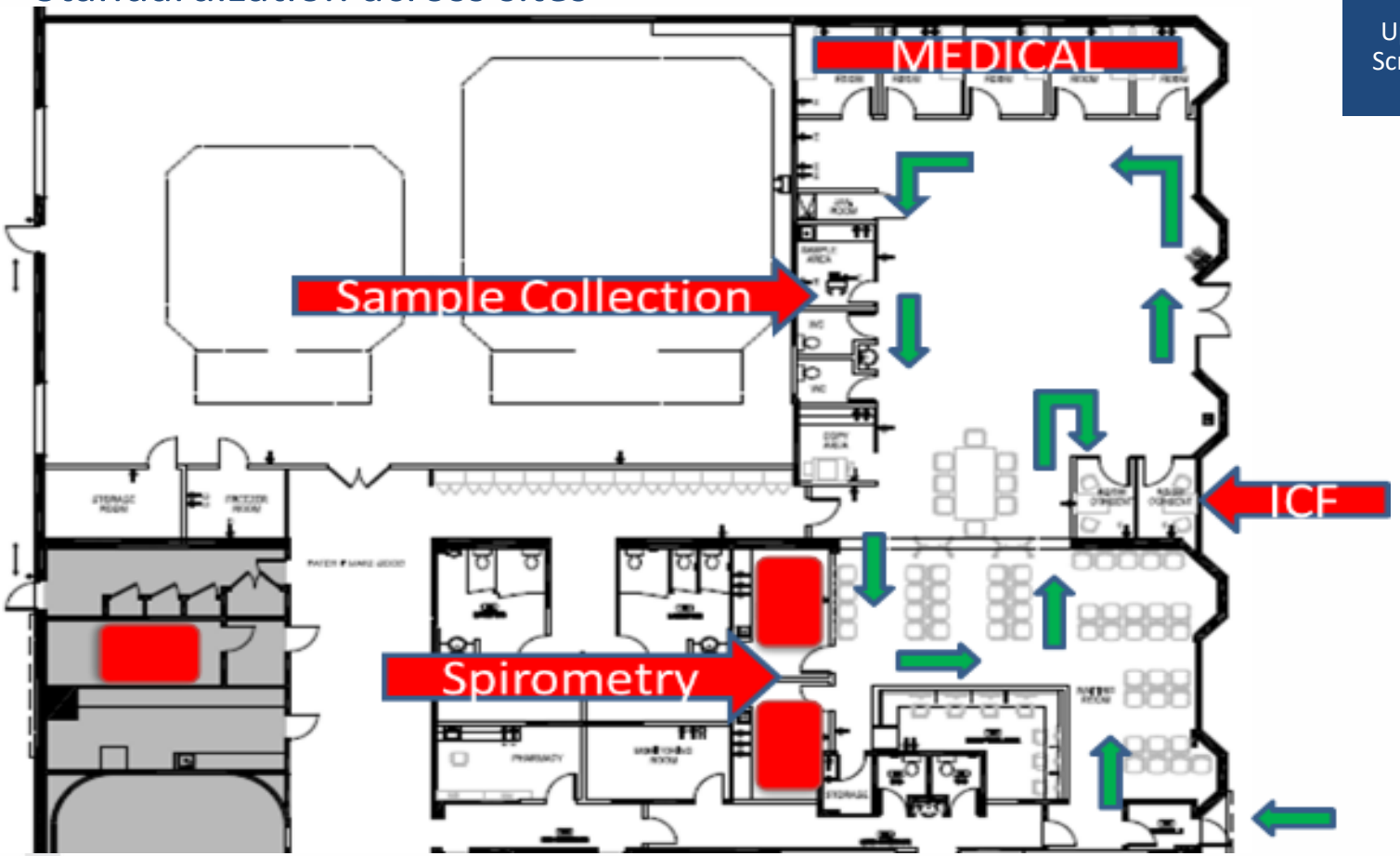
- ICS inhaler – Device is novel
- Partial Blind
- Not identical, 505B2 approach
- FDA discussions need to run 2 studies – Phase III approximately 500 patients per study
- PK subset in one of the studies
- Run the study in US and India
- Overall Global Management → jurisdiction program manager

# Inhaled product: Management Team



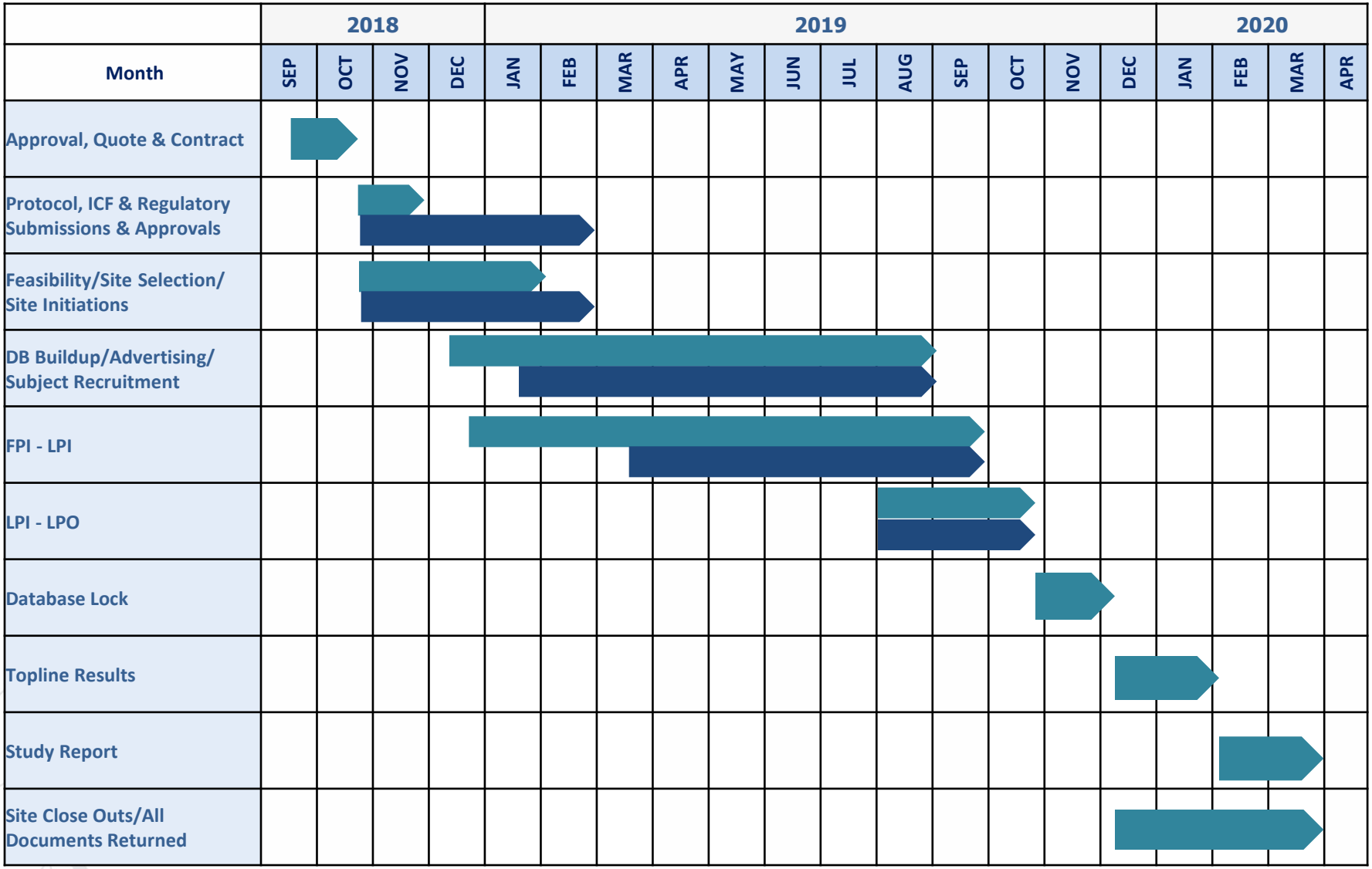
# NA Clinics act as Super Sites

- High Throughput Screening
- Standardization across sites




Up to 72 Daily Screening Visits

# Timelines: Example



# Advantages

- Fully integrated Approach to Global Clinical Respiratory Trials
- Higher Quality Outcomes
- Recruitment advantages
- Regulatory ready deliverables
- Regulatory audit ready
- Cost Efficiencies
- Time Efficiencies

# Conclusions

- The importance of engaging a CRO with therapeutic experience and scientific leadership in respiratory clinical research to understand the key factors in study design to make your study a success.
- Importance of operational attention to detail to obtain the high quality results required for regulatory approval.
- The cost and time efficiencies from global studies in NA and India with experienced CROs like Cliantha.

# Staff of Cliantha North America: Respiratory

- **Our Research Professionals and Experts make all of our great work possible – thank you!**

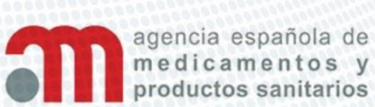
# Regulatory Track Record

cliantha research

















# 926 Professionals

| 669 | 104 | 154 |
| --- | --- | --- |
| Science Professionals | QA-QC Professionals | Support Professionals |