Early Pseudomonas Infection Control (EPIC) Clinical Study

Overview for Families

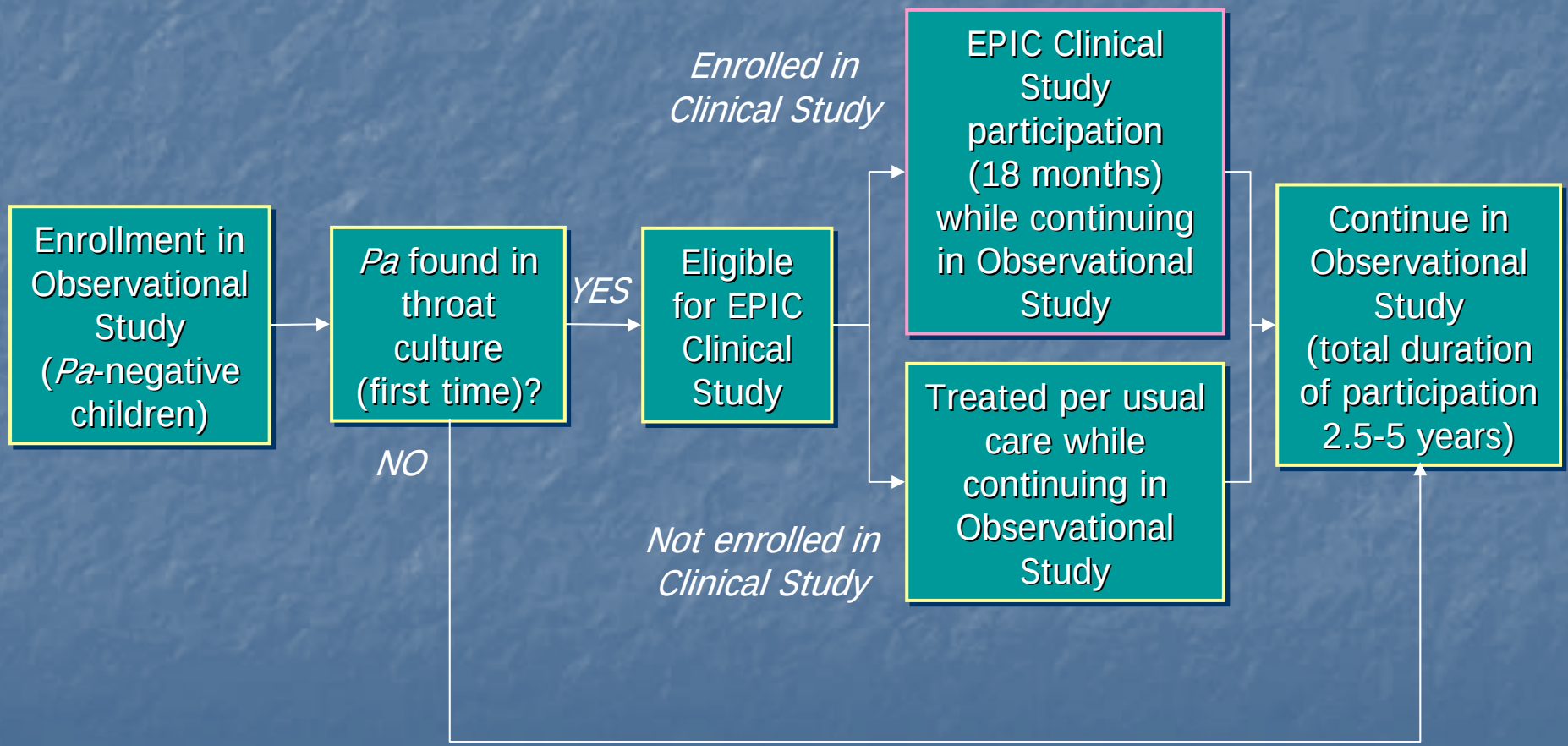
What is the EPIC Clinical Study?

- The EPIC Clinical Study...
  - Compares different treatments for children with CF who have just had their first infection with *Pseudomonas aeruginosa (Pa)*
  - Is coordinated with the EPIC Observational Study and conducted at the same 61 locations
  - Will enroll a total of 300 children, ages 1-12
  - Is sponsored by Cystic Fibrosis Foundation Therapeutics, Inc. and the National Institutes for Health
  - Is the largest study ever jointly funded by these two groups

What is the Purpose of the EPIC Clinical Study?

- To find the most effective and safest treatment that will:
  - Remove *Pseudomonas aeruginosa (Pa)* bacteria from the lungs, AND
  - Have the best immediate and long-term benefits for children with cystic fibrosis

How are the EPIC Clinical and Observational Studies Related?



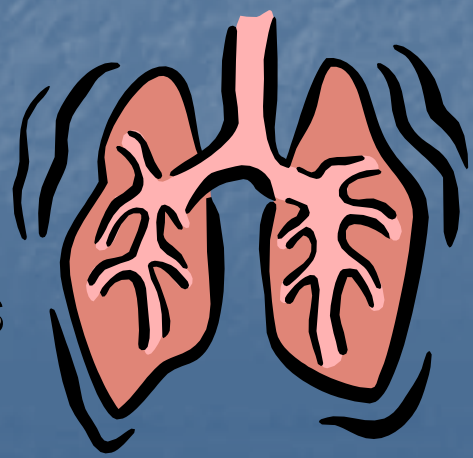
What if We Don't Participate?

- If your child does not participate in the Clinical Study:
  - He/she will still remain in the Observational Study - participation is unchanged
  - Treatment for *Pa* infection will be determined by your child's regular CF doctor

Why is the EPIC Clinical Study Important?

Why is This Study Important?
CF Lung Infections

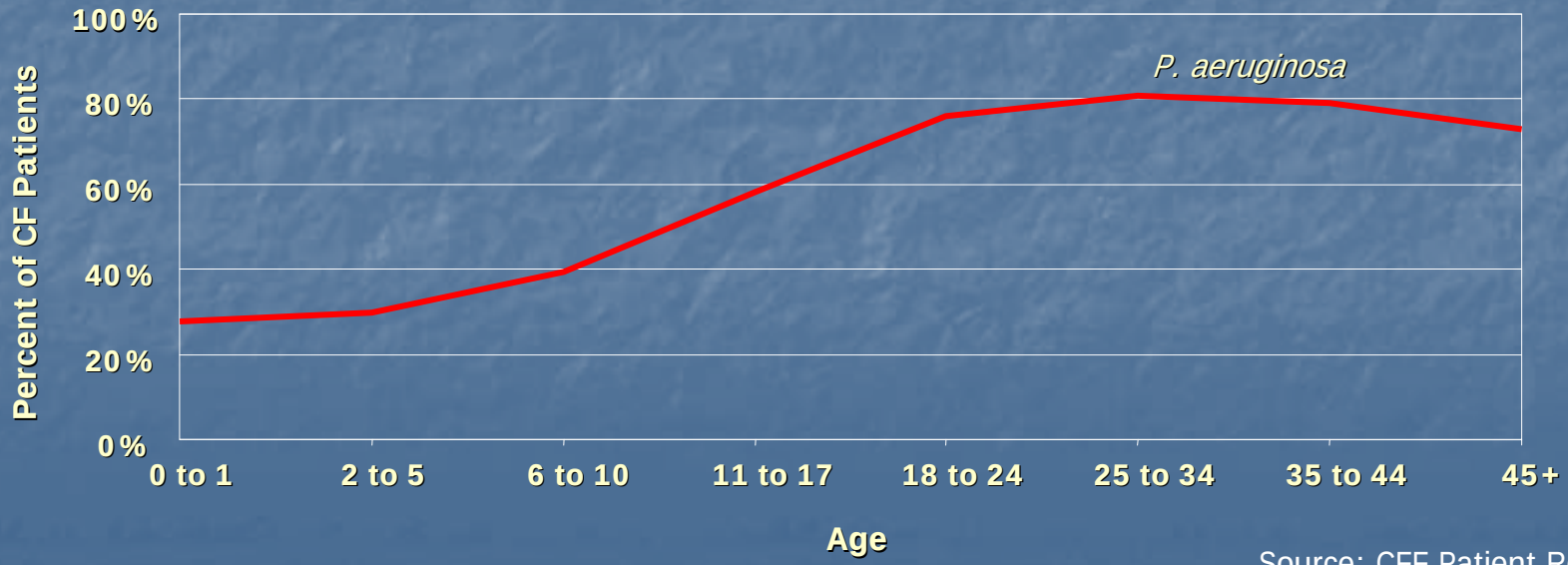
- Children with cystic fibrosis (CF) often have lung infections which occur repeatedly over many years.
- These infections are often caused by the bacteria *Pseudomonas aeruginosa*, or "*Pa.*"
- *Pa* infections in the lungs of children with CF cause many problems, such as:
  - Poor growth
  - Decreased lung function
  - More frequent need for hospitalizations



Why is this Study Important?

Facts about Pa Infections

- *Pa* lung infections may begin in early childhood and become more frequent with age:
  - 28% of children with CF get *Pa* by age 5
  - 40% of children with CF get *Pa* by age 10
  - 80% of adults with CF have *Pa* lung infections

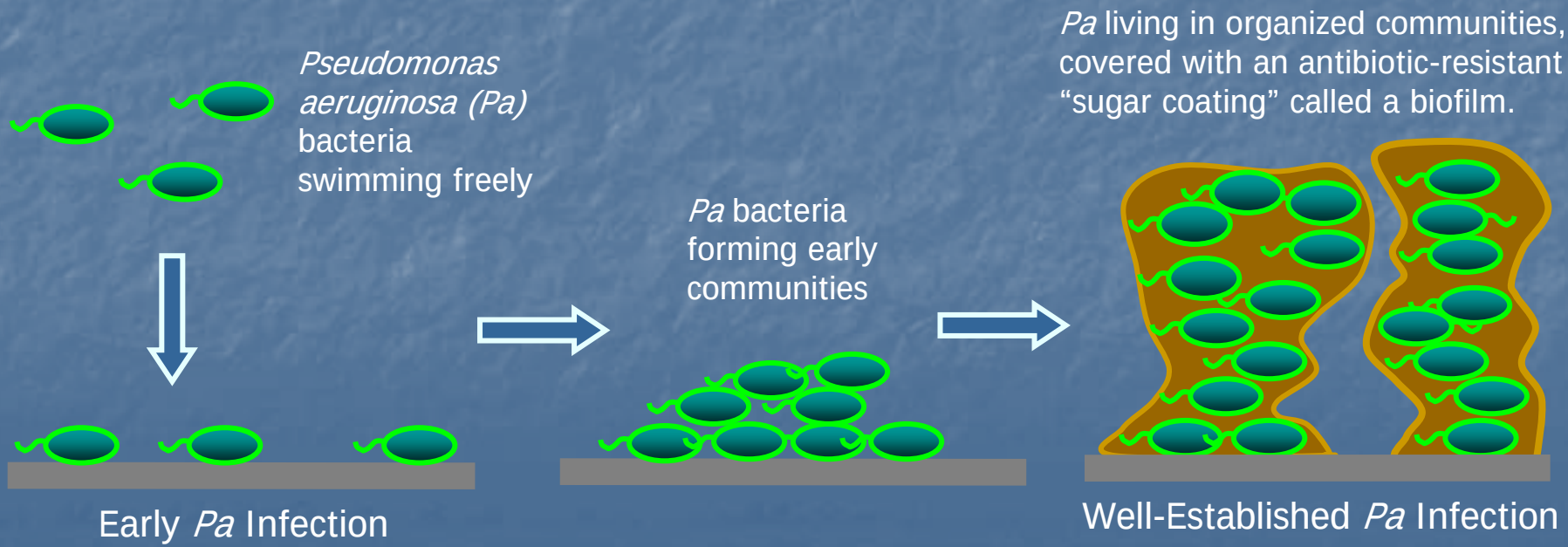


Source: CFF Patient Registry, 2003

Why is this Study Important?

Facts about Pa Infections

- It is important to treat *Pa* infections early because once *Pa* has been in the lungs for a long time:
  - The bacteria changes and is very hard to remove
  - Symptoms get worse
  - More long-term damage can occur



Why is this Study Important?
Clearing Pa from the Lungs

- Studies have shown that early *Pa* infections can be cleared from the lungs with antibiotics.
- Currently several different antibiotic treatments are being used to clear early *Pa* infections.
  - In the U.S., the most commonly used are inhaled tobramycin (TOBI®) and oral ciprofloxacin.
- Most CF doctors today agree that clearing *Pa* from the lungs is good for children with CF... But they don't all agree on the best way to do it.
- The EPIC Clinical Study is here to help!

Why is this Study Important?
Answering Questions About Treatments

The EPIC Clinical Study has been designed to help answer these questions:

1) What is the safest and most effective course of treatment for children with CF?
   - Waiting until *Pa* comes back before re-treating with antibiotics? *OR*
   - Treating with a regular cycle of antibiotics after the first infection, trying to reduce the chance of more *Pa* infections?

Why is this Study Important?
Answering Questions About Treatments

2) Which is a safer, more effective, and longer lasting antibiotic treatment for early *Pa* infections?
   - Inhaled Tobramycin (TOBI®) alone? *OR*
   - TOBI® and ciprofloxacin together?

More Information About the EPIC Clinical Study

What's Involved in Participating?

What's Involved?
Study Visits

- There will be eight scheduled study visits over an 18 month period, including approximately one visit every three months.
- Most study visits will be scheduled to take place at the same time as your child's regular quarterly clinic visits.

- Most study visits will add between 1/2 hour and one hour to your child's routine clinic visit. The first study visit may take longer.

What's Involved?
Study Procedures

- All procedures done at study visits are part of routine care for children with CF.
  - Some research procedures may be performed more often during the study than in routine care.
  - Risks are the same as when these procedures are done during routine care.

What's Involved?
Study Procedures

- The procedures normally done at your child's routine clinic visits will continue.
- Routine procedures will be coordinated with research procedures whenever possible.

- For example, blood samples will be collected for routine tests and research at the same time so your child does not have additional needle pokes.

What's Involved?

Study Procedures

Procedure	Approximate Frequency
Medication & Medical History Review	Each visit
Throat Swab (OP culture)	Each visit
Physical Exam (including height and weight)	Every 3 months
Breathing Test (Spirometry)	Every 3 months
Pregnancy Test (for girls at least 9 years old)	Every 3 months
Joint Exam	Every 6 months
Blood Draw	Every 6 months
Hearing Test (only at some sites)	Every 6-12 months
Chest X-Ray	Every 18 months (at first & last visits)

What's Involved?
Phone Calls

- After each study visit, you will receive up to three phone calls from the study coordinator…
  - To see how your child is doing
  - To review your child's medications and medical history
  - To go over instructions for taking study medication

What's Involved?
Randomization

- Each child who starts the Clinical Study will be placed into one of four different treatment groups.
- The selection is done by computer and is called "randomization." It is like flipping a coin.

- The combination of medications and the timing of treatment for most of the study depends on the group assigned.

What's Involved?

Study Drugs

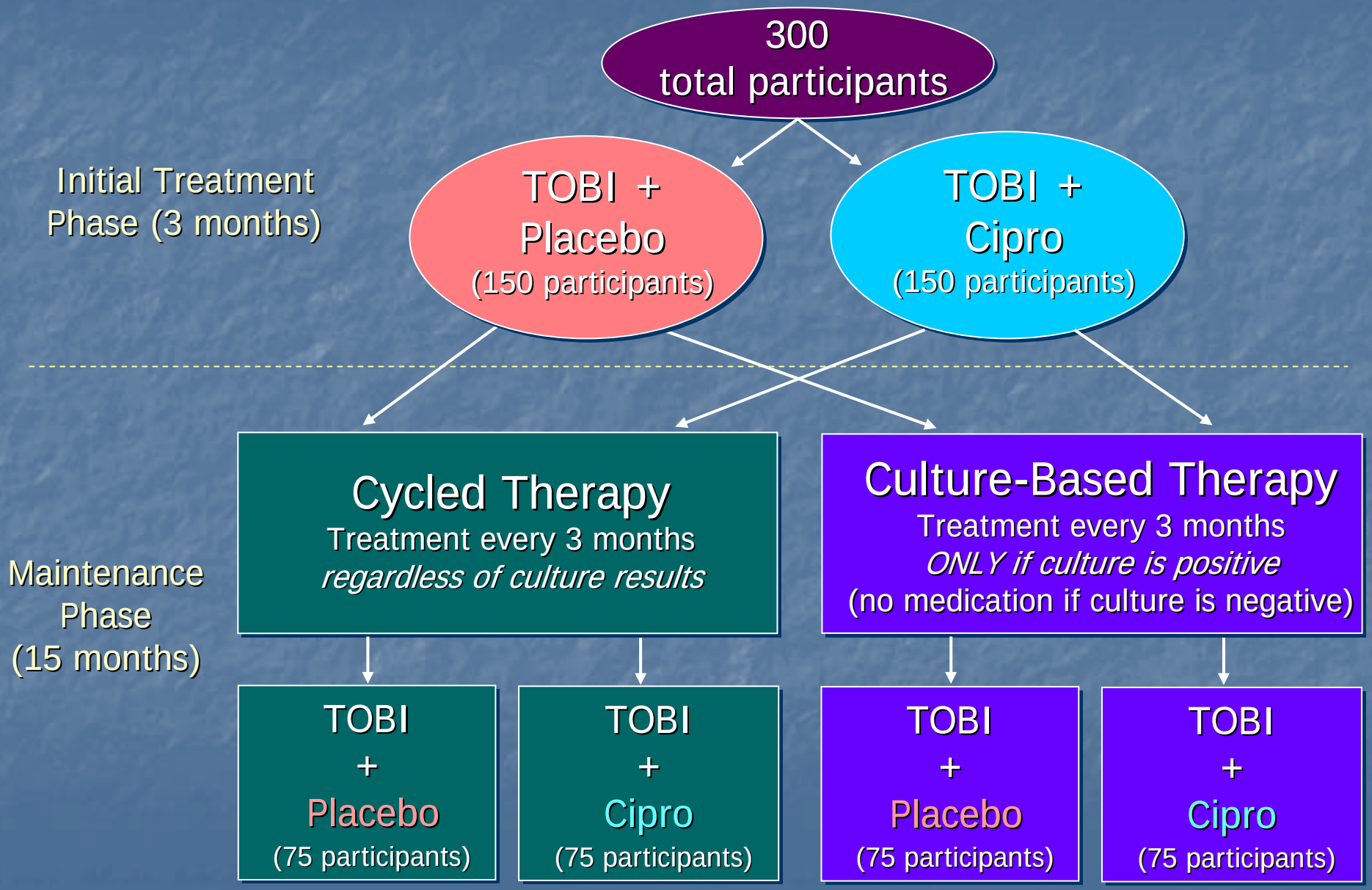
- **ALL** participants will be treated for *Pa* lung infections with inhaled tobramycin (TOBI®), an antibiotic medication widely used by people with CF.
- **PLUS**, depending on randomization assignment:
  - Half of the participants will also receive ciprofloxacin (Cipro®), a second antibiotic taken by mouth.

  - The other half of the participants will receive a placebo in place of Cipro®.
- Neither you nor your child's doctor will know whether your child is receiving Cipro® or placebo.

Study Drugs
Initial Treatment Phase (3 months)

- When they start the study, all children will receive TOBI® for the first 28 days (4 weeks).
- In addition, for the first 14 days (2 weeks):
  - Half of the participants will receive Cipro®
  - The other half will receive placebo
- After 3 weeks, a throat culture will be taken.
  - If positive for *Pa*, your child will receive 4 more weeks of TOBI®.
- After the initial treatment phase, your child will receive further treatment based on the group in which they were placed by randomization....

EPIC Clinical Study Treatment Plan



Study Drugs
Treatment Cycles: Maintenance Phase

Once the Initial Treatment Phase is over...

- During each three-month cycle in which your child receives study drug treatment:
  - TOBI® will be taken for the first 28 days (4 weeks)
  - Cipro® or placebo will be taken for the first 14 days (2 weeks)
  - Your child will be off study drugs for the remaining 8 weeks of the treatment cycle.

What's Involved?

Taking TOBI®

- In this study, TOBI® will be taken twice a day for 28 days at a time.
- TOBI® is inhaled as a fine mist using a nebulizer and compressor system.
- Depending on age, your child may either use a mouthpiece or a face mask with the nebulizer.

- The equipment is portable and easy to use. It will need to be cleaned carefully after each use. Your study coordinator will give you instructions.

What's Involved?
Taking Cipro/Placebo

- Cipro® and matching placebo tablets are available in different sizes/dosages.

- Some participants will receive Cipro or placebo in a liquid form called a suspension instead of a tablet.

- The Study Coordinator will help you choose which is best for your child.
- Total dosage will be based on your child's weight.
- The placebo will look identical to Cipro®. You will not know which your child is taking.

Study Medication & Supplies

- Your child will receive all study medications, supplies, and equipment free of charge.
- Some initial supplies will be given to you by the study coordinator.
- Remaining items will be ordered through CF Services Pharmacy and delivered to your house.

What's Involved?

Possible Side Effects - TOBI®

- Like many inhaled drugs, TOBI® may cause side effects.
- Increased cough, shortness of breath, wheezing, chest tightness, decrease in lung function, throat irritation, and ringing in the ears have all been reported with TOBI® use.
- Some children have also reported an unpleasant taste associated with inhaled TOBI®.
- Some other rare but serious side effects have also been reported.

What's Involved?
Possible Side Effects - Ciprofloxacin

- Side effects for ciprofloxacin may include joint discomfort or pain, dizziness, headache, restlessness, diarrhea, nausea, abdominal pain, arthritis, or skin rash.
- Ciprofloxacin may also make your child more sensitive to the sun.
  - It is important to use sunscreen or wear protective clothing when taking ciprofloxacin.
- Some rare but serious side effects may also occur.

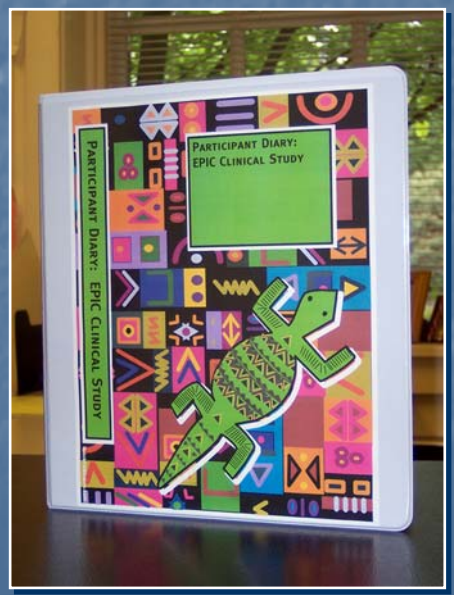
What's Involved?
Antibiotic Resistance

- The use of any antibiotic carries a small risk of promoting the development of resistance in the bacteria present in airway secretions. This is the case with any antibiotic exposure and is not an expected or unique side effect in this study.

What's Involved?

Participant Diary

- Each participant will receive a study diary to take home.
- The diary contains information and instructions you will need during the study.



- You will need to record a variety of information in the diary, such as:
  - When study medicines are taken
  - Changes in your child's health
  - Any new medicines your child is taking

What Else Should We Know?

When you come in for each study visit, you will need to bring with you:

- Your participant diary, so the study coordinator can review the information you've recorded
- All unused study drugs (TOBI® and Cipro®/placebo)
- All empty study drug vials and bottles

What Else Should We Know?
Data and Specimen Banking

- Information, blood samples, and airway bacteria collected for this study:
  - Will be stored ("banked") by the CF Therapeutics Development Network
  - May be used by other CF researchers in the future

- Protecting your child's identity:
  - Information which could identify your child will be removed and will not be given to other researchers.
- Banking is optional:
  - Your child can take part in the study even if you do not agree to banking of data or specimens.

What Else Should We Know?

EPIC Data Safety Monitoring Board (DSMB)

- What is the DSMB?
  - An independent oversight committee
  - Primarily composed of CF and clinical research experts not otherwise involved in the study
- What is their purpose?
  - To regularly review study activities and data during the course of the study
  - To ensure ongoing safety of study participants

Why Should We Participate in this Study?

- Only a small number of children are eligible to participate at each clinical site.
- Your child may benefit from participating in this study by receiving early treatment for *Pa*.
- Information learned in this study may be of great help to ALL children with CF.

We can only answer these important questions with help from people like you.

Thank you for taking the time to learn about this study.

Do you have any questions?