Health Research, Inc.

Prospective Observational Study of Asymptomatic cCMV Transmission to Infants for Virological Evaluation in New York State (PROACTIVE NYS)

Sponsored by:
Eunice Kennedy Shriver **National Institute for Child Health and Human Development (NICHD)**

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PROTOCOL SIGNATURE PAGE

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Council for Harmonisation Guideline for Good Clinical Practice (ICH E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Signature of Investigator of Record	Date
Name of Investigator of Record (printed)	

PROACTIVE NYS
Prospective Observational Study of Asymptomatic cCMV Transmission to Infants for Virological Evaluation in New York State

ABBREVIATIONS, ACRONYMS, and TERM DEFINITIONS

Term/Acronym	Definition
CMV	Cytomegalovirus
cCMV	Congenital Cytomegalovirus
EC	Ethics Committee
NYS DOH NBS	New York State Department of Health Newborn Screening Program
cCMV screen	NYS DOH NBS CMV PCR via dried blood spot
cCMV confirmatory test	CMV PCR or culture from a body fluid following a positive cCMV screen
Confirmed cCMV	Any infant with a positive cCMV screen and a confirmatory CMV PCR or culture from urine (preferred), blood, or cerebrospinal fluid (CSF) obtained within 21 days of life. - Note that this excludes saliva samples
DMC	Data Management Center
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
IDSCC	Infectious Disease Specialty Care Centers
IRB	Institutional Review Board
mPI	Multiple Principal Investigators
ND	Neurodevelopmental
NICHD	National Institute for Child Health and Human Development
NICU	Neonatal Intensive Care Unit
NIH	National Institute of Health
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PO	By mouth
Presumed cCMV	Any infant with a positive cCMV screen and either: - A confirmatory CMV PCR or culture from saliva obtained within 21 days of life - OR a confirmatory CMV PCR or culture from urine, blood, CSF, or saliva obtained on day 22 of life or later
QMS	Quality Management System
QoL	Quality of Life
SAP	Statistical Analysis Plan
sIRB	Single Institutional Review Board
SNHL	Sensorineural hearing loss
SOP	Standard Operating Procedure
Study Day 0	Date of birth
SWOT	Strengths, Weaknesses, Opportunities, and Threats

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PROACTIVE NYS
Prospective Observational Study of Asymptomatic cCMV Transmission to Infants for Virological Evaluation in New York State

SCHEMA

Purpose:	To gain knowledge from a large statewide cohort of cCMV-screen positive children to provide crucial insights into cCMV natural history, treatment decisions and outcomes, and the impact of statewide universal screening.
Design:	Registry
Study Population:	All infants with a positive cCMV screen in New York State
Sample Size:	>500 infants
Study Duration:	2-year longitudinal follow-up study

Primary Objective

- To enroll at least 90% of all cCMV New York State Department of Health Newborn Screen-positive infants across NYS in a long-term follow-up study

Secondary Objectives

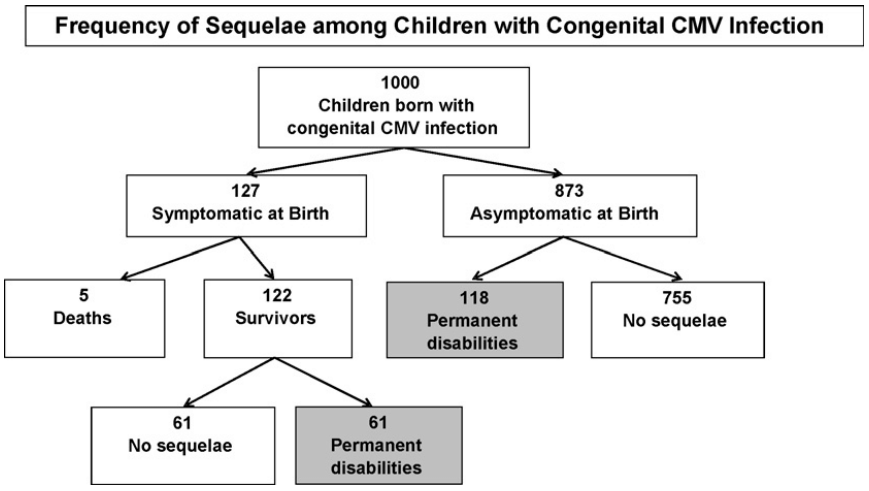
- To determine the rate of confirmed congenital CMV in a statewide cohort
- To describe the distribution of neonatal features among children with confirmed congenital CMV
- To describe trends in antiviral and non-pharmaceutical treatments, adverse effects, and impact on long-term outcomes
- To assess the long-term (2 year) audiologic, neurologic, and developmental outcomes of children with congenital CMV
- To describe the impact of a positive cCMV screen on the quality of life (QoL) of infants and families

1 INTRODUCTION

1.1 Background

Cytomegalovirus (CMV) is the most commonly described congenital infection, affecting 0.5-1% of all births globally [1, 2]. In the United States, it is estimated that 40,000 neonates are born annually with congenital CMV (cCMV) [3]. Of those congenitally infected, clinical manifestations vary widely. While the majority of those with congenital infection (90%) are asymptomatic at birth, 20% of all children with cCMV will develop long-term sequelae (Figure 1) [4]. Common complications of cCMV include sensorineural hearing loss (SNHL), cognitive impairment, and chorioretinitis [2]. Among asymptomatic neonates with cCMV, there is no helpful clinical tool to determine which infants will develop sequelae later in life.

Figure 1. Frequency of Sequelae among Children with Congenital CMV Infection



Much controversy exists as to which neonates are most likely to benefit from antiviral treatment of cCMV. Key studies have designated neonates into various categories of symptomatology and treated those with the most severe illness, showing modest improvement. Typical categorization includes ‘asymptomatic’, ‘asymptomatic with sensorineural hearing loss’, or ‘symptomatic’ disease [2]. Within the symptomatic cohort, they are further categorized as having mild, moderate, or severe disease. The first major treatment study of cCMV found that, among those with ‘undifferentiated symptomatic’ disease, 6 weeks of intravenous (IV) ganciclovir initiated within 4 weeks of life led to improved outcomes compared to placebo [5]. Specifically, infants treated with ganciclovir were less likely to experience hearing deterioration at 6 months of age than those receiving placebo. A follow up study found that *6 months* of oral (PO) valganciclovir led to improved SNHL and neurodevelopmental outcomes compared to *6 weeks* of PO valganciclovir when evaluated at 24 months old [6]. Among those asymptomatic neonates with normal hearing at birth, 10-15% will later develop SNHL [7]. To date, long-term follow-up of minimally symptomatic and asymptomatic neonates has been limited, with no data on annual incidence rates of SNHL. Further, no clear data exist in favor of or against treatment of those who are asymptomatic with SNHL at birth. Adverse effects of valganciclovir, particularly severe cytopenias, are well-described, further complicating the decision to treat or not to treat [2, 8].

1.2 Rationale

Cytomegalovirus (CMV) is the most common congenital infection worldwide, estimated to occur in 0.6% of all pregnancies. Among those with cCMV, 10% of infants are symptomatic at birth, about 40-60% of whom will have permanent sequelae. Of the 90% who are asymptomatic at birth, as per the current literature, 10-15% will have long-term sequelae, most often SNHL. What is unknown is how accurate these frequencies are today. Previous studies have found that treating symptomatic infants with 6 months of oral valganciclovir can improve neurodevelopmental and auditory outcomes. Treatment studies of asymptomatic infants or those with isolated SNHL are more limited, leading to a wide range of treatment preferences by clinicians and parents. Further, as cCMV is most likely to be diagnosed in more severely affected infants, few studies have investigated long-term outcomes of asymptomatic or minimally symptomatic infants.

On October 2, 2023, NYS implemented a 1-year, opt-out pilot program to screen neonates for cCMV as part of the NBS program. Universal screening offers an unprecedented opportunity to develop a long-term, statewide cohort study of all neonates who screen positive for cCMV. Through organized standard-of-care follow up and systematic outcomes evaluations, this cohort will allow an in-depth, long-term evaluation of cCMV. Specifically, the study will investigate cCMV incidence across a large, ethnically and economically diverse state, describe the distribution of symptoms at birth and medical interventions provided, and assess long-term audiologic, neurologic, and developmental outcomes. Quality of life measures and impact of the screening as it relates to the Recommended Uniform Screening Panel (RUSP) will also be investigated. Utilizing a system designed to identify and enroll all cCMV screen-positive infants across NYS, **PROACTIVE NYS** will yield a wealth of knowledge regarding contemporary cCMV epidemiology, response to treatment, long-term audiologic and neurodevelopmental outcomes, and the impact of universal cCMV screening on the NBS program.

1.3 Hypotheses

1. 0.6% of all neonates screened for congenital CMV infection will have a confirmed infection.
2. The majority of neonates with confirmed congenital CMV will be asymptomatic or mildly affected.
3. Children will have a wide range of long-term outcomes.
   - Those with the most severe symptoms as neonates will experience more severe audiologic and neurodevelopmental outcomes.
   - A subset of asymptomatic or mildly symptomatic neonates will develop and/or experience progressive sensorineural hearing loss and cognitive impairment.
4. Infants with more severe sequelae of cCMV will be associated with lower QoL for infants and parents.

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to enroll at least 90% of all cCMV screen-positive infants across NYS in a long-term follow-up study.

2.2 Secondary Objectives

The secondary objectives of this study are to:

1. To determine the rate of confirmed congenital CMV in a statewide cohort
2. To describe the distribution of neonatal features among children with confirmed congenital CMV
3. To describe trends in antiviral and non-pharmaceutical treatments, adverse effects, and impact on long-term outcomes
4. To assess the long-term (2 year) audiologic, neurologic, and developmental outcomes of children with congenital CMV
5. To describe the impact of a positive cCMV screen on the quality of life (QoL) of infants and families

3 STUDY DESIGN

This study is a systematic, longitudinal cohort study of all infants with a positive cCMV screen in New York State. During the 2-year longitudinal study, baseline demographic information, neonatal cCMV clinical features, diagnostic testing results, antiviral administration and other medical interventions, long-term audiologic, neurologic, and developmental outcomes are collected, and infant and family QoL is assessed. Evaluations occur at regularly scheduled visits using standardized assessment tools according to Table 2 - Schedule of Events.

- The 1-year NYS cCMV NBS Pilot Study began screening for cCMV on October 2, 2023, as described in the previously awarded Contract (# 75N94021D00018). The program is conducted as Human Subject Research approved by the NYS Institutional Review Board (IRB) under Expedited Category 5. A waiver of informed consent was granted. Families will be given the ability to opt-out of the cCMV NBS Pilot Study.

- The cCMV NBS Pilot Study performs universal screening for cCMV of all neonates born in NYS during the 12-month cCMV NBS Pilot Study. Screening results are available within 7 days of sample collection. Upon receiving a positive cCMV screen, the infant's primary care provider is notified by NBS Follow-up staff through a phone call and fax. The primary care provider is provided with the infant's newborn screen report which includes the positive CMV result as well as information about cCMV and instructions for the next steps, including notifying the family of the result and referring the baby to an Infectious Disease Specialty Care Center (IDSCC). All infants who screen positive for cCMV are also immediately referred by the NYS NBS to one of eleven clinical sites designated as IDSCC for standard-of-care follow-up testing and management. Screen positive babies are referred to the IDSCC clinical site that is geographically closest to their birth hospital. These IDSCC clinical sites have been certified by the NYS NBS Program (See Study Setting for IDSCC designation details). All are under the supervision of a Pediatric Infectious Diseases board-certified physician and have extensive experience with cCMV diagnosis and management. These IDSCCs are also notified by NBS Follow-up staff regarding positive infants through a FAX and/or phone call, to check the encrypted email, fax, and/or notification of results via the NYS DOH Health Commerce System, a secure website for web-based interactions within NYS. The primary care providers of babies who screen positive for cCMV are instructed to consult with the designated IDSCC, and in most cases will coordinate a visit for the infant/family with the clinical site as soon as possible; in rare cases the primary care provider may coordinate confirmatory testing for the infant if circumstances prevent the family from traveling to the clinical site. All eleven clinical sites have agreed to participate in the longitudinal study, known as PROACTIVE NYS, allowing for potential enrollment of all cCMV screen-positive infants throughout the state. Once evaluated by an IDSCC, NYS DOH is notified of all cCMV confirmatory test results.

3.1 Study Setting

The eleven IDSCC clinic locations serve as the PROACTIVE NYS clinical sites. The certified IDSCC designation was provided by the NYS NBS Program to pediatric infectious disease clinical sites with expertise in cCMV diagnosis and management. In order to obtain IDSCC designation, each site was required to identify a lead board-certified pediatric infectious disease clinician with proven cCMV expertise to serve as the Center's director. Additional designated personnel required for each IDSCC included a clinical care coordinator, social worker, audiologist, and the institution's laboratory director. All IDSCC applications were approved by the institution's CEO or COO to demonstrate institutional support. Upon satisfactory review of IDSCC application materials by NYS NBS Program staff, clinical sites were scheduled for a virtual site visit with NBS Program staff to discuss the CMV pilot and the newborn screening workflow at their site. Following completion of a successful site visits, clinical sites were granted official IDSCC certification. See Appendix I – IDSCC Designation Criteria for complete IDSCC designation criteria.

All IDSCC clinical sites are affiliated with major academic medical centers strategically located throughout NYS (Figure 2). This allows NYS NBS to refer every cCMV screen-positive infant in NYS during the cCMV NBS Pilot Study to a designated IDSCC for clinical care and enrollment in PROACTIVE NYS.

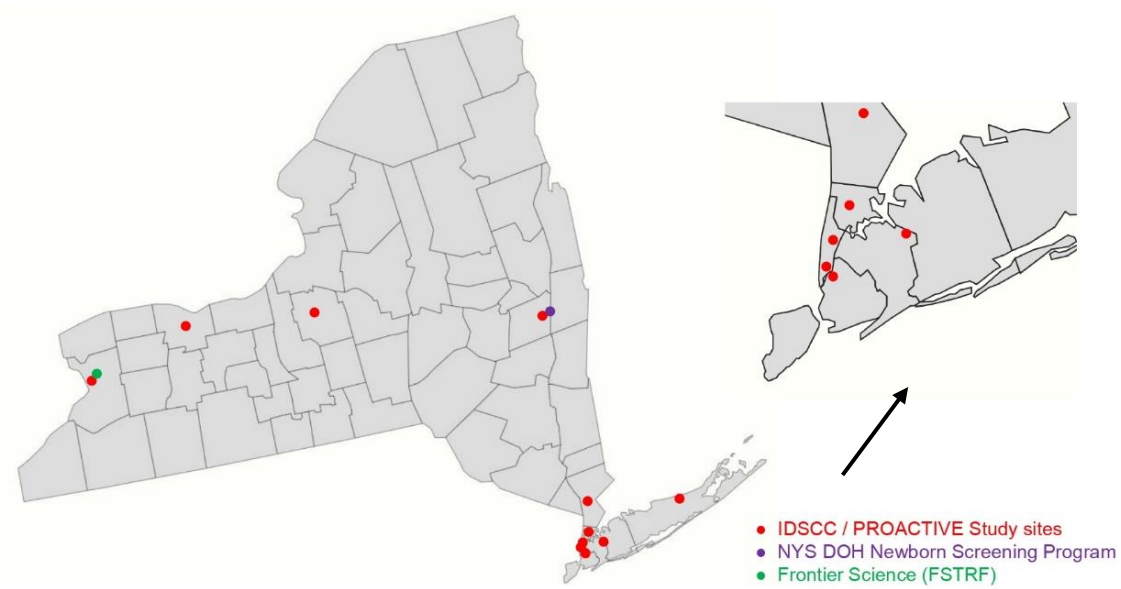


Figure 2. New York State map of entities involved in **PROACTIVE NYS**

All clinical sites have extensive clinical research experience, including CITI certification of all staff linked to this proposal, development of best research practices, study design, participant enrollment, management and follow-up, data entry, data analysis, and manuscript preparation. All clinical sites have access to necessary equipment in order to conduct the study, including appropriate clinical space, computers, and diagnostic laboratory and radiologic testing. All clinical sites have access to appropriate medical specialists for referral, including identified experts in Pediatrics, Audiology, Neurodevelopment, Neurology, Neuropsychology, Ophthalmology, and Otolaryngology, among many other relevant pediatric specialties. In addition, all eleven IDSCC clinical sites serve as Pediatric HIV Referral Centers for the NYS NBS Program. As a result, all clinical sites are closely linked with the NYS NBS Program,

have access to the encrypted NYS Wadsworth Lab system for results, and are able to act on receiving urgent neonatal referrals.

3.2 Facilities

As required by the IDSCC designation process, each clinical site must have access to all spaces, equipment, and resources necessary for conducting **PROACTIVE NYS**, including:

- inpatient and outpatient facilities available according to the needs of the individual patient;
- dedicated pediatric inpatient beds, neonatal intensive care unit as part of a Level III perinatal program[1] and pediatric intensive care unit[2];
    - [1] If the hospital does not provide maternity services, then a neonatal intensive care unit is not required.
    - [2] If the hospital does not have a pediatric intensive care unit (PICU), then a protocol must be described for emergent care, appropriate pediatric transport, and continuity of care.
- onsite facilities for standard clinical-pathological studies, radiological studies; (i.e. X-rays, sonogram, CT, MRI) electrocardiogram studies, electroencephalogram studies, and nuclear medicine studies;
- laboratory capability for all necessary core studies and molecular genetic testing either onsite or by referral to another New York State approved laboratory as specified by the New York State Newborn Screening Program and the Wadsworth Center;
- an infant hearing screening program, directly or by contract, that is overseen by a licensed audiologist.

In addition, all clinical sites must have access to necessary computer equipment for data entry. Each clinical site is provided with 2 tablets for parent response to written questionnaires/ assessments. All sites also must have access to Ophthalmology and Neuropsychology/Child Development experts as needed for patient referrals.

3.3 Enrollment Estimates

During 2019 and 2020, there were approximately 207,000 and 220,000 live births in NYS. Prior studies estimate 0.6% of all neonates are infected with cCMV, though unpublished data from other regions performing universal cCMV screening have found lower rates, closer to 0.25%. Estimates from two ongoing universal cCMV newborn screening programs reported interim screen-positive rates of 0.12% (Ontario, Canada) and 0.27% (Minnesota, USA) (personal communication by A. Handel with Jessica Dunn, MD and Carrie Wolf, MBS, respectively). cCMV dried-blood spot screening assays vary in sensitivity, but generally have very high specificity, approaching 99-100% [9].

Below are the annual IDSCC estimates based on the above variables, assuming 210,000 live births in NYS during the study period, 100% assay specificity, and enrollment of 100% of eligible infants:

cCMV screen-positive rate	cCMV screen sensitivity	Number of infants diagnosed with cCMV
- 0.5% of live births	100%	1,050
- 0.5% of live births	80%	840
- 0.25% of live births	100%	525
- 0.25% of live births	80%	420

Across the 11 clinical sites identified in this proposal we have the ability to enroll at least 90% of those infants with confirmed cCMV.

In addition to those identified by the NYS NBS with cCMV, it is expected to enroll a very small cohort of infants who have a negative screen but are identified clinically and confirmed to have cCMV with a positive urine or blood CMV PCR obtained within the first 21 days of life.

It is expected that a small group of premature infants (born prior to 37 weeks gestation) are infected postnatally with CMV (e.g. by blood transfusion). Premature infants often undergo repeat NBS testing; postnatal CMV infection may therefore be detected on a sample obtained after 21 days of life. As this population may be at risk of developing long-term sequelae similar to infants infected in utero, they should be approached for enrollment in **PROACTIVE NYS** if they meet criteria described in Inclusion Criteria - Category 4.

4 STUDY POPULATION

4.1 Participant Recruitment & Enrollment

Upon evaluation at an IDSCC, caregivers of all cCMV screen-positive infants are approached for enrollment in **PROACTIVE NYS**. This cohort will include those infants ultimately diagnosed with confirmed cCMV and those with negative confirmatory testing. Although not supported through the Task Order, clinical sites also enroll infants who screen negative for cCMV but are later diagnosed clinically with cCMV through standard clinical testing. As asymptomatic infants are unlikely to undergo clinical cCMV testing following a negative cCMV NBS result, this subset may include infants with more prominent cCMV sequelae.

All parents/guardians of cCMV-screen positive infants are informed of the study at their initial cCMV clinical evaluation at the IDSCC. Contact information is collected at that time. If cCMV screening begins prior to approval from NICHD to initiate **PROACTIVE NYS**, these families are re-contacted to discuss enrollment once the study is approved. Informed consent is then obtained (See IRB Approval section) from the infant's parent/legal guardian, and those whose parent/legal guardian agree are enrolled.

4.2 Inclusion Criteria

Potential participants must meet all of the criteria specified below to be included in this study; in these criteria, "at entry" is used to refer to the day of enrollment in the study:

4.2.1 Neonates born in New York State during cCMV NBS Pilot Program (September 27, 2023 – October 1, 2024)

4.2.2 cCMV evaluation provided by a designated NYS IDSCC

4.2.3 Family willing and able to complete all study procedures

4.2.4 Study participants meet criteria for one of the four following categories:

1. Category 1 (Confirmed cCMV identified by NBS Program):
   a. cCMV screen positive AND
   b. cCMV confirmatory test positive
2. Category 2 (Confirmed cCMV not identified by NBS Program):
   a. cCMV screen negative AND
   b. cCMV confirmatory test positive
3. Category 3 (False-positive cCMV screen):
   a. cCMV NBS positive AND
   b. Negative cCMV confirmatory test

4. Category 4 (Premature infants with confirmed CMV infection on late positive NBS):
    a. Infant born prior to 37 weeks gestation
    b. cCMV positive on any NBS collected prior to 44 weeks gestational age
    c. Positive cCMV confirmatory test obtained within 14 days of a positive NBS

4.3 Exclusion Criteria

4.3.1 Neonate whose parents refuse participation in the long-term follow-up study

4.4 Participant Withdrawal or Termination from the Study

Participant caregivers may voluntarily withdraw from the study. Participants may also be terminated from the study by the site investigator under the following circumstances:

- Participant re-locates away from the study site (with no options to transfer to another site) or is otherwise determined to be lost-to-follow-up
- Investigator determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant
- The study is stopped or canceled by the sponsors or government or regulatory authorities
- Site participation in the study is canceled by the sponsors, government or regulatory authorities, or the sIRB

For any participant who is withdrawn or is terminated from the study prior to scheduled completion of follow-up, study staff documents the reason for the withdrawal or termination in detail and makes every effort complete final evaluations. If the circumstances that led to a participant's withdrawal or termination change (e.g., they return to the study site area after having re-located previously), the site investigator should contact the study PIs to discuss options for resuming follow-up.

5 STUDY VISITS AND PROCEDURES

Data collection time points are entered in a timeline that parallels the typical clinical follow-up schedule for an infant with cCMV. Participant data is entered as an enrollment/initial diagnosis time point, followed by regularly scheduled follow-up visits. Families are encouraged to sign up for institutional patient portal system(s) for access to cCMV treating physician. Urgent issues can be handled via telemedicine or in-person as indicated.

5.1 Enrollment Visit

The Enrollment Visit includes data from the first 4 weeks of life. This allows for entry of all relevant prenatal, perinatal, and early postnatal data needed to determine if the patient has confirmed cCMV and to classify the infant's cCMV disease severity based on previously published categories [2]. See Table 1 for cCMV category definitions. Variables collected include demographic information, maternal prenatal CMV status (if known) and delivery complications, neonatal signs and symptoms of cCMV, diagnostic testing performed to confirm cCMV and identify any clinical manifestations, and treatments started. As the cCMV NBS Pilot Study may begin prior to initiating **PROACTIVE NYS**, older infants may be enrolled in the study, with diagnostic testing obtained during the first 4 weeks of life entered into the age appropriate visit timepoint.

5.1.1 Infants with false-positive CMV newborn screening:
Any infant who has a positive NYS DOH CMV newborn screen but a negative confirmatory CMV PCR may be approached for enrollment. These infants are considered to have a false-positive CMV newborn screen (Inclusion Criteria Category

3). Baseline data is collected as clinically indicated at the Enrollment Visit. Once the infant is determined to *not* have cCMV, all subsequent study procedures and data collection will end. Enrolling these infants is crucial for describing the subset of infants with false-positive CMV newborn screening.

Table 1. Congenital CMV Disease Severity Definitions [2]

Moderately to severely symptomatic congenital cytomegalovirus disease

- Multiple manifestations attributable to congenital cytomegalovirus infection: thrombocytopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis (raised transaminases or bilirubin), or
- Central nervous system involvement such as microcephaly, radiographic abnormalities consistent with cytomegalovirus central nervous system disease (ventriculomegaly, intracerebral calcifications, periventricular echogenicity, cortical or cerebellar malformations), abnormal cerebrospinal fluid indices for age, chorioretinitis, sensorineural hearing loss, or the detection of cytomegalovirus DNA in cerebrospinal fluid

Mildly symptomatic congenital cytomegalovirus disease

- Might occur with one or two isolated manifestations of congenital cytomegalovirus infection that are mild and transient (eg, mild hepatomegaly or a single measurement of low platelet count or raised levels of alanine aminotransferase). These might overlap with more severe manifestations. However, the difference is that they occur in isolation

Asymptomatic congenital cytomegalovirus infection with isolated sensorineural hearing loss

- No apparent abnormalities to suggest congenital cytomegalovirus disease, but sensorineural hearing loss (≥21 decibels)

Asymptomatic congenital cytomegalovirus infection

- No apparent abnormalities to suggest congenital cytomegalovirus disease, and normal hearing

Definitions as published by Kimberlin and colleagues,[6] with minor emendation from discussions of the International Congenital Cytomegalovirus Recommendations Group

5.2 Follow-Up Visits

For those infants placed on CMV antiviral therapy, Follow-Up Visits occur every six weeks until the infant is 6 months old, (guidelines for completion of any drug regimen for symptomatic treatment), and then every 6 months until the child is 24 months old. Infants with confirmed cCMV who are not receiving antiviral therapy are evaluated every 6 months. Variables collected at Follow-Up Visits include signs and symptoms of cCMV (including audiology follow up), treatments given and adverse effects, and interim and final outcome measures. Additional details of data collected can be found in the text below and attached case report forms (CRFs). Most study visits are performed in-person, though virtual-visits may be offered as deemed appropriate by the clinical team. Additional details may be collected from the infant's family or referred providers (e.g. audiology) as appropriate, including by electronic health record review, fax, email, telephone, or other method convenient for the family.

5.3 Variables Collected

5.3.1 Demographics

Upon enrollment, demographic information is collected from all infants with confirmed cCMV, including: infant's sex, race, ethnicity, gestational age, age at time of clinically-indicated specimen collection (note that no research biospecimen collection is planned at this time), birth weight, and head circumference.

cCMV Diagnostics and Sequelae

Clinically-obtained data from each child with confirmed cCMV is collected. See Appendix II - **PROACTIVE NYS** REDCap Case Report Forms for specific variables to be collected. The following general information will be collected:

- Prenatal findings such as documented maternal acute CMV infection during pregnancy, prior cCMV diagnosis, maternal CMV test results (if available), and prenatal diagnostic imaging results
- Delivery data including gestational age, any issues identified by OB, admission to NICU (and cause), neonatal length, weight and head circumference
- Neonatal signs and symptoms of cCMV
- Neonatal cCMV diagnostic testing including urine (preferred) or blood CMV PCR, neonatal CMV IgM/IgG results (if obtained), complete blood count, liver function testing, diagnostic imaging, newborn hearing screen results, ophthalmologic findings (if performed)

5.3.2 **Treatment**

We will collect data on treatments provided, including specific antiviral medication prescribed (including intravenous ganciclovir or oral valganciclovir), dose, dosing interval, duration of treatment, age at treatment initiation, duration of treatment, adverse effects (specifically cytopenias, acute liver injury, acute kidney injury), and premature cessation of treatment due to adverse effects. Clinical providers are also asked about the rationale for starting or not starting antiviral treatment for each study participant.

Non-Medical Interventions

Data on non-medical interventions including cochlear implants, American Sign Language training and use, and specialized therapies provided such as Early Intervention referral and enrollment, auditory-verbal therapy, physical therapy, and occupational therapy is collected.

5.4 Outcome Assessments

Outcomes are assessed using a pre-determined follow-up schedule using standardized approaches. All outcomes measures are readily available to clinicians across NYS, are cost-effective, have been validated for use in the specified age group, are accessible to families regardless of geography or English fluency, and are maximally informative for expanding the evidence base on the clinical utility of conducting population-wide cCMV screening in newborns. All measurements planned have been reviewed to ensure they do not contain negative or stigmatizing language. In particular, the measurements do not perpetuate negative bias toward individuals with hearing impairment, physical or cognitive disabilities, or other vulnerable populations. All written/verbal assessments (including Neurodevelopmental and QoL assessments) are based on standardized tools and therefore easily reproducible. Audiologic and Ophthalmologic assessments will be performed with standard medical approaches, equipment, and documentation, allowing for reproducibility in other settings. All

laboratory tests are performed in College American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) certified laboratories.

5.4.1 Audiologic Outcomes

Audiologic testing is performed on a regular scheduled basis to assess for early and late onset hearing impairment. Consistent with New York State law [10], all neonates will undergo a newborn hearing screen regardless of cCMV testing results. Infants diagnosed with cCMV are referred for complete Pediatric Audiology assessment. As recommended by the American Academy of Audiology [11], repeat audiologic diagnostic testing is performed every 3-6 months. Audiologic diagnostic modality used is dictated by the infant's age and developmental capabilities. Testing results are recorded as decibel threshold in 5-decibel intervals for each ear. If present, type of hearing impairment will be recorded. Any interventions provided, including hearing aids, cochlear implants, American Sign Language Education, and auditory-verbal therapy are documented.

5.4.2 Neurodevelopmental Outcomes

Parents complete standardized developmental screening tools (described in Table 2 - Schedule of Events, available in English and Spanish) every 6 months through 2 years old. Parents complete the questionnaires at the beginning of each clinic session. Those infants who fail any domain of the developmental screening instrument are referred to Early Intervention. Those who fail the developmental screening questionnaires twice (e.g., at 6 months old and again at 12 months old) are referred to a Developmental Pediatric or Child Neuropsychology expert for clinical assessment. Scores within each developmental domain on the screening questionnaires and results of the neurodevelopmental assessment will be recorded in the patient's REDCap database. All infants with severe cCMV (as defined by the treating provider) are referred to Early Intervention during infancy and receive a Neuropsychology referral at 1 year of age regardless of their performance on the screening instruments.

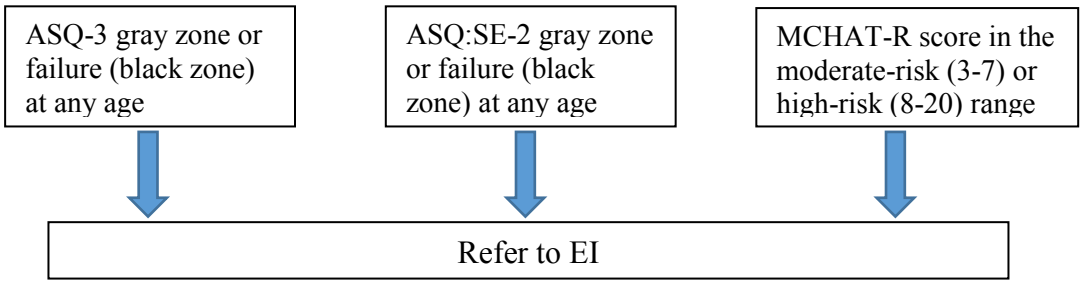
Neurodevelopmental Screening Plan:

Instruments and Timing

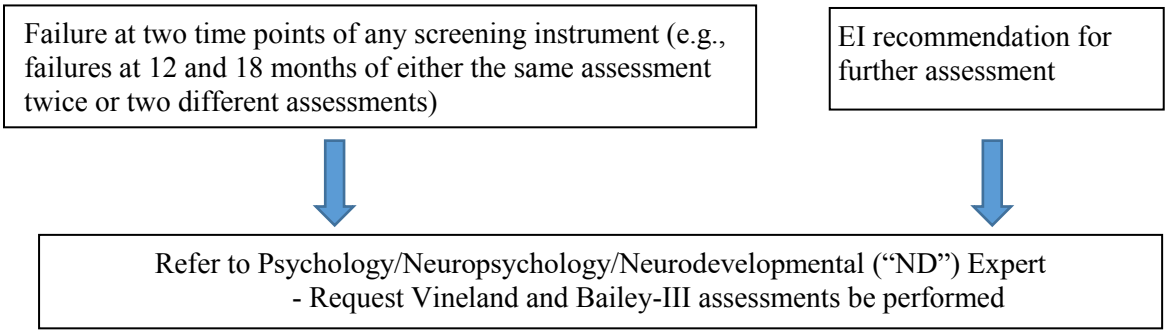
- 6 months old
  - Ages & Stages Questionnaires Third edition (ASQ-3)
  - ASQ-Social-Emotional, Second Edition (ASQ:SE-2)
- 12 months old
  - ASQ-3
  - ASQ:SE-2
- 18 months old
  - ASQ-3
  - ASQ:SE-2
  - M-CHAT-R
- 24 months old
  - ASQ-3
  - ASQ:SE-2
  - M-CHAT-R

Neurodevelopmental Assessment Referral Plan:

Early Intervention (EI) Referral:



Psychology/Neuropsychology/Neurodevelopmental ("Psychology") Referral Plan



5.4.3 Ophthalmologic Outcomes

All infants with symptomatic cCMV at birth are referred for Ophthalmologic evaluation within the first 4 weeks of life. Recent findings from the Ottawa cohort found that ophthalmologic abnormalities were only identified in infants with symptomatic cCMV (including abnormal head ultrasound), occurring in 3% of infants with cCMV (personal communication). Therefore, asymptomatic infants are not required to undergo an ophthalmologic exam, which may be uncomfortable for the infant, difficult to perform, and requires extensive resources to arrange for a large cohort. If an abnormality is identified, the infant undergoes repeat testing as recommended by the Ophthalmologist, with at least one visit annually.

5.4.4 Quality of Life Assessment

Two cross-sectional QoL assessments of all enrolled infants is performed at one- and two-years following study initiation. By assessing all infants at two time points, data is captured from participants at a wide range of ages and clinical stages, providing insight across a broad participant population. Changes are also assessed in response over time among those who complete both QoL assessments.

Table 2. Schedule of Events

Evaluation	**Entry**	**Post-Entry Evaluations**						
Chronologic age	**Entry Visit**	**6 weeks**[1] (+/- 2 weeks)	**12 weeks**[1] (+/- 4 weeks)	**18 weeks**[1] (+/- 4 weeks)	**6 months** (+/- 4 weeks)	**12 months** (+/- 8 weeks)	**18 months** (+/- 8 weeks)	**24 months** (+/- 8 weeks)
Informed Consent	X							
NYS NBS CMV screen result	X							
Maternal history	X							
Medical history/new diagnoses	X	X	X	X	X	X	X	X
Growth measurements	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X
CMV PCR (Urine and/or blood) [3]	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
CBC w/ diff	X							
AST, ALT	X							
Creatinine	X[2]							
Head ultrasound	X							
Audiologic assessment [4]	X				X	X	X	X
Ophthalmologic assessment [5]	X				X	X	X	X
Neurodevelopmental assessments [6]					X	X	X	X
Quality-of-Life Assessments [7]				X				X
Cerebrospinal fluid analysis	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Abdominal ultrasound	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
MRI brain	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Treatment/Monitoring								
- Document antiviral treatment prescribed (Y/N)?	X	X	X	X	X	X	X	X
- Treatment name / dose	X	X	X	X	X	X	X	X
- Antiviral toxicity assessment		X	X	X	X	X	X	X
- CBC w/ diff		X	X	X	X	X[2]	X[2]	X[2]
- Creatinine		X	X	X	X	X[2]	X[2]	X[2]
- AST, ALT		X	X	X	X	X[2]	X[2]	X[2]
- GGT	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]

[1] 6-week, 12-week, 18-week assessments are only needed for those infants with confirmed cCMV receiving CMV antiviral therapy. Infants with confirmed cCMV not receiving CMV antiviral therapy undergo assessments every 6 months

[2] Optional testing as indicated by primary care team

[3] Urine CMV PCR is the preferred test for confirming cCMV diagnosis

[4] Audiologic testing is performed every 3-6 months for all infants with confirmed cCMV. For those infants with an abnormal audiologic testing, more frequent assessments may be performed at the discretion of the Audiologist.

[5] Ophthalmologic evaluation is not required for asymptomatic neonates. Timing of follow-up ophthalmologic evaluations are at the discretion of the Ophthalmologist, but must occur at least once annually for infants with symptomatic cCMV.

[6] Neurodevelopmental assessment schedule: Participants undergo developmental screening with the Ages and Stages Questionnaire-3®, (ASQ-3) and the Ages & Stages Questionnaire: Social-Emotional, Second Edition ®, (ASQ:SE-2) at ages 6, 12, 18, and 24 months. Participants also undergo the MCHAT-R ®, autism screening at 18 and 24 months old. Those who fail any developmental domain are referred to Early Intervention. Those who fail any two developmental screening questionnaires (e.g., the same or different assessments failed at 6 months old and again at 12 months old) are referred to a Developmental Pediatric or Child Neuropsychology ("Neurodevelopmental (ND) assessment") expert for clinical assessment. Infants with severe cCMV receive an Early Intervention referral upon diagnosis and a Neuropsychology referral at 1 year of age regardless of their performance on the screening instruments. The ND assessment should include the Vineland Adaptive Behavior Scales 3rd Edition and the Bayley-III Bayley Scales of Infant and Toddler Development. Data from these assessments is entered in CRFs linked to the patient ID number of that infant.

[7] Quality-of-Life (QoL) assessment: All enrolled participants with confirmed cCMV receive a QoL assessment questionnaire at the one-year anniversary of the study, and again when the child is 2 years old.

5.5 Planned analyses:

- Descriptive statistics is used to determine the rates of participants with abnormalities in clinical, laboratory, and imaging abnormalities.
- Descriptive statistics is used to describe patterns in diagnostic and treatment practices.
- Clinical variables are analyzed when participants reach 6, 12, 18, and 24 months of age. Some participants will be on study for longer than 24 months. Percentage of participants with deficits in the outcome measures who is calculated. The outcome measures of those with abnormalities in clinical, laboratory, and imaging evaluations are compared to those without abnormalities. Participants are also categorized by previously published disease severity criteria [2] and a comparative analysis is performed. See Table 2 for category definitions.

6 PARTICIPANT MANAGEMENT

6.1 Issues Related to Universal cCMV Newborn Screening

As cCMV is not yet included in the Recommended Uniform Screening Panel, understanding its implications for parents and children is crucial. cCMV treatment recommendations vary widely between region and provider, particularly among those infants with less severe sequelae. Making a diagnosis of cCMV is therefore wrought with sensitive, challenging topics that often lack a clear answer. Carefully addressing and studying those concerns is crucial to determining the strengths and limitations of universal cCMV screening.

6.1.1 Under- and over-diagnosis

cCMV "under-diagnosis" refers to those infants with a negative cCMV newborn screen but diagnosed clinically with cCMV (through CMV urine PCR obtained during the first 21 days of life). As most infants with cCMV are asymptomatic, well infants with a negative cCMV NBS are unlikely to undergo clinical testing. As a result, "missed cases" identified clinically consist of more severely affected infants or those with hearing loss detected at birth. Any infants with "missed cCMV" on newborn

screening are invited to enroll in our study. This small cohort provides important information about infants who are not identified through universal cCMV screening.

cCMV "over-diagnosis" refers to those infants who screen positive for cCMV but have a negative urine CMV PCR. Prior studies show that this is uncommon [12]. Since all cCMV-screen positive infants are referred to their local IDSCC, These infants are systematically followed through **PROACTIVE NYS**. Since these infants are not be diagnosed with cCMV, they are followed less frequently than those with confirmed cCMV, but remain available for QoL evaluations and other targeted follow-up.

6.1.2 Under and Overtreatment of screen-positive infants
Treatment data from all infants who screen positive for cCMV is collected. Treatment decisions are made by the treating clinician and family. Data is analyzed by severity of symptoms, including infants who are clinically asymptomatic, asymptomatic with isolated hearing loss, and more severely affected. The number of infants treated for cCMV is described and treatment rates, medication toxicity rates, and outcomes by symptoms and severity of symptoms are compared.

6.1.3 Parental anxiety & vulnerable child syndrome
Parent and infant QoL measurements are performed as a cross sectional single assessment one year after study initiation. This approach allows responses to be obtained from a broad range of families, including those with young infants and those whose infants (symptomatic or not) are approaching one year of age. In addition, the assessment includes families whose children experience a wide range of cCMV sequelae. Parents of children who had a false-positive cCMV screen, whose experience is likely very different from those of cCMV-infected infants are included. Additional assessments are planned following the initial enrollment period.

6.1.4 Added burden on state NBS programs, especially follow-up
The long-term follow-up study is being conducted in close coordination with the NYS cCMV NBS Pilot Study, as described above. This allows for close integration of the programs' impact on the NBS Program and referral implications for the IDSCCs.

7 STATISTICAL CONSIDERATIONS

7.1 Outcome Measures

The following goals are used to assess success in enrolling and maintaining follow-up of infants with confirmed cCMV throughout **PROACTIVE NYS**.

- Enrollment: ≥90% of cCMV screen-positive infants are enrolled in PROACTIVE NYS
- 1-year follow-up: ≥90% of enrolled infants with confirmed cCMV attend a 1-year follow-up visit
- 2-year follow-up: ≥80% of enrolled infants with confirmed cCMV attend a 2-year follow-up visit

In addition, study co-PIs and Frontier Science Statistical and Data Management Center (DMC) closely monitor enrollment rates at each clinical site through the continuously updated interactive dashboard and REDCap database. Missing data queries and low enrollment rates are reviewed with the IDSCC clinical site PI. Those sites failing to enroll ≥60% of referred infants over the course of the year are not funded during the subsequent calendar year.

7.2 Randomization and Stratification

This study does not involve randomization or stratification.

7.3 Monitoring

Implementation of this study is monitored at multiple levels, consistent with standard clinical trial procedures. A study monitoring plan that details monitoring roles and responsibilities and data to be reviewed at each level will be prepared before the study opens to accrual. Sections 11 and 12 provide for more information on on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, and participant safety across sites is provided below.

7.3.1 Monitoring by the Protocol Team

Study Progress and Quality of Study Conduct

The protocol team (under guidance of PI S. Nachman) is responsible for continuous monitoring of study progress, including timely achievement of key milestones, and quality of study conduct.

The protocol team will monitor participant accrual based on reports that will be generated at least monthly by the DMC. The team has developed a study accrual plan that includes site-specific and total enrollment projections over the course of the accrual period, and actual accrual will be monitored relative to these projections. This includes enrollment of 90% of infants referred to that site for positive CMV Newborn Screen results. Distal monitoring will include check of birth date information with NYS screening results, and confirmation of CMV via blood or urine PCR testing.

The protocol team will monitor the timing of site-specific study activation, which will determine when each site will begin accruing participants, and actual accrual following activation. The number of potential participants screened, reasons for screen failures, and number of participants enrolled will be closely monitored. Sites will be put on probation after 3 months of continual falling below 80% enrollment, asked to do a SWOT analysis, and will have conference to monitor further progress.

Accrual performance will be reported by the DMC, by site and across sites, and the team will review and discuss study progress at least monthly. For any site that is delayed in completing the study activation process, or that falls short of its accrual projections, the team will communicate with the site to identify the barriers the site has encountered and the operational strategies and action plans to address these. Sites that fail to enroll above 60% over the entire year will be dropped from further funding.

The protocol team will also monitor participant retention as defined as completion of every 6-month study visits and completion of all neurodevelopmental assessments.

On behalf of the protocol team, the DMC will monitor other key indicators of the quality of study conduct (e.g., data quality, data completeness) based on reports generated by the DMC and take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

Participant Safety

The protocol team (including a medical representative from each site) will closely monitor participant safety through routine review of safety data reports generated by the DMC. As this is not a treatment study and has no protocol defined therapy, all adverse events and safety events will be reported and collated. Sites are to use standard of care when administering any medications. These reports will be reviewed monthly. The protocol mPI will continually evaluate the pattern and frequency of reported events and assess for any individual occurrences or trends of concern.

7.4 Analyses

Data from each site will be included in all analyses. It will include parameters as indicated by the items collected. Each subtype of disease state will be assessed (severe, moderate, mild or asymptomatic disease) Analysis planning will include input from site PIs as well as team statisticians.

8 DATA HANDLING AND RECORD KEEPING

8.1 Statistical and Data Management Center (DMC)

8.1.1 Infrastructure

All software used by Frontier Science is verified and validated to ensure that it is audit ready. The following core software is custom configured to support the specific needs of **PROACTIVE NYS**:

8.1.2 Project Website

A custom project website, which includes a public webpage and a Portal Gateway webpage (restricted to designated study and participating site staff to access data management systems and other resources needed to conduct the study), is available to aid in the organization of data management activities and ensure that the study team and clinical sites have centralized access to the necessary data and adjoining metadata, study resources, and computerized systems needed to guide their efforts.

The public website will serve as the "face" of the study, and host generally available information such as an overview of the study, introduction to key personnel, study resources, updates on study progress, and contact information. It will provide the public with transparency into the study and its resulting progress. More importantly, it will serve as the access point to the secure Portal Gateway sign-in (Figure 3).

Figure 3. Study Website

The Portal Gateway website will provide the clinical sites with direct and centralized access to all software applications required for data management support. It will host all project data management operations, including data collection and management systems required to support all data collection activities. Using a two-factor authentication system, the study team will additionally have access to web-based study specific resources such as study documents, announcements, and training materials. The website will be designed to provide entry into all software and systems required to enter, review, collate, organize, and report on the data collection activities throughout the course of the study. Furthermore, the study team and designated statisticians will be able to securely access data on the Portal Gateway. The website also will provide administrative information and support to collaborators, such as email lists, other contact information, and various team reports. Document perusal/retrieval facilities and linkages/interfaces to other websites will also be made available depending on the needs of the study team.

8.1.3 Central Database

A Central Database will be created for the study using a relational database management system. The Central Database will serve as a warehouse for enrollment data and study data collected using REDCap Academic (see below). Data queried from the Central Database will be used as the source for quality assurance auditing and on-demand retrieval for statistical analysis and reporting. The use of a centralized database allows for additional reporting and quality control activities not otherwise available in an out-of-the-box commercial EDC system such as REDCap. Accessing and querying database tables in a variety of ways allows countless reports, metrics, tables and listings to be generated on demand providing greater flexibility to meet the specific needs of the study team and its collaborators.

8.1.4 REDCap® Academic

REDCap® Academic (REDCap hereafter) is used as the EDC system for **PROACTIVE NYS**.

In addition to providing blank eCRFs, Frontier Science provides an eCRF Completion Guide for the study. The eCRF Completion Guide provides additional study-specific instructions and help text that clinical sites can use as they onboard new studies and determine how to design their source data collection materials for the study.

See Appendix II - **PROACTIVE NYS** REDCap Case Report Forms.

8.1.5 Stars

Stars is the enrollment system which ensures that the participating clinical sites are approved to enroll participants onto the study and verify the participant is eligible via a series of questions assessing the study's eligibility criteria, known as the eligibility checklist. Clinical site responses to the eligibility checklist provide a real-time assessment of eligibility before a participant is enrolled. Upon successful enrollment, a PID is assigned to the participant in the study.

8.1.6 Data Exchange System

Frontier Science will configure its data exchange system to transfer participant enrollment information, in real- time, from Stars to REDCap, and to transfer REDCap clinical data into the Central Database to facilitate additional reporting, querying and exchanging of data with study stakeholders. Other project-specific integrations can be implemented as needed.

8.1.7 Reports

Frontier Science creates and distributes monthly accrual reports to project leadership to facilitate accrual tracking. Existing standardized programs and reports will be configured and used wherever possible, but additional programs and reports will be created as deemed necessary by the study team and NICHD study leadership.

8.1.8 Data Visualization

Data dashboard: The visualization tools configured by Frontier Science will assist in conveying the findings in a more accessible and timely manner, facilitating decision-making and collaboration (refer to Figure 4 for a prototype of an Interactive Data Visualization Dashboard). In addition, to foster data sharing per the mandated *NIH Data Management & Sharing Policy*, some interactive data visualizations will be running on a public-facing website. See *Sharing Results* section for more details.

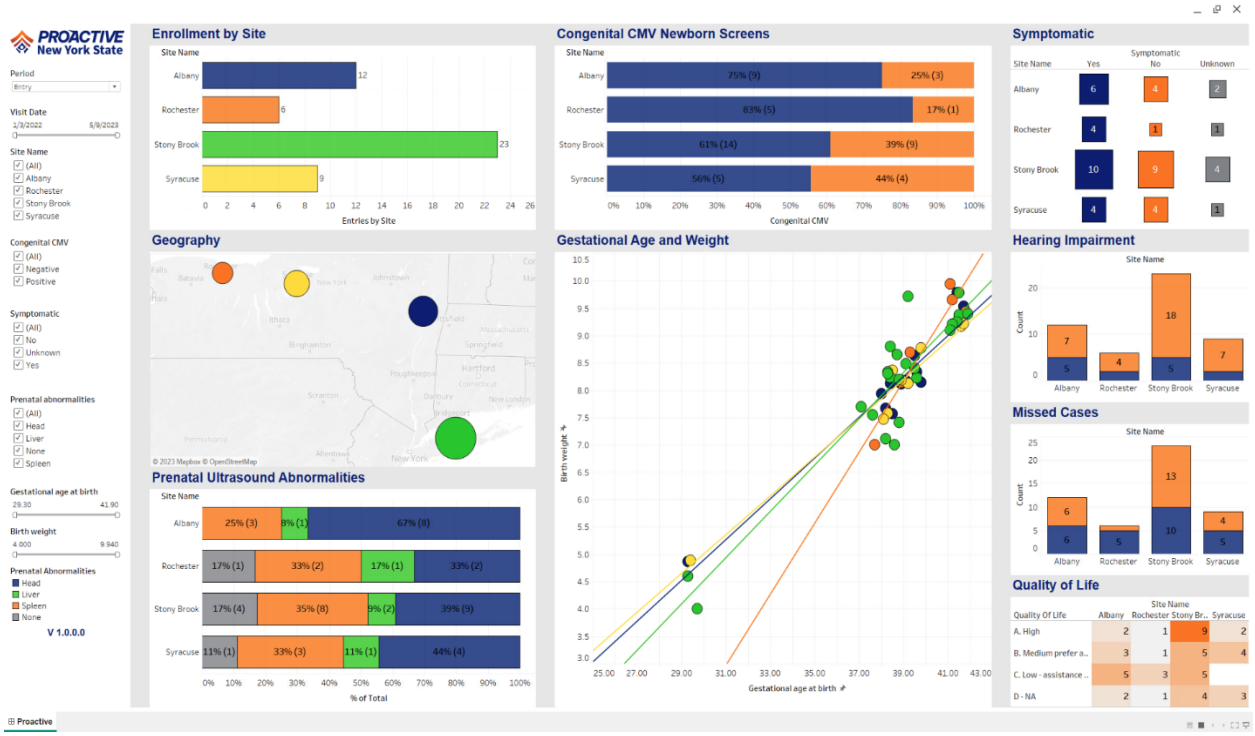


Figure 4. Interactive Data Visualization: Dashboard

8.1.9 Data Retrieval

Authorized users have access to the clinical data in REDCap. In addition, study data is made available to the study team and designated statisticians on demand using Frontier Science's data retrieval tools. As mentioned above, all retrieval tools will be made centrally available in the Portal Gateway.

8.1.10 External user training

Frontier Science provides training to all participating entities on the study to ensure that they are familiar with the various tools that are used to enter, collect, and transfer the study data to Frontier Science. All end users of Frontier Science systems are provided with 24/7/360 user support.

8.1.11 Quality assurance and quality control measures

Frontier Science operates within a Quality Management System (QMS) framework that ensures that the organization acts in accordance with contemporary ethical and

regulatory principles. Frontier Science observes, within the context of its QMS system, regulatory principles including 21 Code of Federal Regulations (CFR) Part 11, the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and the Federal Information Security Management Act of 2002 (FISMA). It also adheres to accepted guidelines and best practices per ICH E6 (R2) (GCP), the Society of Clinical Data Managers (SCDM) Good Clinical Data Management Practices (GCDMP), and Good Automated Manufacturing Practice (GAMP®5).

8.1.12 Biostatistics

The Frontier Science Biostatistical team supports data analysis and creates specific data monitoring reports throughout the study. A statistical analysis plan (SAP), based on the study protocol, is written by the statistical team. The SAP will provide details of the methodology and planned analyses to address the study objectives and will undergo a review process with study leadership.

Each analysis will be performed using SAS and will include tables and figures specified in the SAP. All tables and figures from each of the analyses will undergo validation and QC activities by Frontier Science.

8.1.13 Database archival and disposition

At the conclusion of the study, all data is archived and given to the sponsor and clinical sites will be provided a copy of the data entered by their facility. An inventory is maintained to track all items in the study archive as well as any requests for archival access.

8.1.14 Linkage to Identifying Information

Our study tracks infants longitudinally over two years at pre-determined time points. As a result, each participant is assigned a PID, which will be used to add new data to their REDCap file. Each clinical site maintains a password-protected, encrypted log of their enrolled study participants, contact information, and assigned PIDs. The PID log will not be available for access by the other study clinical sites, including the study Co-PIs.

8.2 Essential and Source Documents and Access to Source Data

All data entered on CRFs will be with study-specific PIDs. Sites will keep a log in a locked file of individuals by PID who are enrolled on study. Outside of site staff at that site, no one else will have access to unblinded data. All unblinded source documents will be kept as per each site's IRB regulations.

8.3 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the sites IRBs SOPs.

9 COLLABORATION

Starting late 2022, a close collaborative effort has already been implemented by NYS DOH cCMV NBS and the eleven study sites. NYS NBS has arranged monthly virtual meetings of NYS cCMV NBS Pilot Study staff and all IDSCC clinical site directors. Meeting agendas have included roll-out of the cCMV NBS Pilot Study, discussion of best practices for cCMV diagnosis and treatment, and **PROACTIVE NYS** study design. Meeting minutes are available to all clinical sites, DOH collaborators, and the NICHD. The two programs and the IDSCC clinical sites are therefore already seamlessly integrated, with feedback provided continuously between the NYS NBS and IDSCC

leaders who oversee clinical management of cCMV positive infants and enrollment/follow-up in **PROACTIVE NYS**.

10 ANNUAL UPDATES

Each IDSCC site is be required to submit annual updates regarding confirmation of CMV methodology, staff changes to be added to PROACTIVE NYS log on, and any changes to site leadership.

11 ADVISORY COMMITTEE

The NYS cCMV NBS Pilot Study has engaged a group of cCMV experts to serve as Advisory Committee Members. This groups includes experts in Audiology, Newborn Screening Programs, Bioethics, Pediatric Infectious Diseases, and a parent of a child with cCMV who is a national leader in cCMV advocacy. Some of these individuals may be invited to serve on the advisory committee for **PROACTIVE NYS**. The **PROACTIVE NYS** Advisory Committee will be convened at least once annually, and individual members may be contacted more frequently for concerns specific to their expertise.

12 HUMAN SUBJECTS PROTECTIONS

12.1 Institutional Review Board/Ethics Committee Review and Approval

A sIRB is utilized for all clinical sites participating in **PROACTIVE NYS**. Advarra serves as the sIRB. All IRB reliance agreements comply with the NIH sIRB Policy (NOT-OD-16-094). The parent/guardian informed consent document will be approved by the sIRB and available in English and Spanish. As per local site regulations, consents will be provided either on paper or with eConsent. For those parents who prefer a language other than English or Spanish, screening, informed consent, and clinical care is performed in the preferred language with the assistance of a certified medical translator, which is appropriately documented in the informed consent documentation. All institutional (local) required and applicable regulatory, ethics, and other approvals of **PROACTIVE NYS** are obtained and adhered to.

12.2 Parental Permission

Informed consent will be obtained from the parents/guardians of all study participant prior to enrollment. The informed consent document will be reviewed and approved by Advarra, the study sIRB.

12.3 Potential Benefits

Information learned in this study may be of benefit to participating children and others in the future, particularly information that may lead to more treatment options for children living with cCMV.

12.4 Potential Risks

This study is observational and without required interventions or collection of biospecimen. There is a small risk of loss of confidentiality and privacy because personal health information is being exchanged. However, strict confidentiality procedures will minimize this risk.

12.5 Reimbursement/Compensation

There is no compensation for study visits as they are part of routine medical care for infants with congenital CMV. There are no specific study procedures. Rather, data will be collected on any and all routine care procedures.

12.6 Privacy and Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing as described in Section 11.2.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site will be identified by PID only. Likewise, communications between study staff and protocol team members regarding individual participants will identify participants by PID only.

12.7 Management of Incidental Findings

Site clinicians will inform parents (or guardians if applicable)] of all clinically meaningful physical exam findings and laboratory test results, including results of any clinically performed relevant tests. When applicable, site clinicians will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

12.8 Management of New Information Pertinent to Study Participation

Study staff will provide participants with any new information learned over the course of the study that may affect their willingness to remain in follow-up.

13 ADMINISTRATIVE PROCEDURES

13.1 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the study informed consent forms approved, as appropriate, by applicable IRBs/ECs, and any other applicable regulatory entities; this includes the sIRB.

For any future protocol amendments, upon receiving final IRB/EC and other applicable regulatory entity approvals, as well as meeting any additional study-specific requirements as determined by the protocol team, sites should implement the amendment immediately. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

13.2 Study Implementation

This study will be conducted in accordance with the protocol and all applicable US, local, and international regulations.

Study implementation at each site will also be guided by site-specific SOPs. These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

13.3 Protocol Deviation Reporting

All protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to applicable IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported to leadership of PROACTIVE within 7 business days

13.4 ClinicalTrials.gov

This study is not subject to the Food and Drug Administration Amendments Act of 2007 or the NIH Policy on Dissemination of NIH-funded Clinical Trial Information. However, it will be registered in ClinicalTrials.gov to meet International Committee of Medical Journal Editors requirements.

14 PUBLICATIONS

14.1 Public Results Distribution

The findings of this study are disseminated through readily-available, timely mechanisms. The cCMV Online Dashboard is available in two formats: a password-protected, in-depth database available for clinical sites only, and a public-facing website with higher-level findings in order to ensure patient confidentiality. The website serves as a parent resource with outward facing educational materials, links to each of the 11 clinical sites and links to any manuscripts accepted for publication.

The study website is: www.proactivenys.org

14.2 Academic Results Distribution

In addition to the interactive dashboard and **PROACTIVE NYS** website, results will be published in academic settings. Manuscripts will be submitted to major general medical and pediatric journals describing the cohort's findings at birth and outcomes assessments at 6, 12, and 24 months old. Additional publications will describe treatments provided and adverse effects, predictors of delayed SNHL or delayed cognitive/language development, QoL assessments, and lessons learned / impact on the NYS NBS Program, among others. Findings will also be reported at academic conferences, including the Congenital Cytomegalovirus Public Health & Policy Conference and IDWeek.

15 REFERENCES

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APPENDIX I

IDSCC Designated Criteria

NEW YORK STATE | Department of Health | Wadsworth Center

NEW YORK STATE DEPARTMENT OF HEALTH
WADSWORTH CENTER NEWBORN SCREENING PROGRAM

Criteria for Approval of
Infectious Disease Specialty Care Centers

An Infectious Disease Specialty Care Center is defined as an Article 28 general hospital that has at least one infectious disease specialist. In addition to meeting the requirements specified for a general hospital in New York Codes, Rules and Regulations (NYCRR), Title 10, Part 405, an Infectious Disease Center will meet the criteria specified below. The center can diagnose and treat pediatric infectious diseases. If the Infectious Disease Specialty Care Center will operate at more than one location, each subsite must be identified in the application.[1]

I. Hospital Administration

Administration shall be responsible for:

- general operation of the center in accordance with written policies and procedures;
- employment or availability of qualified personnel, who maintain privileges at the hospital;
- compilation of statistical data, review and revision of reporting systems and data collection;
- notification to the newborn screening program whenever there is a change in medical director;
- provision of an update of all changes in personnel.

II. Specialty Care Center Facilities

Specialty Care Center facilities must include:

- inpatient and outpatient facilities available according to the needs of the individual patient;
- dedicated pediatric inpatient beds, neonatal intensive care unit as part of a Level III perinatal program[2] and pediatric intensive care unit;[3]

---

[1] The Permanent Facility Indicator (PFI) will identify the Infectious Disease Specialty Care Center in the application. If the Infectious Disease SCC will operate in more than one location, each sub-site must be specified by its address in the application. Each sub-site will: a) be on the operating certificate of the Article 28 facility that is the main site and be identified by a PFI number; or b) be a hospital affiliated physician practice group whose physicians are employed by the hospital and have admitting privileges to the main site; and c) assure access to all services at the main site specified in these criteria.
[2] If the hospital does not provide maternity services, then a neonatal intensive care unit is not required.
[3] If the hospital does not have a pediatric intensive care unit (PICU), then a protocol must be described for emergent care, appropriate pediatric transport, and continuity of care.

- onsite facilities for standard clinical-pathological studies, radiological studies; (i.e. X-rays, sonogram, CT, MRI) electrocardiogram studies, electroencephalogram studies, and nuclear medicine studies;
- laboratory capability for all necessary core studies and molecular genetic testing either onsite or by referral to another New York State approved laboratory as specified by the New York State Newborn Screening Program and the Wadsworth Center;
- an infant hearing screening program, directly or by contract, that is overseen by a licensed audiologist.

In addition to these standard clinical requirements, the laboratory shall have the capability to perform the following core tests either onsite or by referral to another New York State approved laboratory:

- Urine or saliva CMV PCR.

III. Personnel

A. Core Personnel:

The core personnel consist of medical director and any additional board certified/eligible pediatric specialist in infectious disease.

Medical Director, Infectious Disease Specialty Care Center

The medical director shall:

- be a board certified/eligible infectious disease specialist, or have at least 3 years of relevant experience in pediatric infectious disease.
- ensure that all children referred to the site are seen by the director or another pediatric specialist in infectious disease.
- ensure each child referred to the center receives a prompt initial comprehensive evaluation, on an inpatient or outpatient basis, as indicated. The comprehensive evaluation includes a medical, psychological and social history, physical exam and appropriate diagnostic studies;
- ensure appropriate treatment of the child is initiated and assure the development and implementation of a plan for ongoing management with parental involvement;
- ensure the child receives appropriate developmental screening, evaluation and follow-up;
- ensure supportive services are in place to assist families with identifying resources and applying for benefit programs related to the financial aspects of care. They will also provide education about the disorder and training about self-care for patients and their families;
- ensure the child has a primary care provider;

- ensure completion of adequate and prompt reports on clinical evaluations, make recommendations for treatment and follow-up and provided other necessary records to referring physicians and, when requested, to the screening laboratory;
- ensure guidance is provided for transitioning to adult care;
- ensure appropriate evaluation is done for patients already under treatment at the time of referral;
- ensure a referral is made to Early Intervention services, if appropriate.

B. Other Core Personnel

The following personnel shall be available onsite for consultation:

- Board certified/board eligible pediatric specialist(s) in infectious disease;
- Registered nurse or nurse practitioner coordinator;
- Medical social worker;
- Laboratory director, who meets the qualifications, specified in Part 19 Clinical Laboratory Directors, Section 19.2-19.4, Title 10 Official Compilation of Codes, Rules and Regulations of the State of New York, The Laboratory Director's Certificate of Qualification as issued by the NYS Clinical Laboratory Evaluation Program (CLEP).

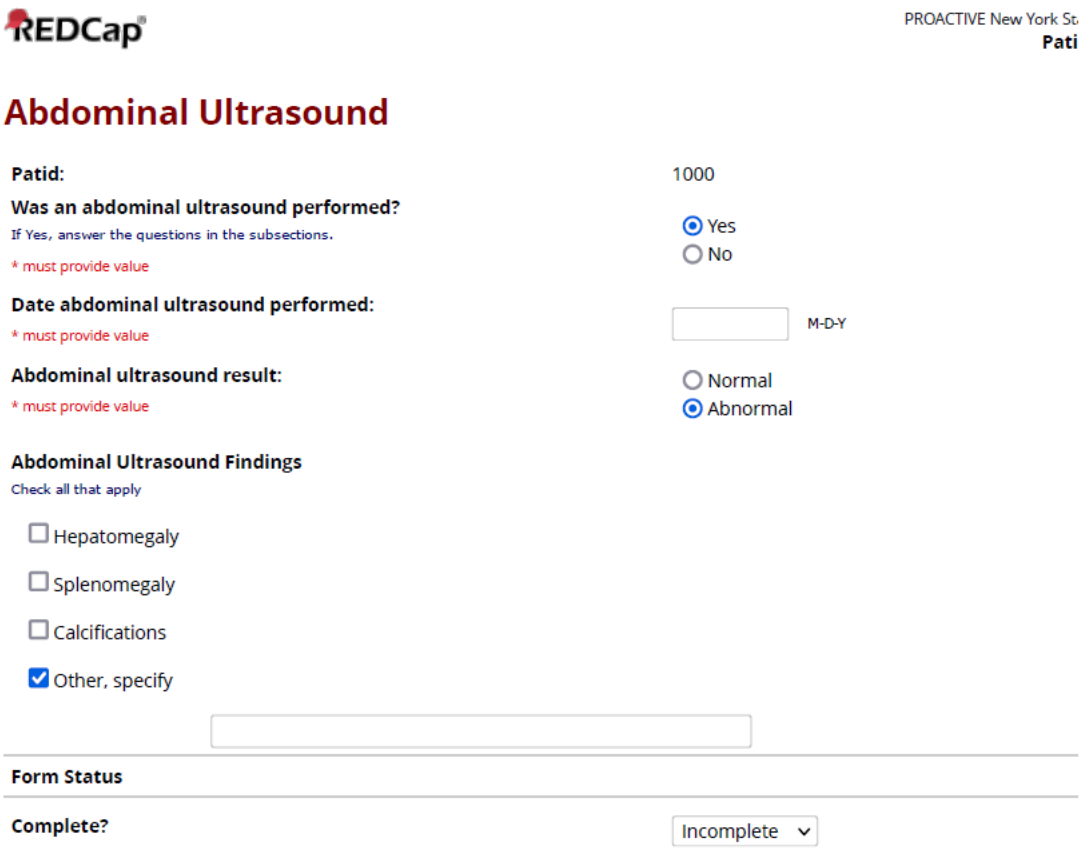
C. Additional Personnel

Consultation shall be available onsite or by referral in all specialties related to the care of the patient, including a:

- Board certified/board eligible audiologist;
- Recognized developmental specialist;
- Board certified/board eligible neonatologist;
- Board certified/board eligible pediatric opthalmologist;
- Board certified/board eligible pediatric hematologist;
- Board certified/board eligible pediatric neurologist;
- Licensed physical therapist (experienced in working with pediatric patients); and
- Licensed speech language pathologist (experienced in working with pediatric patients).

APPENDIX II

PROACTIVE NYS Redcap Case Report Forms



REDCap

PROACTIVE New York St
Pati

Abdominal Ultrasound

Patid: 1000

Was an abdominal ultrasound performed?
If Yes, answer the questions in the subsections.
* must provide value
(●) Yes
( ) No

Date abdominal ultrasound performed:
* must provide value
[ ] M-D-Y

Abdominal ultrasound result:
* must provide value
( ) Normal
(●) Abnormal

Abdominal Ultrasound Findings
Check all that apply

[ ] Hepatomegaly
[ ] Splenomegaly
[ ] Calcifications
[x] Other, specify

Form Status

Complete? Incomplete

Antiviral Treatment

Patid: 1000

Instructions: For a dose change, enter the stop date on the original dose line and then complete a new line with the start date of the new dose. If a medication is temporarily stopped, enter the stop date on the original dose line; when it restarts, start it on a new line.

	Antiviral Drug	Total Daily Dose (mg/kg/day)	Daily Dosing Interval (hours)	Start Date at this Dose Amount	Stop Date at this Dose Amount	Reason for Stop
1				M-D-Y	M-D-Y	
2				M-D-Y	M-D-Y	
3				M-D-Y	M-D-Y	
4				M-D-Y	M-D-Y	
5				M-D-Y	M-D-Y	
6				M-D-Y	M-D-Y	
7				M-D-Y	M-D-Y	
8				M-D-Y	M-D-Y	
9				M-D-Y	M-D-Y	
10				M-D-Y	M-D-Y	
11				M-D-Y	M-D-Y	
12				M-D-Y	M-D-Y	
13				M-D-Y	M-D-Y	
14				M-D-Y	M-D-Y	
15				M-D-Y	M-D-Y	
16				M-D-Y	M-D-Y	
17				M-D-Y	M-D-Y	
18				M-D-Y	M-D-Y	
19				M-D-Y	M-D-Y	
20				M-D-Y	M-D-Y	

Form Status

Complete? Incomplete

Audiology Assessment

Patid: 1000

Was an audiology test performed?
If Yes, answer the questions in the subsections.
* must provide value

- (•) Yes
- ( ) No

Audiology Assessment Results
Check all that apply

Check if Performed	Date Performed	Left Ear	Right Ear
[x] Otoacoustic emissions (OAE)	M-D-Y	( ) Normal ( ) Absent	( ) Normal ( ) Absent
[x] Auditory Brainstem Response (ABR)	M-D-Y	Hearing Threshold (db)	Hearing Threshold (db)
[x] Visual Response Audiometry (VRA)	M-D-Y	Hearing Threshold (db)	Hearing Threshold (db)
[x] Conditioned Play Audiometry (CPA)	M-D-Y	Hearing Threshold (db)	Hearing Threshold (db)
[x] Standard Audiometry	M-D-Y	Hearing Threshold (db)	Hearing Threshold (db)

Type of hearing impairment identified:

- ( ) None
- ( ) Conductive
- ( ) Sensorineural
- ( ) Mixed
- ( ) Undetermined

Hearing impairment category:

- ( ) 0-20 dB (normal)
- ( ) 21-40 dB (mild)
- ( ) 41-55 dB (moderate)
- ( ) 56-70 dB (moderately-severe)
- ( ) 71-90 dB (severe)
- ( ) >90 dB (profound)

Form Status

Complete? Incomplete

CSF Analysis

Patid: 1000

Was CSF analysis performed?
If Yes, answer the questions in the subsections.
* must provide value

(●) Yes
( ) No

Date CSF analysis performed:
* must provide value

M-D-Y

Check if performed	Results if performed	Units
☑ Protein:	nnn.n	(mg/dL)
☑ RBC:	nn	(cells/mm3)
☑ Neutrophils:	nnn	(%)
☑ Eosinophils:	nnn	(%)
☑ Lymphocytes:	nnn	(%)
☑ Monocytes:	nnn	(%)
☑ CMV PCR (qualitative):	( ) Detected ( ) Not detected	
☑ CMV PCR (quantitative):		(copies/ml)
☑ Glucose:	nnn	(mg/dL)
☑ WBC:	nn	(cells/mm3)

Form Status

Complete? Incomplete

Enrollment Category

Patid: 1000

Under which category did this participant register/enroll to PROACTIVE New York State?

* must provide value

- (●) Category 1 (Confirmed cCMV identified by NBS Program) a. cCMV screen positive AND b. cCMV confirmatory test positive
- ( ) Category 2 (Confirmed cCMV not identified by NBS Program) a. cCMV screen negative AND b. cCMV confirmatory test positive
- ( ) Category 3 (False-positive cCMV screen) a. cCMV NBS positive AND b. Negative cCMV confirmatory test
- ( ) Category 4 (Premature infants with confirmed CMV infection on late positive NBS) a. Infant born prior to 37 weeks gestation b. cCMV positive on any NBS collected prior to 44 weeks gestational age c. Positive cCMV confirmatory test obtained within 14 days of a positive NBS

Form Status

Complete? Complete

Entry CMV Screening and Maternal History

PatId: 1000

PROACTIVE NYS entry visit date:

Regardless of when the baby is enrolled to the study, only enter the date that was collected during the baby's first month of life.

10-25-2023 M-D-Y

* must provide value

Initial NYS newborn screen CMV result:

* must provide value

- (•) Positive
- ( ) Negative
- ( ) Invaild test result

Was a repeat NYS Newborn Screen CMV test performed?

If Yes, complete up to four repeat test results.

* must provide value

- (•) Yes
- ( ) No
- ( ) Unknown

Repeat #1 NYS Newborn Screen CMV test result:

Leave blank if not performed

- ( ) Positive
- ( ) Negative
- ( ) Invalid test results

Repeat #2 NYS Newborn Screen CMV test result:

Leave blank if not performed

- ( ) Positive
- ( ) Negative
- ( ) Invalid test results

Repeat #3 NYS Newborn Screen CMV test result:

Leave blank if not performed

- ( ) Positive
- ( ) Negative
- ( ) Invalid test results

Repeat #4 NYS Newborn Screen CMV test result:

Leave blank if not performed

- ( ) Positive
- ( ) Negative
- ( ) Invalid test results

Congenital CMV confirmatory test:

* must provide value

- ( ) Positive
- ( ) Negative

Was the mother ever diagnosed with CMV infection or CMV seropositivity prior to delivery?

* must provide value

- ( ) Yes
- ( ) No
- ( ) Unknown

Are maternal CMV serology results available?

If Yes, complete the section for serology timing and results.

* must provide value

- (•) Yes
- ( ) No
- ( ) Unknown

Maternal CMV Serology Timing and Results:

Check all that apply and provide IgM and IgG results.

Select all timepoints that apply	IgM Results	IgG Results
☑ Prior to conception	○ Positive ○ Negative	○ Positive ○ Negative
☑ First trimester	○ Positive ○ Negative	○ Positive ○ Negative
☑ Second trimester	○ Positive ○ Negative	○ Positive ○ Negative
☑ Third trimester	○ Positive ○ Negative	○ Positive ○ Negative
☑ Postnatal	○ Positive ○ Negative	○ Positive ○ Negative

Was a maternal IgG avidity performed?

If Yes, complete the IgG avidity interpretation.

* must provide value

○ Yes
○ No
○ Unknown

Maternal IgG avidity interpretation:

○ High
○ Intermediate
○ Low

Was an amniocentesis performed to diagnose cCMV?

◉ Yes
○ No
○ Unknown

Amniotic fluid CMV viral load (copies/mL):

n

Were there prenatal ultrasound abnormalities?

If Yes, check all the abnormalities that apply.

* must provide value

◉ Yes
○ No
○ Unknown

Prenatal ultrasound abnormalities:

Check all that apply

- ☐ Placental thickening
- ☐ Hepatomegaly
- ☐ Splenomegaly
- ☐ Pyelectasis
- ☐ Megalouretes
- ☐ Ascites
- ☐ Fetal hydrops
- ☐ Abnormality of amniotic fluid
- ☐ Microcephaly
- ☐ Cerebral ventriculomegaly
- ☐ Intracranial calcifications
- ☐ Lentriculostriate vasculopathy
- ☐ Periventricular echodensities
- ☐ Hepatic echodensities
- ☐ Intestinal echodensities
- ☐ Cystic structures in the germinal zone
- ☐ Prenatal ultrasound abnormality, other

Form Status

Complete? Complete

Final Contact

Patid: 1000

Enter the date the participant's participation in PROACTIVE New York State officially concluded:

This date will be one of the following:

-The date the participant completed the final visit in the PROACTIVE NYS follow up schedule

-The date the participant's parent(s)/guardian(s) informed site staff that their child would no longer be participating in future PROACTIVE NYS visits

-The date of the site's decision to officially conclude the participant's participation in PROACTIVE NYS due to "Lost to follow-up/ Unable to contact"

-The date of the participant's death (enter the date of death and not the date the site learned of the death)

* must provide value

M-D-Y

Aside from individual missed visit(s), did the participant otherwise complete the full PROACTIVE New York State schedule of visits?

* must provide value

- ○ Yes
- ◉ No

Select the reason the participant did not complete the full PROACTIVE New York State schedule of visits:

* must provide value

- ○ Parent(s)/Guardian(s) decision
- ○ Lost to follow-up/Unable to contact
- ◉ Death

Describe the circumstances of the participant's death:

(DO NOT INCLUDE any Protected Health Information [PHI] or Personally Identifiable Information [PII])

* must provide value

Form Status

Complete? Incomplete

Head Ultrasound

Patid: 1000

Was a head ultrasound performed?
If Yes, answer the questions in the subsections.
* must provide value
- (•) Yes
- ( ) No

Date of head ultrasound:
* must provide value
[ ] M-D-Y

Head ultrasound findings:
* must provide value
- ( ) Normal
- (•) Abnormal

Head Ultrasound Findings
Check all that apply
- [ ] Intracranial periventricular calcifications
- [ ] Lenticulostriate vasculopathy
- [ ] Ventriculomegaly
- [ ] Hemorrhage
- [ ] Hydrocephalus
- [ ] Choroid plexus or germinal matrix cyst
- [x] Other, specify

[ ]

Form Status

Complete? Incomplete

Laboratory Testing

Patid: 1000

Was any laboratory testing performed?
If Yes, select each lab test performed and enter results if available.
* must provide value

(•) Yes
( ) No

Laboratory Results:
Check if performed and enter low/high specimen result and specimen date if available.

Check if Performed	Lowest Result	Units	Lowest Result Specimen Date	Highest Result	Units	Highest Resu Specimen Da
☑ WBC:	nn.n	(x10E3/uL)	M-D-Y	nn.n	(x10E3/uL)	M-D-Y
☑ Neutrophils:	nn.n	(%)	M-D-Y	nn.n	(%)	M-D-Y
☑ Hemoglobin:	nn.n	(g/dL)	M-D-Y	nn.n	(g/dL)	M-D-Y
☑ Platelets:	nnn	(x10E3/uL)	M-D-Y	nnn	(x10E3/uL)	M-D-Y
☑ ALT:	nn	(U/L)	M-D-Y	nn	(U/L)	M-D-Y
☑ AST:	nn	(U/L)	M-D-Y	nn	(U/L)	M-D-Y
☑ GGT:	nnn	(U/L)	M-D-Y	nnn	(U/L)	M-D-Y
☑ Creatinine:	n.n	(mg/dL)	M-D-Y	n.n	(mg/dL)	M-D-Y
Bilirubin						
☑ Indirect:	n.n	(mg/dL)	M-D-Y	n.n	(mg/dL)	M-D-Y
☑ Direct:	nn.n	(mg/dL)	M-D-Y	nn.n	(mg/dL)	M-D-Y
☑ Total:	nn.n	(mg/dL)	M-D-Y	nn.n	(mg/dL)	M-D-Y

Form Status

Complete? Incomplete

MRI Brain

Patid: 1000

Was an MRI brain performed?
If Yes, answer the questions in the subsections.
* must provide value
- (•) Yes
- ( ) No

Date of MRI brain:
* must provide value
[ ] M-D-Y

MRI brain result:
* must provide value
- ( ) Normal
- (•) Abnormal

MRI Brain Findings
Check all that apply

- [ ] Periventricular calcifications
- [ ] Lenticulostriate vasculopathy
- [ ] Ventriculomegaly
- [ ] White matter disease
- [ ] Hemorrhage
- [ ] Migrational abnormalities (polymicrogyria, lissencephaly)
- [ ] Periventricular leukomalacia or cystic abnormality
- [ ] Cerebral atrophy
- [ ] Corpus callosum dysgenesis
- [ ] Cerebellar hypoplasia
- [x] Other, specify

[ ]

Form Status

Complete? Incomplete

Neonatal CMV Testing

Patid: 1000

Was CMV serology performed on the infant?

If Yes, provide the date the CMV serology was performed and the IgM and IgG results.

* must provide value

(•) Yes ( ) No

Date CMV serology performed: M-D-Y

IgM results: ( ) Positive ( ) Negative

IgG results: ( ) Positive ( ) Negative

Was IgG avidity performed on the infant?

If Yes, provide the date the IgG avidity was performed and the interpretation.

* must provide value

(•) Yes ( ) No

Date IgG avidity was performed: M-D-Y

IgG avidity interpretation: ( ) High ( ) Intermediate ( ) Low

Was a confirmatory CMV test performed?

If Yes, provide the date the Confirmatory CMV test was performed and the results.

* must provide value

(•) Yes ( ) No

Date confirmatory CMV test performed: M-D-Y

Confirmatory CMV Test Results

Check if performed and provide results. Include viral loads in copies/mL and log scale, if available.

Check if performed	Result	Viral Load Result (copies/mL)	Viral Load Result (log copies/mL)
☑ Urine CMV PCR	( ) Positive ( ) Negative		n.nn
☑ Urine CMV Culture	( ) Positive ( ) Negative		n.nn
☑ Saliva CMV PCR	( ) Positive ( ) Negative		n.nn
☑ Blood/Plasma CMV PCR	( ) Positive ( ) Negative		n.nn

Was a confirmatory CMV test repeated?

If Yes, provide the date the confirmatory CMV test was repeated and the results.

* must provide value

(•) Yes ( ) No

Date of confirmatory CMV test(s) repeat: M-D-Y

Repeat Confirmatory CMV Test Results

Check if performed and provide results. Include viral loads in copies/mL and log scale, if available.

Check if performed	Result	Viral Load Result (copies/mL)	Viral Load Result (log copies/mL)
☑ Urine CMV PCR	○ Positive ○ Negative		n.nn
☑ Urine CMV Culture	○ Positive ○ Negative		n.nn
☑ Saliva CMV PCR	○ Positive ○ Negative		n.nn
☑ Blood/Plasma CMV PCR	○ Positive ○ Negative		n.nn

Form Status

Complete? Incomplete

Neonatal Data and Medical Problems

Patid: 1000

Gestational age at birth: (weeks) (days)

Birth weight: grams

Birth length: cm (round value to nearest tenth)

Birth head circumference: cm (round value to nearest tenth)

What was the delivery route?

- ○ Vaginal delivery
- ○ C-section

What was the Apgar score?

1 minute:	
5 minutes:	
10 minutes:	

Where was newborn care provided?

- ○ Newborn nursery
- ○ NICU
- ○ Home birth
- ○ Other

Were any neonatal medical problems identified? * must provide value

- ◉ Yes
- ○ No

Cardiovascular:

- ☐ Patent ductus arteriosus
- ☐ Ventricular septal defect
- ☐ PPHN (persistent peripheral hypertension of the newborn)
- ☐ Cardiac arrhythmia
- ☐ Cyanotic or acyanotic heart defects
- ☐ Cardiovascular, other
- ☐ Hypotension requiring vasopressor support

Genetic:

- [ ] Genetic defect

Dermatologic:

- [ ] Hemangioma
- [ ] Nevus simplex
- [x] Dermatologic, other

70 characters remaining

Gastrointestinal:

- [ ] Feeding intolerance
- [ ] GERD
- [ ] Cholestasis
- [ ] Failure to thrive
- [ ] Necrotizing enterocolitis (NEC)
- [ ] Gastroschisis/omphalocele
- [ ] Small or large intestinal obstruction
- [ ] Hirschsprungs disease
- [ ] Diaphragmatic hernia
- [ ] Tracheoesophageal fistula (TEF/EA)
- [x] Gastrointestinal, other

Hematologic/Oncologic:

- [ ] Anemia
- [ ] Hyperbillirubinemia
- [ ] Bleeding and coagulation disorders
- [ ] Hematologic/oncologic, other

HENT:

- [ ] Cleft lip/palate
- [ ] Upper/lower airway malacia
- [ ] Subglottic stenosis
- [x] HENT, other

Immunologic:

- [ ] SCID
- [ ] Neutropenia
- [ ] Immunologic, other

Infectious (excluding CMV):

- [ ] Bacterial meningitis
- [ ] Bacteremia
- [ ] Urinary tract infection
- [ ] Congenital toxoplasmosis
- [ ] HSV-1 or HSV-2 infection
- [ ] Congenital syphilis
- [ ] Perinatal HIV exposure/infection
- [x] Infectious, other

Metabolic:

- [ ] Hypoglycemia
- [ ] Hypocalcemia
- [ ] Inborn error of metabolism
- [ ] Infant of a diabetic mother
- [ ] Hypothyroidism
- [ ] Hyperthyroidism
- [ ] Adrenal dysfunction
- [x] Metabolic, other

Musculoskeletal:

- [ ] Hip dysplasia
- [ ] Fracture
- [ ] Muscular dysplasia
- [ ] Musculoskeletal, other

Neurologic:

- [ ] Hypoxic-ischemic encephalopathy (HIE)
- [ ] Seizures
- [ ] Hypotonia
- [ ] Hydrocephalus
- [ ] Intraventricular hemorrhage
- [x] Neurologic, other

Ophthalmologic:

- [ ] Retinopathy of prematurity
- [ ] Congenital cataract
- [ ] Microphthalmia
- [x] Ophthalmologic, other

Pulmonary:

- [ ] Aspiration pneumonia (meconium or other)
- [ ] Pulmonary hypertension
- [ ] Respiratory distress syndrome (RDS)
- [ ] Transient tachypnea
- [ ] Apnea
- [ ] Pneumothorax
- [ ] Plural effusion/chylothorax
- [ ] Respiratory failure requiring supplemental oxygen
- [x] Pulmonary, other

Form Status

Complete? Incomplete

Non-pharmaceutical cCMV Interventions

Patid: 1000

Was the child referred to Early Intervention?

- (•) Yes
- ( ) No
- ( ) Unsure

Please select any of the developmental services the child is receiving:

- [ ] None
- [ ] Occupational therapy
- [ ] Physical therapy
- [ ] Special Education
- [ ] Speech therapy
- [ ] Vision services
- [x] Other

Was the child referred to any medical specialists due to cCMV-related issues?

- (•) Yes
- ( ) No
- ( ) Unsure

Please select any of the developmental services the child is receiving:

- [ ] Neurology
- [ ] ENT
- [ ] GI
- [x] Other

Please select any audiologic services the child is receiving:

- [ ] American Sign Language training
- [ ] Hearing aid
- [ ] Cochlear implants
- [x] Other

Please describe any other patient interventions for cCMV complications:

Form Status

Complete? Incomplete

Ophthalmology Assessment

Patid: 1000

Was an ophthalmologic screening performed?
If Yes, answer the questions in the subsections.
* must provide value

- (•) Yes
- ( ) No

Date of ophthalmologic screening:
* must provide value

M-D-Y

Ophthalmologic screening result:
* must provide value

- ( ) Normal
- (•) Abnormal

Ophthalmologic Screening Findings
Check all that apply

- [ ] Chorioretinitis
- [ ] Microphthalmia
- [ ] Optic nerve hypoplasia/aplasia
- [ ] Cataracts
- [x] Other, specify

Form Status

Complete? Incomplete

Physical Exam and Medical Diagnoses

Patid: 1000

Are there any physical exam findings?
If Yes, provide the date and select each physical exam finding that applies.
* must provide value

- (•) Yes
- ( ) No

Date of physical exam:
* must provide value

10-25-2023 M-D-Y

Select all that apply from each section:

- [ ] Hepatomegaly
- [ ] Microphthalmia
- [ ] Splenomegaly
- [ ] Jaundice (present at time of or prior to entry visit)
- [ ] Microcephaly
- [ ] Hydrops

Rash

- [ ] Petechiae
- [ ] Purpura
- [x] Other rash, specify

Neonatal/Infant Neurological Abnormalities

- [ ] Hypotonia
- [ ] Hypertonia
- [ ] Poor suck
- [ ] Seizures
- [ ] Myoclonic jerks

Other Abnormalities

- [x] General
- [x] HENT
- [x] Respiratory
- [x] Neurologic
- [x] Eye
- [x] Neck
- [x] Genitourinary
- [x] Integumentary
- [x] Cardiovascular
- [x] Gastrointestinal
- [x] Musculoskeletal

Form Status

Complete? Incomplete

REDCap

PROACTIVE New York St
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Physical Measurements

Patid: 1000

Were physical measurements taken at Entry?
If Yes, answer the questions in the subsections.
* must provide value

- (•) Yes
- ( ) No

Date of measurements: M-D-Y

Entry weight: grams

Entry head circumference: cm (round value to nearest tenth)

Entry length: cm (round value to nearest tenth)

Form Status

Complete? Incomplete

Visit Tracking

PatId: 1000

What is the reason for this report:

* must provide value

- ○ Participant completed scheduled visit
- ○ Participant was scheduled but missed visit
- ○ Participant was not scheduled and no additional evaluations are available since the last PROACTIVE NYS visit
- ◉ Participant was not scheduled but additional evaluations are available since the last PROACTIVE NYS visit

Date of report:

M-D-Y

* must provide value

What is the primary source of information?

* must provide value

- ○ Completed study visit with the participant and parent(s)/guardian(s) or other family
- ○ Phone, text, email, or other contact with the parent(s)/guardian(s), other family, or designated contact person
- ◉ Contact with participant's health care provider/physician or EMR

Did contact with the health care provider/physician reveal any completed testing or evaluations since the participant's last PROACTIVE New York State visit?

* must provide value

- ◉ Yes
- ○ No

Indicate any testing/evaluations completed since the last PROACTIVE New York State visit.

(select all that apply)

* must provide value

- ☐ Physical exam and medical diagnoses
- ☐ Laboratory testing
- ☐ Imaging results
- ☐ Audiology assessment
- ☐ Ophthalmology assessment
- ☐ Treatment-related information
- ☐ Physical measurements
- ☐ CMV, PCR and CSF testing

If you checked...	You will complete or update the following evaluation(s)...
Physical exam and medical diagnoses	Physical Exam and Medical Diagnoses
Laboratory testing	Laboratory testing
Imaging results	Head Ultrasound, MRI Brain, Abdominal Ultrasound
Audiology assessment	Audiology assessment
Ophthalmology assessment	Ophthalmology assessment
Treatment-related information	Antiviral Treatment
Physical measurements	Physical Measurements
CMV, PCR and CSF Testing	CSF Analysis

Form Status

Complete? Incomplete

APPENDIX III

Statistical and Data Management Center (DMC)

1. History/Background

   Based on the excellence of their past performances, and the large and complicated dataset this study is expected to generate, Frontier Science and Technology Research Foundation, Inc. (FSTRF, also known as Frontier Science) is designated as the Statistical and Data Management Center (DMC) for the follow-up study. Frontier Science is an accomplished not-for-profit organization whose mission is to collaborate with investigators and sponsors to conduct scientifically meaningful high-quality clinical trials, while advancing the application of statistical science and practice and data management techniques in science, health care and education. Since its founding in 1975, Frontier Science has provided innovative, yet cost-effective, data management, biostatistics, and technical services to research networks, pharmaceutical companies, and academic investigators.

   With a reputation as a highly capable research partner, Frontier Science lends its expertise to the design, conduct, analysis, and reporting of clinical trials (Phase I through IV) and observational studies. Comprising three locations in the United States and European affiliates in Greece and Scotland, the organization collaborates with investigators, clinical sites, laboratory centers and technicians in more than 1,200 establishments worldwide. With its main office located in Amherst, New York, Frontier Science is well-poised to focus on the impact of cCMV as it relates to all New Yorkers.

   Frontier Science maintains a successful history of partnering on clinical trials, and has supported statistical, data management and coordinating centers for numerous projects. It has participated in several multi-site, multi-trial clinical research networks, including more than thirty-three years with the AIDS Clinical Trials Group (ACTG); the Pediatric AIDS Clinical Trials Group and its successor, the International Maternal Pediatric and Adolescent AIDS Clinical Trials (IMPAACT) Network; the Eastern Cooperative Oncology Group (ECOG) during 1975-2016; International Breast Cancer Study Group (IBCSG) for forty-two years and the Pediatric HIV/AIDS Cohort Study (PHACS) for 17 years. It also currently directs the Data Management and Report Unit (DMRU) of the Data Management, Auditing, and Coordinating Center (DMACC) for the Cancer Prevention Clinical Trials Network (CP-CTNet), as well as the Coordinating Center for the HIV/Cervical Cancer Prevention 'CASCADE' Clinical Trials Network and Tuberculosis RePORT International Coordinating Center (TB-RICC) for TB-RePORT (Regional Prospective Observational Research in Tuberculosis) International (TBRI).

   Frontier Science maintains a highly-trained workforce committed to delivering quality service and meeting the unique needs of each of its collaborators. With more than 300 dedicated staff members, including statisticians, statistical programmers, protocol and laboratory data managers, medical coders, software programmers, randomization coordinators, database operations administrators and information technology (IT) security professionals, Frontier Science provides a comprehensive approach to each of its projects. It also maintains a team of technical writers and business analysts who are trained in quality systems documentation and computer systems validation. Most staff have backgrounds in statistics, health care disciplines, computing science and related fields, and all staff undergo continuous education and training. Additionally, Frontier Science has established in-house working groups of relevant subject matter experts and exceptionally experienced individuals to analyze and integrate industry trends, best practices and new technologies to ultimately ensure that the organization remains apprised of the ever-evolving clinical trial landscape.

   Frontier Science's operations require it to ensure complete business continuity in the event of an emergency. Therefore, the organization places critical emphasis and planning towards its ability to effectively maintain and quickly restore all vital functions during and after an emergency. Frontier

Science's Business Continuity Plan (BCP) has been developed with these factors in mind, and carefully sets forth the factors and steps necessary to prepare for a crisis (disaster or emergency). The BCP allows the organization to remain functional for the duration of the crisis, and take all appropriate actions to help ensure the organization's continued viability.

Frontier Science approaches each of its projects in a calculated manner to ensure compliance with various regulations, and to ensure full data quality and integrity. As part of this process, and as part of its commitment to industry standards such as those set forth in the Good Clinical Data Management Practices (GCDMP) published by the Society of Clinical Data Management, each study is required to have a corresponding data management plan (DMP). The DMP will act as a governing document for Frontier Science Data Management staff assigned, specifically including the role of the data managers, medical coders, and data manager assistants (DMAs) in maintaining data quality and best practices for quality assurance and quality control that apply to a specific study. The DMP will also list all critical milestones and data review activities, along with material about study-specific reports, communications, or other information that the Data Managers will need to successfully monitor and clean all incoming data. The DMP is accompanied by a Quality Assurance/Quality Control (QA/QC) plan that sets forth the specific schedule required for all quality control activities. Data managers use these documents to guide their efforts during the course of the study and to track each data check activity required to ensure for complete and accurate data.

Utilizing its established infrastructure, Frontier Science will provide the **PROACTIVE NYS** study a wide range of technical services and support to:

- Design and implement data collection instruments in REDCap Academic promoted in a cloud-based environment
- Provide technical and infrastructure support for all electronic software data collection systems utilized on the study, in addition to any other applications required to ensure adequate oversight and administration of the study (reporting, study administration, data visualization, etc.)
- Collaborate on compliance issues to ensure participant safety and data security/confidentiality, including the provision of guidance documentation and quality assurance support
- Provide study clinical site training on database use and entry
- Maintain and provide quality control of data submitted across all study sites
- Manage an interactive, continuously updated visualization dashboard of all enrolled participants
- Provide biostatistical support for interim and final analyses
- Design and maintain public and private (study personnel only) websites for distribution of preliminary study data
- Assist with manuscript preparation

2. REDCap® Academic

REDCap has been validated as a commercial system fit for use by Frontier Science Quality Assurance department, and bespoke software built by Frontier Science developers to interface with REDCap is validated in accordance with the Frontier Science software lifecycle policy. REDCap can be configured as required for both cloud-based and offline-setting for both facility-based and remote/field-based data collection activities. Frontier Science will ensure that the REDCap software is appropriately configured for the most efficient use on the study by working with all relevant partners to establish requisite data flow activities and utilizing and leveraging its global eCRF library (e.g. neuropsychology eCRFs) which contains thousands of forms from its decades of experience supporting NIH-funded large clinical trials groups. Once configured for the needs of the project, REDCap will be available to IDSCC sites who will enter the data collected from the participants into

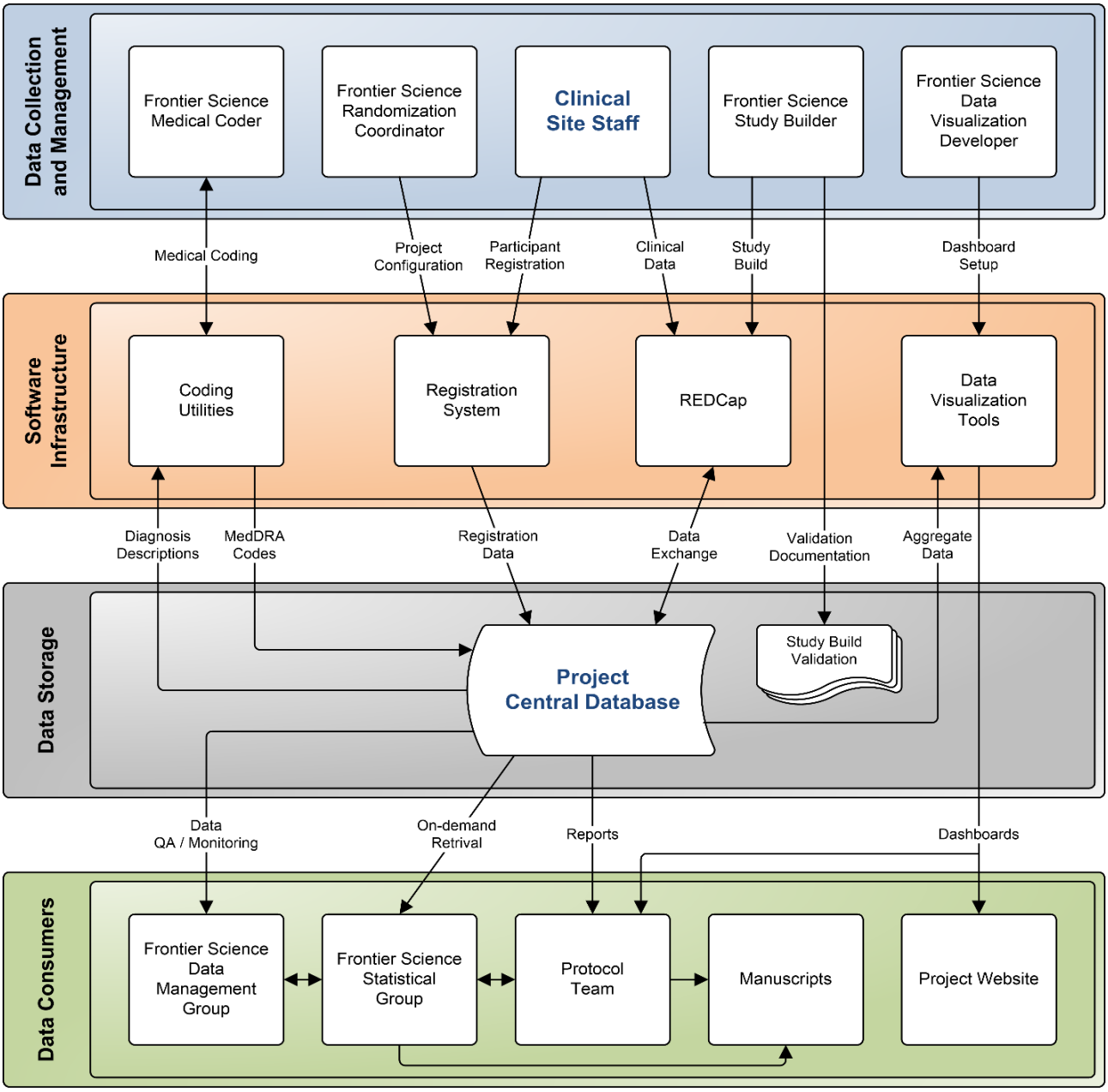
the system directly. All data will be transferred to Frontier Science, who will store the data and maintain adequate safeguards to ensure full security and integrity of the study database.

As part of its data validation procedures, Frontier Science data managers utilize automated edit checks on Electronic Case Report Forms (eCRFs) to identify potential errors at the time of data entry for key data elements by flagging required fields, potential errors or questionable data as well as requiring the clinical site user to take action to resolve them. Skip logic is integrated in the eCRFs for the purpose of directing clinics to complete each required field based on previously answered questions and preventing data entry for unnecessary fields. Frontier Science will also implement range checks that require explicit data entry confirmation for overwrite, as well as non-conformant data checks for missing and non-conformant data.

3. Coding and Utilities
   Frontier Science contains a Medical Coding Department comprised of individuals trained and certified in medical and drug coding procedures. The Coding Department uses MedDRA to encode clinical and adverse events, and WHO Drug Dictionary to encode medications taken by participants. Frontier Science Medical Coders are certified by the American Health Information Management Association and/or the American Academy of Professional Coders, and perform all medical coding tasks required for the various studies in which they participate within the context of Frontier Science. The Coding Department adheres to standard procedures and review processes to ensure consistency through a collection of SOPs, work instructions, reference guides, and templates. This includes checklists to guide coding, quality review, and ancillary tasks such as dictionary up-versioning which is performed twice annually. For ongoing studies, this may require that certain records in the database are recoded as the new dictionary and accompanying codes are released. A working group comprised of Frontier Science coders as well as representatives from other collaborating associations submit requests for new MedDRA terms as needed and if reflected in the new release, incorporates them into their current terms. Requests for new medication codes are submitted online through a designated change request page provided by the WHO Drug vendor.

4. Data acquisition and processing
   Figure 5 illustrates the relationship among several inflow and outflow components of the proposed infrastructure. As depicted, there will be multiple sources of study data. Frontier Science will acquire participant enrollment information from the clinical sites. Users at the clinical sites will then enter study data into REDCap. Frontier Science will configure its data exchange system which will transfer participant enrollment information, in real-time, from Stars to REDCap to initialize the list of participants, and will transfer the Stars participant enrollment information and REDCap study data into the Central Database. Data from the Central Database will be used as the source for quality assurance, medical coding, reporting, data visualization dashboards, on-demand retrievals for statistical analysis, and exchanging data with the study team.

Figure 5. Virtual Data Management Infrastructure and Data Flow



5. Quality assurance and quality control measures

Frontier Science maintains a robust quality management system (QMS) that is supported by a team of experienced quality assurance professionals. Components of the QMS include internal audits, CAPA and incident tracking, a comprehensive training plan (discussed above), guidance document creation and management, and continuous improvement. All of these activities collectively ensure that Frontier Science is inspection ready and also allows Frontier Science to assist other participating entities in establishing their own quality systems. A full time, independent Compliance Officer oversees the Quality Management activities at Frontier Science.

6. Data storage

All data is stored at Frontier Science's production site, located in Albany, NY, and which is a SOC II certified data center. The data center is equipped with a dedicated oxygen-depleting fire suppression system and dedicated climate control units. In addition, the data center has backup systems in place.

For example, the data center is provisioned with Uninterruptible Power Supplies (UPSs) which provide surge protection and uninterrupted switchover to short term backup, while diesel generator power provides indefinite power backup. Physical access is restricted and monitored by designated colocation support staff. A Disaster Recovery site is located in a blast-hardened storage bunker in Romulus, NY.

7. Database development and validation
   In order to ensure full data integrity and proper design of the study within the electronic environment, Frontier Science executes a robust study build validation process that ensures full testing and documentation of the entire build process. Study Build at Frontier Science closely mirrors a software development lifecycle (SDLC) which has been vetted over the course of several vendor audits. These audits have provided evidence that the organization's SDLC is not only sufficient but extremely robust per industry standard. Study builders are similarly trained extensively in the "SDLC process", or validation process, followed for study build. Each study build is documented with a validation package that includes a study requirements workbook (analogous to functional requirements) to define the data elements and edit checks for each eCRF. Test cases are drafted and a testing plan is reviewed and signed prior to formal testing in a User Acceptance Testing (UAT) environment. Results of test cases are tracked in VersionOne (a COTS validated agile software development product) and a testing report is developed and signed to document the results of formal UAT testing, prior to pushing an eCRF version to production. A traceability matrix ensures that all forms and edit checks are tested prior to release.

8. Database archival and disposition
   The data may be stored indefinitely as Frontier Science follows a robust backup process and maintains all backups for as long as required by the sponsor. Archival likewise follows a robust procedure, whereby a designated individual or individuals will be responsible for ensuring that the study archive is complete.

9. Team governance and organizational structure
   The PROACTIVE NYS project will be under an mPI leadership model. Two of the PIs both works at the Renaissance School of Medicine at the State University of New York at Stony Brook, while the third works at the New York State Department of Health (DOH). Dr. Caggana's focus will be on the management of the initial cCMV newborn screening and the initial follow-up and diagnostic work-up of those babies, which will help determine their eligibility for PROACTIVE NYS.

   Additionally, Dr. Caggana will serve as the Contact PI for this project. Drs. Nachman and Handel have been collaborating on similar projects for the past 6 years. The expected work has been divided, with Dr. Nachman primarily focusing on management issues such as finances, collaboration with the Wadsworth Newborn Screening program, and FSTRF data completeness and data queries. She will also participate in periodic evaluation of research progress and publication policies. Dr. Handel will focus primarily on the scientific rationale of the study, including objectives, CRF development, analysis of data, and publication of results.

   All three leads have been working together for the past year designing the project, having calls with the study sites and NYS DOH, and helping to design the study website, hosted by Frontier Science (FSTRF), the study's data management center, developing patient facing forms regarding the new diagnostic tool and the study as well as planning site budgets and accountability.

   Meeting schedule with agenda: Dr. Handel will run monthly meetings with each of the sites, focusing on addressing issues related to illness, newly identified hearing loss, and medication toxicities. Minutes will be kept from these calls and added to an electronic trial master file (eTMF) for organizational and track record purposes. Dr. Nachman will participate in these meetings by

addressing recruitment and CRF completion rates, as well as missing data from each site. Dr. Caggana will update sites on sensitivity and specificity of the testing in an ongoing basis.

Dr. Handel and Dr. Nachman will be meeting weekly after study kickoff. Their agenda will depend on issues identified that week. Urgent meeting can also be scheduled as their offices are several doors from each other and they have extensively collaborated on both research and patient care issues on an ongoing basis for the past 6 years. Their weekly collaborations may move to every other week during year two and three of the study.

A yearly progress report will be co-authored and submitted to the funding agency. A publication SOP will be developed for the study and include solicitation of topics, authorship, and timelines for abstract and manuscript review.

10. Conflict resolution procedures
    If a potential conflict develops, the PIs shall meet and attempt to resolve the dispute. If they fail to resolve the dispute, the disagreement shall be referred to an arbitration committee consisting of senior Pediatric ID members from each site, along with a senior representative from NYS DOH, and FSTRF.

11. Decision process for scientific direction and allocating funds and resources
    Dr. Caggana will focus on QA of the Newborn Screen CMV PCR testing and assessing the sensitivity and specificity of cCMV by confirmation of status on all infants identified. Drs. Handel and Nachman have agreed that their focus will be long term follow-up at this time. The next steps will be evaluation of events by each study timepoint, with the potential to engage outside collaborators when issues are identified. This includes possible development of a serum/plasma repository for infants with hearing loss, genetic assessments for other causes of hearing loss, and a proposal for longer term follow-up past 2 years of age. Key to these proposals will be an assessment of how often events are noted in the first years in this cohort of cCMV infants. Funding will need to be identified to assess these projects.

    Currently, the budget is specific for each site and includes funds for purchase of tools needed for the study. Budget for the data management center is also specific and matches the needs of the study. The distribution of the submitted budget takes into consideration existing resources and the dissemination of work. Each PI will be responsible for their own operational budget, but will work together to manage the overall budget and reallocate funds as necessary.