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National Center on Birth Defects and Developmental Disabilities (NCBDDD)

Centers for Disease Control and Prevention (CDC)

Surveillance Network: Maternal, Infant, and Child Health Outcomes Following Medication for Opioid Use Disorder during Pregnancy (MAT-LINK) – Phase I

FINAL REPORT

September 2022

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1. Executive Summary

From 1999 to 2014, the prevalence of opioid use disorder (OUD) among people who were pregnant in the United States quadrupled from 1.5 to 6.5 per 1,000 delivery hospitalizations.[1] In addition to the inherent risks of opioid use to the person who is pregnant (e.g., overdose, relapse, infectious diseases), more cases of neonatal abstinence syndrome (NAS) have occurred.[2] Furthermore, recent evidence suggests that children born with NAS may experience developmental delays, although the complexities around the roles that social determinants of health and other prenatal or postnatal exposures may play have not been fully understood.[3,4] Additionally, opioid use during pregnancy has been associated with other serious health effects, including poor fetal growth, preterm birth, intrauterine fetal demise, and specific birth defects.[5] The developmental trajectory of children with NAS and these other adverse health outcomes has not been systematically studied. While medications for OUD (MOUD), such as methadone and buprenorphine, are recommended for people with OUD during pregnancy, there are knowledge gaps regarding the risks and benefits of each MOUD regimen as well as if there are improved pregnancy, maternal, and infant health outcomes with certain medications or prescribing patterns.[6]

The Maternal, Infant, and Child Health Outcomes Following Medication for Opioid Use Disorder during Pregnancy (MAT-LINK) project aims to improve understanding of the spectrum of maternal and infant health outcomes associated with OUD during pregnancy, in particular the role of MOUD. MAT-LINK also examines the role of mediating and moderating factors on these outcomes, including exposure to multiple substances, maternal comorbidities, and other psychosocial factors. Results from MAT-LINK can improve policies, clinical practice recommendations, and clinical decision-making. In addition, this project also developed and implemented a data platform to collect and link maternal, infant, and child data across clinical sites, which can then be modified for other exposures during pregnancy.

2. Introduction

2a. Background

From 1999 to 2014, the prevalence of OUD among people who were pregnant in the United States quadrupled from 1.5 to 6.5 per 1000 delivery hospitalizations.[1] The American College of Obstetricians and Gynecologists (ACOG) states that for people who are pregnant with OUD the recommended therapy is opioid agonist pharmacotherapy (e.g., buprenorphine, methadone). MOUD is preferable to medically supervised withdrawal because withdrawal is associated with high relapse rates that lead to worse outcomes.[7]

There is limited information comparing maternal, pregnancy, infant, and child outcomes associated with different MOUD during pregnancy, especially since people who are pregnant are often excluded from clinical trials. As a result, people who are pregnant with OUD and their healthcare providers are forced to use expert opinion to guide most clinical care decisions. Two of the greatest knowledge gaps are around maternal risks with different medication regimens and longer-term outcomes for children who were prenatally exposed to different opioids. There are known risks to the person who is pregnant; it is also well established that opioid use during pregnancy increases NAS, and recent evidence suggests that children who were born with NAS may experience developmental delays more often compared with those without clinical signs of withdrawal.[3,4,8] However, the developmental trajectory of children prenatally exposed to opioids, including different types of opioids, has not been systematically studied, nor has the impact of MOUD in pregnancy.

In addition, polysubstance use (i.e., use of more than one substance of potential abuse) is common among people with OUD; however, the individual and combined effects of substances are often difficult

to disentangle, and the impact of polysubstance use on the effectiveness of MOUD is not well understood. Therefore, more comprehensive data are needed to monitor the safety, clinical effectiveness, and risks and benefits of MOUD in pregnancy. A small number of studies have compared outcomes between methadone and buprenorphine among people who are pregnant with OUD. However, the majority of these studies had methodologic issues limiting the generalizability of their findings, including not assessing and adjusting for polysubstance use and other confounders during pregnancy. In addition to this concern, some of the observed differences in infant outcomes might inherently be due to differences in maternal characteristics that affect the choice of regimen, and differences in timing of entry to care and retention in care. In the absence of clear, individualized clinical recommendations, MOUD decisions may be driven by other factors, including provider availability and training on a specific MOUD, medication availability, health insurance coverage, patient preferences, transportation issues, and perceived stigma associated with specific medications.

In 2019, CDC received funding from the Office of the Assistant Secretary for Planning and Evaluation's (ASPE) Patient-Centered Outcomes Research Trust Fund (PCOR-TF) to establish MAT-LINK, a network to examine practice patterns and outcomes associated with MOUD during pregnancy. This surveillance network created a data platform and standard data elements to collect linked maternal and child data among people taking MOUD during pregnancy at four clinical sites across the United States (Phase I): Boston Medical Center, Kaiser Foundation Research Institute Northwest in Oregon and Washington, The Ohio State University, and University of Utah. In 2020, CDC received additional funding from ASPE to expand MAT-LINK by including three more clinical sites (University of New Mexico, University of Rochester, and University of South Florida) and extending child follow-up through 6 years of age (Phase II). This final report shares information and deliverables related to Phase I of MAT-LINK.

2b. Purpose and Objectives

The purpose of MAT-LINK was to establish a health outcomes surveillance network across multiple clinical sites to rapidly collect linked maternal and infant data and monitor the maternal, pregnancy, infant, and child health outcomes in the context of MOUD during pregnancy.

The project objectives for Phase I were to

1. Establish an organizational structure to include federal partners, clinical and public health partners, and a CDC steering committee;
2. Develop a data platform to collect linked maternal and infant data among people treated for OUD during pregnancy; and
3. Analyze and disseminate preliminary results to inform patient-centered care for people who are pregnant with OUD and for children with prenatal opioid exposure.

2c. Clinical Sites

Clinical sites were selected for inclusion in MAT-LINK based on the criteria listed in Table 1.

Table 1. Clinical Site Inclusion Criteria

Phase I Inclusion Criteria
• Demonstrate access to clinical data • Demonstrate existing or previously successful linkage • Demonstrate ability to access and review pertinent health records • Provide authorization to access data source • Demonstrate ability to collaborate on public health surveillance activities • Provide data on births that are at least as recent as 2014

After releasing a Request for Proposals (RFP), 24 applications were received from across the United States. The applications were reviewed by three independent reviewers and received scores according to the established inclusion criteria. For each applicant, an average score across reviewers was calculated, and applicants were ranked by average score. The top eight applicants were then asked to participate in an interview to provide additional information on their IT infrastructure. Ultimately, four clinical sites were awarded funding to participate in Phase I of MAT-LINK:

1. Boston Medical Center
2. Kaiser Foundation Research Institute Northwest
3. The Ohio State University
4. University of Utah

3. Objectives and Deliverables

Objective #1
• **Establish an organizational structure to include federal partners, clinical and public health partners, and a CDC steering committee to provide critical input on data collection approaches and analytical priorities.**

Deliverable 1.1: An organizational structure

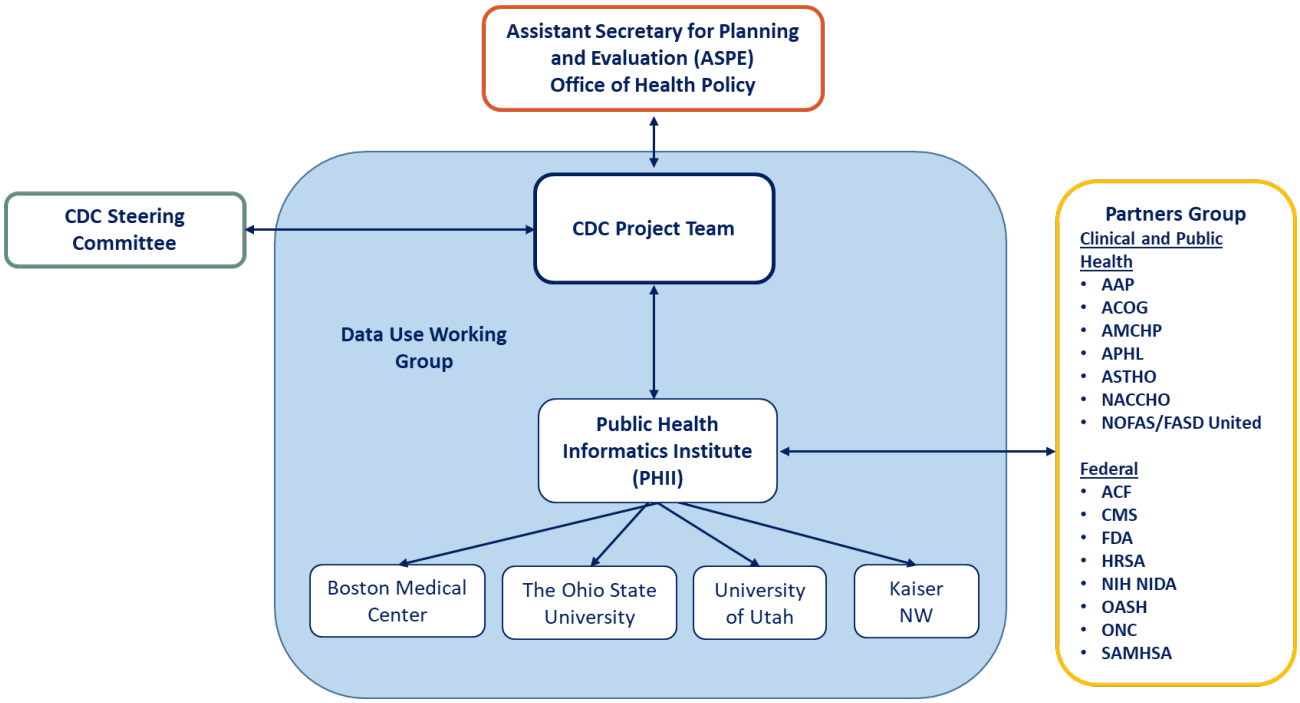
The Steering Committee is composed of CDC leadership charged with providing guidance and oversight of the project. Meetings between the CDC Project Team and Steering Committee occur quarterly; these meetings include updates on ongoing activities and discussion of critical decisions. Membership of the Steering Committee comprises leadership and subject matter experts from CDC's NCBDDD, the National Center for Injury Prevention and Control (NCIPC), and the Deputy Director for Public Health Science and Surveillance (DDPHSS). Individuals who have served or are currently serving on the Steering Committee include Karen Remley, MD, MBA, MPH, FAAP; Coleen Boyle, PhD, MSHyg; Margaret (Peggy) Honein, PhD, MPH; Cheryl Broussard, PhD; Dana Meaney-Delman, MD, MPH; Amanda Cohn, MD; Georgina Peacock, MD, MPH, FAAP; Blythe Ryerson, PhD, MPH; Christopher Jones, PharmD, MPH; Sarah Bacon, PhD; Heather Clayton, PhD, MPH; Robin Wagner, PhD, MS; and Heather Strosnider, PhD, MPH.

The Public Health Informatics Institute (PHII) facilitates meetings with the Partners Group, which includes representatives from federal agencies and clinical and public health partners. Meetings with the Partners Group occur every 4 months to review high-level MAT-LINK accomplishments, obtain input on MAT-LINK structure and analyses, and share updates on partner activities.

The CDC Project Team is responsible for day-to-day management of MAT-LINK, including developing the surveillance network design, clinical site inclusion criteria, data collection protocol, tools and guidance documents, and coordinating with PHII as the implementation partner.

PHII serves as the implementation partner and oversees the funding and contract deliverables with the awarded clinical sites. PHII also manages the data collection and surveillance infrastructure, providing technical assistance to the clinical sites and ensuring the safeguarding of the data.

Figure 1. Organizational Chart



Abbreviations: American Academy of Pediatrics (AAP), American College of Obstetricians and Gynecologists (ACOG), Association of Maternal and Child Health Programs (AMCHP), Association of Public Health Laboratories (APHL), Association of State and Territorial Health Officials (ASTHO), National Association of County and City Health Officials (NACCHO), National Organization on Fetal Alcohol Syndrome (NOFAS)/FASD United, Administration for Children and Families (ACF), Centers for Medicare & Medicaid Services (CMS), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), National Institutes of Health National Institute on Drug Abuse (NIH NIDA), HHS Office of the Assistance Secretary for Health (OASH), Office of the National Coordinator for Health Information Technology (ONC), Substance Abuse and Mental Health Services Administration (SAMHSA)

Deliverable 1.2: List of core set of variables

A list of the core variables related to surveillance of OUD during pregnancy was included in the manuscript "The MATernaL and Infant NetworK to Understand Outcomes Associated with Treatment of Opioid Use Disorder During Pregnancy (MAT-LINK): Surveillance Opportunity" published in the *Journal of Women's Health* in December 2020. The list of variables is included in Appendix A.

Deliverable 1.3: Analytic plan

In the early stages of MAT-LINK, an analytic plan was drafted with input from the CDC Steering Committee and Partners Group as well as clinical sites. It includes prioritized research questions, table shells, and sets of analyses. The CDC Project Team holds monthly calls with clinical site principal investigators (PIs) to discuss analyses, including processes, ideas, dissemination, and challenges.

An abbreviated version of the analytic plan is included in Appendix B. This document includes key analytical questions MAT-LINK will explore after data collection is complete.

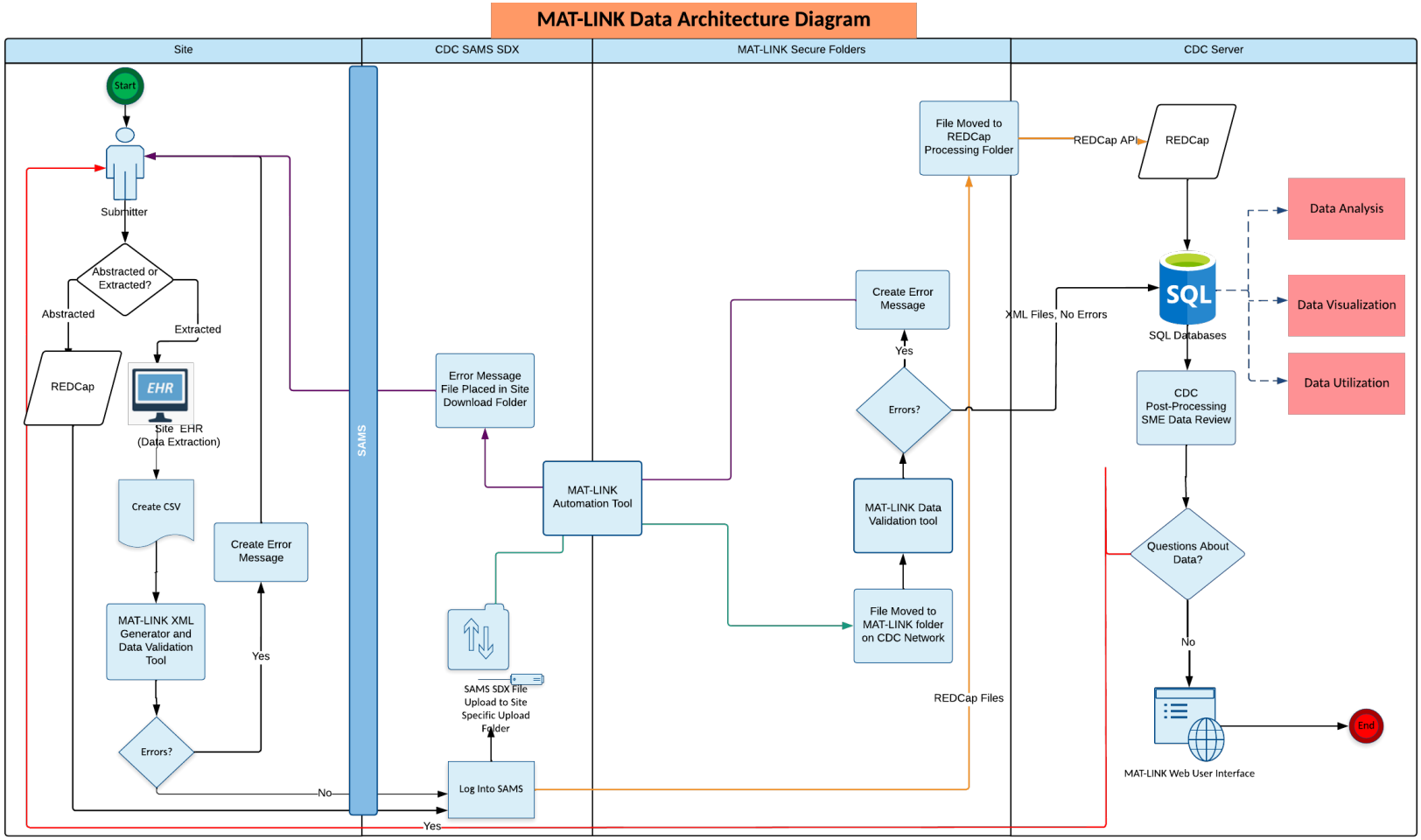
Deliverable 1.4: Issue brief

A manuscript informed by the analytic plan that describes the methods behind the development of MAT-LINK has been drafted and submitted to CDC clearance prior to submitting for publication. This manuscript serves as the MAT-LINK issue brief.

Objective #2
• **Develop a data platform to collect linked maternal and infant data among people treated for OUD during pregnancy.**

A data infrastructure was established and implemented across all clinical sites (Figure 2). For extracted data, a DataExtractor Tool was developed and customized with 34 XML schemas to support standardizing the format of extracted data from data warehouses, EHR systems, and other data sources. To reduce the need for prior XML knowledge at a clinical site, the DataExtractor Tool includes multiple support documents, such as a data dictionary, standard CSV templates for compiling the data, XML generation, and validation scripts to generate XML files. Clinical sites then send data to CDC using the Secure Data Exchange (SDX), which automatically reads and runs a series of validation processes before depositing the data into a raw data server as a relational database. For abstracted data, a Research Electronic Data Capture (REDCap) project specific to MAT-LINK was created for data collection and duplicated for use at all MAT-LINK clinical sites. All data are reviewed for quality by automated and manual checks before being finalized and placed into the analytic database.

Figure 2. MAT-LINK Data Architecture



Abbreviations: Electronic health records (EHR), comma-separated values (CSV), Extensible Markup Language (XML), Secure Access Management Services (SAMS), Structured Query Language (SQL), application programming interface (API), subject matter expert (SME)

Deliverable 2.1: Notice of Funding Opportunity (NOFO)

A NOFO was used to identify MAT-LINK's implementation partner. The NOFO was published in April 2019 on the CDC website and PHII was selected as the implementation partner. https://www.cdc.gov/publichealthgateway/partnerships/capacity-building-assistance-OT18-1802.html

Deliverable 2.2: A report summarizing the process for accessing the data

MAT-LINK data are protected under the CDC Assurance of Confidentiality. This protection enables CDC programs to assure participating institutions that the confidentiality of the data collected will be protected to the greatest extent possible. After data collection is completed, a restricted MAT-LINK dataset will be hosted at the National Center for Health Statistics' (NCHS) Research Data Center (RDC). External researchers may submit a proposal to request access to the dataset, then go to the RDC's physical locations outside Washington, D.C., and Atlanta, Georgia. External researchers may also submit a proposal to access the data from within the CDC firewall. A document describing the methods for requesting access to MAT-LINK data has been developed and will be posted on CDC's MAT-LINK webpage after data collection is complete and a dataset is publicly available.

Deliverable 2.3: User guide

A user guide that includes a description of how MAT-LINK data were collected, the data dictionary, and an abstraction guide has been developed and will be posted on CDC's MAT-LINK webpage after data collection is complete and a dataset is publicly available. This user guide can support external researchers in developing proposals and navigating MAT-LINK data after they obtain access.

Objective #3
• **Analyze and disseminate preliminary results to inform patient-centered care for people who are pregnant with OUD and for children with prenatal opioid exposure.**

Deliverable 3.1: Presentations

The MAT-LINK team shared progress and achievements at various meetings and conferences over the timespan of the project. A comprehensive list of all presentations is listed under the Presentations and Publications section of this report.

Deliverable 3.2: Manuscripts

A manuscript providing the justification behind developing MAT-LINK was published in December 2020, and a manuscript describing the methods of MAT-LINK will be published in 2023. As the MAT-LINK clinical sites continue submitting data, other manuscripts will be developed about the timing of opioid and/or polysubstance exposure, MOUD initiation, and comorbidities, among other topics. A list of all

manuscripts that have been published or are under development is included in the Presentations and Publications section of this report, and an abbreviated analytic plan is in Appendix A.

4. Lessons Learned

MAT-LINK is the first surveillance system to collect comprehensive, linked dyad-based data related to MOUD during pregnancy from multiple clinical sites. As clinical sites began piloting data collection, lessons learned have been utilized to continuously improve processes in real time and will ultimately inform similar data systems. Thus, a surveillance evaluation was conducted in the fall of 2021 to assess MAT-LINK's timeliness, flexibility, and data quality. Results of this evaluation were published on CDC's website.

4a. Communication and Collaboration

One key to MAT-LINK's success has been consistent communication and collaboration between CDC, PHII, and the clinical sites as well as the CDC Steering Committee and Partners Group. The MAT-LINK data system is robust and complex; it requires diligence and expertise from the entire MAT-LINK team. To facilitate efficient communication and file storage, a SharePoint website was developed. SharePoint is hosted under the Secure Access Management Services (SAMS), which is the firewall for the CDC network and thus enables a secure way for the MAT-LINK team to discuss specific data questions that may have sensitive information (e.g., dyad IDs) within a protected server.

Key features of the SharePoint website include

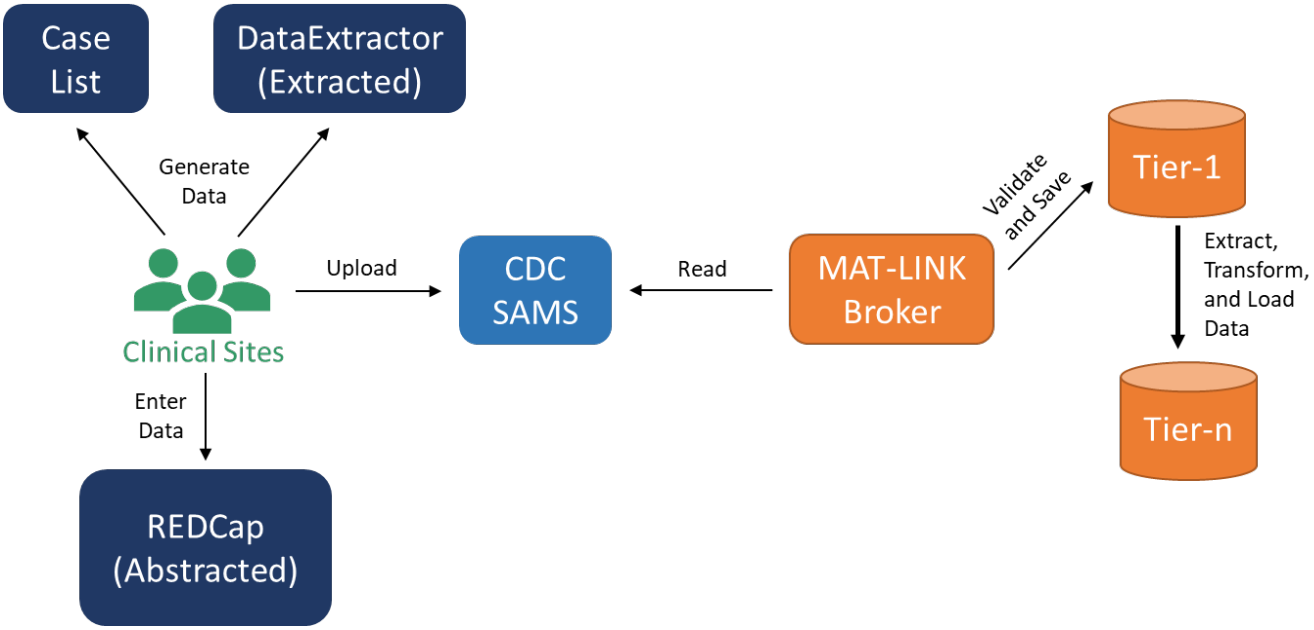
- **Biweekly newsletter** with project updates, deadlines, upcoming release dates and calls, and other resources
- **Discussion board** for MAT-LINK clinical sites and CDC/PHII staff to pose questions to better understand data collection
- **Data resources** including data standard operating procedures, notes and recordings from meetings, and other information
- **Question and answer tracker** for clinical sites to submit data or IT issues to the MAT-LINK team
- **Data feedback tracker** for the CDC MAT-LINK team to send specific data questions to the clinical sites

Additionally, frequent calls between CDC, PHII, and the clinical sites were extremely helpful to address challenges. Establishing a monthly call for all clinical site data managers to discuss and troubleshoot issues facilitated increased collaboration across clinical sites. Monthly individual clinical site calls between the clinical sites, CDC, and PHII were useful for discussing contractual timelines and specific data questions, some of which could not be discussed with other clinical sites due to data protections and confidentiality. Finally, monthly calls between CDC and all clinical site PIs facilitated fruitful discussions on analyses, sustainability of this work, and best practices for management of OUD in pregnancy.

4b. Data Modernization

MAT-LINK was developed with flexibility and scalability in mind (see Deliverable 2, Figure 2). The IT architecture was designed to expand as the project needs develop. By utilizing REDCap and the DataExtractor Tool, the system is dynamic for existing clinical sites, and the entire architecture can be implemented by new clinical sites. Through this robust IT architecture, MAT-LINK can obtain comprehensive and high-quality data while maintaining strict confidentiality.

Figure 3. MAT-LINK Data Flow



Note: Abstracted data are manually retrieved from various chart sources, and extracted data are queried from available structured data.

5. Future Considerations

5a. Scalability

MAT-LINK was awarded additional funding from ASPE's PCOR-TF to expand MAT-LINK to three additional clinical sites and extend child follow-up from 2 through 6 years of age. This expansion is considered MAT-LINK Phase II. With this expansion, MAT-LINK has demonstrated its ability to add new clinical sites with relative ease. Due to the thorough piloting and validation of the data collection instruments with the Phase I clinical sites, minimal changes were required for the Phase II clinical sites. Additionally, all clinical sites were able to extend data collection through 6 years of age without the need for additional data architecture. As longitudinal data collection continues, more clinical sites or follow-up time as well as additional variables could be added without changing existing data structures.

5b. Interoperability

Developing this surveillance network required frequent communication between CDC, PHII, and the clinical sites. Because each clinical site uses a unique data management system, it was challenging to standardize variables, definitions, and code. Detailed mapping of clinical site-specific processes was performed. Exchanging information on site-specific processes, understanding how each clinical site operates, and troubleshooting issues by providing technical assistance were key to strengthening the standardization and implementation of the system across all clinical sites. When possible, the use of standard ontology, such as RxNorm, International Classification of Diseases (ICD), Systematized Nomenclature of Medicine (SNOMED), and CVX helped make the process more efficient. Establishing core variables and data standards for MAT-LINK will better inform future efforts of this network as well as similar data systems.

5c. Collaboration

MAT-LINK has excelled at collaborating across federal, clinical, and public health partners. Establishing a MAT-LINK Partners Group early in the development of MAT-LINK was critical for informing the scope of the network, clinical site inclusion criteria, and a core list of variables. Quarterly calls with the Partners Group allows the MAT-LINK team to provide regular updates and facilitate an open space for partners to share current activities on topics related to MOUD during pregnancy. Additionally, participating in ASPE's Maternal Health Consortium provides an opportunity to share data modernization efforts and possible applications to other projects.

6. Presentations and Publications

6a. Presentations

- **February 12, 2019** – Shin Kim presented "Division of Congenital and Developmental Disorders: Opioid Portfolio," which included an overview of this project, to the leadership of CDC's NCBDDD.
- **June 7, 2019** – Shin Kim presented an overview of MAT-LINK to the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD) annual meeting.
- **June 22, 2019** – Elizabeth Dang presented an overview of MAT-LINK at the Research Society on Alcoholism annual meeting.
- **March 19, 2020** – Shin Kim and Cody Bennett presented an overview of the MAT-LINK data components to the Acting Director of CDC's NCBDDD.
- **March 9, 2020** – Shin Kim presented an update on MAT-LINK activities at the ICCFASD annual meeting.
- **August 18, 2020** – Marcela Smid and Julie Shakib, co-Principal Investigators from the University of Utah, presented on MAT-LINK at CDC's Public Health Grand Rounds on Reducing Polysubstance Use in Pregnancy.
    a. https://www.cdc.gov/grand-rounds/pp/2020/20200729-reducing-polysubstance-pregnancy.html
- **October 20, 2020** – Elisha Wachman, Principal Investigator from Boston Medical Center, presented on NAS practices and implications for the NAS case definition to the Council of State and Territorial Epidemiologists (CSTE) NAS Workgroup.
- **November 16, 2020** – Shin Kim presented an overview of MAT-LINK at the American Medical Informatics Association (AMIA) annual conference.
- **July 19, 2021** – Shin Kim and Nisha George presented an overview of MAT-LINK at ASPE's PCORTF Maternal Health Consortium Webinar.
- **January 20, 2022** – Lucas Gosdin presented "Intro to MAT-LINK for IMMPaCt" to the International Micronutrient Malnutrition Prevention and Control Team (IMMPaCt) at CDC's Division of Nutrition, Physical Activity, and Obesity to share background and current progress on MAT-LINK.
- **April 25, 2022** – Suzanne Gilboa presented a comparison of MAT-LINK and SET-NET to the Center Director of CDC's NCBDDD.

6b. Publications

Published Manuscripts

- Tran EL, Kim SY, England LJ, et al. The MATernaL and Infant NetworK to Understand Outcomes Associated with Treatment of Opioid Use Disorder During Pregnancy (MAT-LINK): Surveillance Opportunity. *J Womens Health (Larchmt)*. 2020;29(12):1491-1499. doi:10.1089/jwh.2020.8848

Upcoming Manuscripts

- *Longitudinal Surveillance for Maternal and Child Health Outcomes Associated with Use of Medications for Opioid Use Disorder during Pregnancy: MAT-LINK.* The purpose of this report is to provide a detailed description of the MAT-LINK surveillance methods including data sources, types of variables, secure data transfer and storage, and making data available for future analyses. In addition, a surveillance evaluation of MAT-LINK is described as well as a description of some population characteristics by MOUD status from Phase I clinical sites. (In CDC clearance)
- *Polysubstance Use in Pregnancy: Surveillance, Interventions, and Next Steps.* This manuscript describes the Public Health Grand Rounds held in August 2020 that discussed adverse maternal and child health outcomes caused by polysubstance use and how data can improve our understanding of polysubstance use during pregnancy. (Pending publication in the CDC Reports for *Journal of Women's Health*)
- *Medication for Opioid Use Disorder During Pregnancy.* This analysis provides a description and comparison of demographics for the MAT-LINK surveillance population by MOUD groups, including methadone, buprenorphine, and no MOUD. This includes information on the timing of MOUD, duration of MOUD, and dosing. (Under development)

7. References

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9. Appendix A: Variables

Category	Variables

Maternal health history	• Demographic information
	• Social determinants of health (e.g., education, incarceration status, insurance status, and ZIP code)
	• Pre-pregnancy height and weight
	• Pre-existing conditions
	  ○ Psychosocial history
	  ○ Substance use disorders
	  ○ Mental health conditions
	  ○ Other chronic conditions

During and after current pregnancy	• Prenatal visits
	• Pregnancy weight
	• Obstetric history
	• Pregnancy-related infectious and noninfectious conditions
	• OUD treatment, including MOUD—including timing, dose, duration, and frequency when available
	  ○ Misuse or illicit opioid use before OUD treatment initiation (e.g., codeine, hydrocodone, oxycodone, heroin)
	  ○ OUD pharmacologic treatment (methadone, buprenorphine ± naloxone, naltrexone, and other site-specific options)
	  ○ Medically supervised withdrawal ± medications
	  ○ Psychosocial/behavioral therapy
	  ○ Opioid-related return to substance use after initiation of OUD treatment
	  ○ Overdose (opioid and nonopioid)
	• Maternal prescription medications (non-MOUD)
	• Maternal prenatal and postdelivery substance exposure test results
	• Other substance use—including timing, dose, duration, and frequency when available
	  ○ Alcohol
	  ○ CBD oil (e.g., vaped or ingested)
	  ○ Cigarettes/cigarillos
	  ○ Cocaine
	  ○ Hallucinogens (e.g., LSD, PCP, and ecstasy)
	  ○ Inhalants (e.g., glue, nitrous oxide, and felt tips)
	  ○ Kratom

	○ Marijuana (e.g., cannabis, weed, pot) ○ Methamphetamine ○ Other tobacco substances (e.g., vaping [e-cigarettes with nicotine], cigars, and smokeless tobacco [e.g., snus, snuff, chew, and hookah]) • Method of contraception at postpartum follow-up • Emergency department visits and nondelivery hospitalizations • Maternal death
Delivery (maternal) hospitalization	• Pregnancy outcome • Plurality • Delivery complications, location, and type • Medications administered during labor and delivery • Discharge destination and length of hospital stay
Birth (neonatal) hospitalization	• Infant sex • Measurements at birth or first measurement • Neonatal resuscitation measures in the delivery room • Newborn screening (e.g., blood spot testing, congenital heart disease, and hearing loss) • Newborn substance exposure test results • Newborn conditions, including the following: ○ Anemia ○ Asphyxia ○ ECMO, number of days on ECMO ○ Hemolytic disease ○ Interventricular hemorrhage ○ Intrauterine growth restriction/small for gestational age ○ Hyperbilirubinemia/jaundice ○ Necrotizing enterocolitis ○ Oxygen administered ○ PDA ○ Major congenital anomaly/birth defects ○ Sepsis ○ Vertical transmission of infectious diseases ○ NAS ▪ NAS protocol ▪ Newborn signs and symptoms related to NAS,[a] including the following:

	• Autonomic dysfunction (e.g., sneezing, nasal congestion, yawning, fever, and cutaneous mottling)
	• Diarrhea or loose stools
	• Feeding problems (e.g., vomiting and poor feeding)
	• Hypertonia
	• Hyperactive Moro reflex
	• Irritability (e.g., continuous, excessive, or high-pitched cry and poor sleep)
	• Myoclonus
	• Respiratory distress/symptoms
	• Seizures
	• Tremors
	• Pharmacologic newborn management, including timing, dose, duration, and frequency
	• Nonpharmacologic newborn management
	  ○ Feeding method (e.g., breastfeeding or formula feeding)
	  ○ Rooming-in
	• Hospitalization location(s) and length of stay
	• NICU admission
	• Newborn death before discharge
	• Discharge weight, destination, and newborn living situation
	• Discharge planning (e.g., plan of safe care, child protective services referral, and pediatrician identified for follow-up)
	• Readmission or emergency room visit after birth hospitalization within 28 days related to NAS, treatment given, and length of stay

Child health history	• Primary care provider visits
	  ○ Primary reason for visit
	  ○ Growth measurements
	  ○ Developmental and behavioral surveillance and results from screening instruments
	• Referral to specialists and receipt of services (e.g., WIC, Early Head Start, and Early Intervention [Part C])
	• All diagnoses and medications
	• Laboratories (genetic, separate from newborn screen; lead; and infectious diseases)
	• Dates of hospitalization, emergency room or urgent care visits, and surgeries

	• Child death

[a]Signs and symptoms of NAS will be site specific and depend on the NAS protocols used at each site.

Abbreviations: CBD, cannabinoid; ECMO, extracorporeal membrane oxygenation; LSD, lysergic acid diethylamide; MOUD, medications for opioid use disorder; PCP, phencyclidine; PDA, patent ductus arteriosus; THC, tetrahydrocannabinol; WIC, The Special Supplemental Nutrition Program for Women, Infants, and Children.

10. Appendix B: Analytic Plan

Maternal and Infant Network to Understand Outcomes Associated with Medication for Opioid Use Disorder during Pregnancy (MAT-LINK) Analytic Plan

MAT-LINK Summary

The purpose of the Maternal and Infant Network to Understand Outcomes Associated with Medication of Opioid Use Disorder during Pregnancy (MAT-LINK), funded by the Patient-Centered Outcomes Research Trust Fund (PCOR-TF), is to establish a surveillance network to collect data on maternal, pregnancy, infant, and child health outcomes in the context of management with MOUD during pregnancy. The goal is to generate new data from medical records that can be used to inform clinical management of people who are pregnant with OUD and to expand our understanding of associated outcomes. To accomplish this, the project will ascertain linked data from maternal and child medical records for nearly 5,000 mother-child pairs.

Pregnant Person Analyses

1. What is the distribution of characteristics in this population of people who are pregnant with OUD (e.g., age, race, ethnicity, body mass index, pre-pregnancy and pregnancy conditions) by MOUD groups? Are there differences in overdose and active substance use between MOUD groups?

2. What is the distribution of nonpharmacologic treatment (e.g., counseling, peer support groups) for OUD in pregnancy by MOUD group? What are the associated factors with non-pharmacologic treatment?

3. What are the rates of COVID-19 testing and test positivity in this population of people who are pregnant with OUD and are there differences in health characteristics or outcomes? How did the COVID-19 pandemic influence MOUD-related care in this population of people who are pregnant with OUD?

4. What is the distribution of pregnancy and birth outcomes by MOUD groups? What are the associated factors with these outcomes?

5. What are differences in labor pain management (e.g., morphine equivalents, length of stay) by MOUD group? What are differences in labor management (e.g., induction, augmentation, vaginal delivery, operative delivery, cesarean delivery) by MOUD group?

6. How is mental health a factor in MOUD in pregnancy? What is the distribution of pre-existing and postpartum mental health conditions among the MOUD groups?

7. Over the first year after delivery, describe the continuation of MOUD with consideration of overdose, active substance use, and child custody status.

8. Describe infectious disease characteristics in this population with emphasis on post-partum hepatitis C care, including hepatitis C treatment, viral loads, and MOUD.

Neonatal Outcomes

1. What percentage of neonates develop NAS? This analysis will incorporate clinical site differences in NAS definitions and use data about clinical diagnosis of NAS based on documentation in the medical record, diagnosis based on ICD codes, and NAS diagnostic data (e.g., pharmacologic treatment).

2. How does NAS vary by maternal MOUD group? NAS severity will be based on needing pharmacotherapy, days on pharmacotherapy, adjunctive medications, and length of stay secondary to NAS.

3. What is the distribution of NICU admissions and hospital length of stay among neonates by maternal MOUD group? What is the distribution of NICU admissions and hospital length of stay secondary to NAS? How does the distribution vary by NAS status and NAS severity?

4. What is the distribution of clinical signs consistent with NAS among neonates by MOUD group?

5. Describe short-term and long-term outcomes of neonates with NAS treated with as needed opioids versus standard taper.

6. Compare the utilization of morphine and methadone for neonates with NAS, including length of stay, length of treatment, secondary medications, readmissions, and ER visits.

7. Compare short-term and long-term outcomes of neonates assessed with Finnegan versus ESC, including length of stay and opioid treatment days.

8. Examine long-term outcomes (e.g., neurodevelopmental outcomes, healthcare utilization outcomes) based on pharmaceutical treatment of neonates for NAS versus not.

9. Of neonates who were tested for opioids, what percentage had a positive result for unprescribed substances? Of neonates tested for other substances, what percentage had a positive result? How do these results vary by maternal MOUD group?

10. To what extent does diagnosis of NAS based on CSTE criteria agree with clinical diagnosis of NAS based on documentation in the medical record? To what extent do ICD codes for NAS agree with clinical diagnoses and CSTE criteria?

11. How do neonatal feeding practices vary by MOUD group? How are NAS-related outcomes impacted?

12. Do poor outcomes in neonates vary by maternal MOUD group?

13. Is there an increased incidence of any congenital abnormalities in infants by MOUD group? Describe neonatal outcomes by retention in care, active substance use, infant growth, and child developmental outcomes across different MOUD groups.

Child Outcomes

1. Do growth and developmental outcomes in children vary by MOUD group? How do the substance used by the person who was pregnant and sociodemographic factors impact these outcomes?

2. Is having a history of NAS associated with developmental delays in children? Does this vary by MOUD group?

3. Is there a difference in referral for specialty evaluation and/or social services for children based on MOUD group or a history of NAS?

4. Describe the growth trajectory of children and predictors of growth (e.g., weight, length, head circumference, Z-scores, growth-related diagnoses) by MOUD group.

5. What are the healthcare utilization outcomes (e.g., ER visits, primary care visits, readmissions) and health diagnoses for children in this population and how do they vary by MOUD group?

6. Is there a difference in retention of child custody by biological parents based on MOUD group?