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A Proposed Framework to Address Needs of Clinical Data for Informed Medication Use in Pregnancy

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Abstract

The objective of this paper is to communicate a proposed framework for addressing research limitations and communication barriers that contribute to a lack of data for making clinical treatment decisions about medication use in pregnancy. To address this global public health concern, a cross-stakeholder coalition composed of several workstreams is proposed. The intent is to foster collaborative discussion regarding potential solutions to address gaps in communication, engagement, and data generation and collection. Topic areas that require focus include development of awareness initiatives, cultural transformation efforts, collaboration initiatives, research standards, data compilation projects, and new data capture methods. Objectives to aid these efforts are outlined, and collaboration among researchers, regulators, health care providers, and patients is emphasized.

Keywords

pregnancy, pregnant, medicine, medication, drug, data, fetus, newborn

Introduction

This article is the third in a 3-part series on the topic of medication use and pregnancy. The first paper outlined the urgent global need for better guidance and clinical decision making in medicines and pregnancy.[1] The second paper summarized the strengths and weaknesses of current data collection efforts and explored underlying limitations that prevent many of these initiatives from resulting in more data-driven decision making.[2] This third article proposes an overall plan with workstreams to explore potential solutions to address the identified limitations in communication, awareness, culture, engagement, data generation and collection, and new data capture (Figure 1). The purpose of this article is to stimulate comments and participation in the collaborative effort outlined.

Up to 90% of women use an average of 3 or 4 medicines during pregnancy.[3] This reality is in stark contrast with the fact that most medicines are not indicated for use in pregnancy.[1] While relatively recent Food and Drug Administration (FDA)[4,5] and European Medicines Agency[6] regulations regarding the study of drugs in pediatric populations have helped to overcome the taboo of research in children, the study of drugs in pregnant women is still very much prohibited. Academic and industry engagement is a key to evidence- and label-based medical information for health care providers (HCPs) and patients, but methodological issues and liability concerns contribute to misinformation and to the avoidance of the study and use of medication in pregnancy, thus limiting informed decision making.[2]

A transformation is needed to foster evidence-based decision making in this important and unresolved area of public

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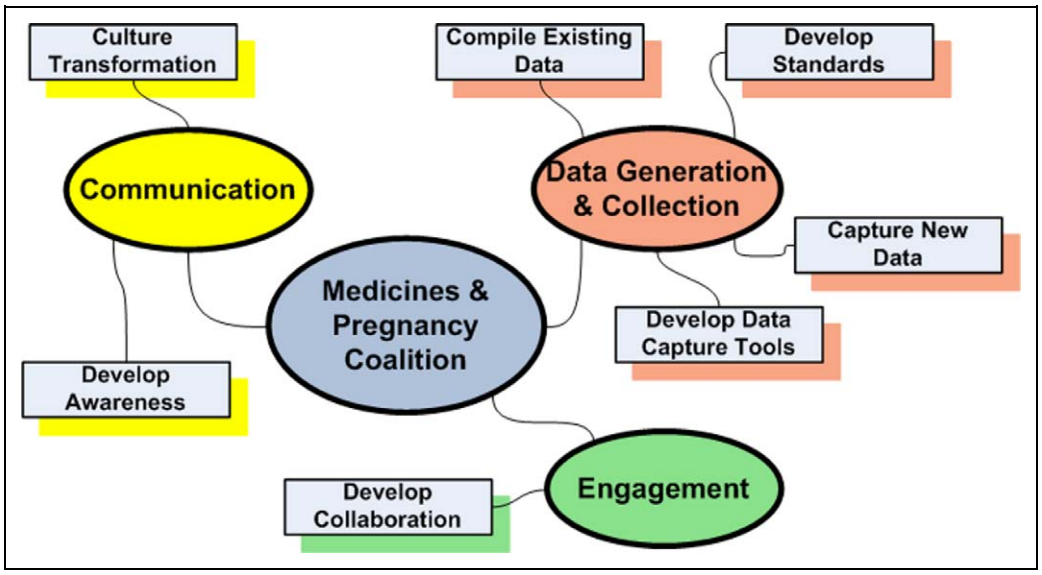

Figure 1. Proposed workstreams and work groups.

health. Critical limitations in several areas, each touching multiple stakeholders, need to be addressed.[2] Current efforts must be built on, with integrated and cross-collaboration to address identified gaps and to implement effective change in front-line clinical practice. Patient engagement to address misconceptions around risk is needed. The premise of this paper is that a coalition effort involving all stakeholders is important to advancing research and communication to make a positive impact in this arena.

In 2013, the DIA (Drug Information Association)—a global, neutral, and nonprofit professional society of individuals working in medical product development—convened expert panel discussions on the topic of "Clinical Data for Informed Medication Use in Pregnancy" at its European and US annual meetings. The objectives of these panel discussions were to identify existing efforts and resources; discuss gaps, needs, and related issues; develop a core set of principles to aid cross-functional alignment; and explore proposals for next steps that could lead to potential solutions. As a follow-up to these discussions, the DIA created a hub for work group communication and storage of work group resources and outputs. The intent was to aid in initial efforts to address identified concerns about medication use in pregnancy through the creation of workstreams and associated work groups. It is envisioned that a consortium of stakeholders will come together through these work groups to address issues in an ongoing manner.

The focus of the current article is to report on the outcomes and proposals resulting from discussions among the DIA's "Clinical Data for Informed Medication Use in Pregnancy" panel participants. The identified needs and unanswered questions in this article have been summarized into 3 fundamental topic categories around which scientific work groups can be formed to address specific and actionable approaches to issue resolution (Figure 1):

Communication: Develop awareness and culture transformation.

Engagement: Develop collaboration.

Data generation and collection: Develop standards; compile existing data; develop data capture tools; and capture new data.

Communication Workstream

Since the thalidomide tragedy, concerns and anxiety regarding potential adverse effects of drug and chemical exposure on the developing fetus are constantly present.[7] However, women and HCPs, as well as regulators and academicians, commonly overestimate the teratogenic risk of medications. The misperception of teratogenic risk is partly the result of the manner in which data on safety are presented, with the assumption that every drug is a potential teratogen, even if proven otherwise. The litigious atmosphere surrounding birth defects in pregnant women exposed to drugs has often led HCPs to avoid use of medications, "to be on the safe side."[7] Yet, quite often, not treating the maternal condition renders the opposite of maternal and fetal safety. This has been documented with the tripling of hospitalization rates for pregnant women experiencing severe vomiting after the market withdrawal of Bendectin®[8] and the increase in depression relapse among pregnant women discontinuing selective serotonin reuptake inhibitors.[9]

Any preconception visit should include a detailed discussion regarding prescribed and over-the-counter medications. The

Table 1. Communication workstream objectives.

Develop Awareness	Culture Transformation
• Raise awareness to key stakeholders (eg, regulators, providers, researchers, patients) of unmet need regarding lack of data for treatment decision making • Promote education and research on safe medication use during pregnancy that includes benefit-risk information for patients (on- and off-label use) • Identify top 10 chronic disease states where information is needed to provide the greatest impact, utilize in education and other efforts, and share best practices once identified • Develop the study of medication use as a global prioritized agenda • Define key considerations that drive the hesitancy and reluctance to medicate during pregnancy; develop associated metrics and collect data	• Develop ethical and legal principles and guidelines to promote research of medication use in pregnant women, address hurdles, and define in what circumstances pregnant women can be included in clinical research • Facilitate changes in the regulatory environment to better allow drug research in pregnant populations; influence regulatory acceptance of data for labeling to better aid in physician and patient decision making • Influence institutional review boards and investigational ethics committees to remove clinical trial enrollment and consent barriers for pregnant patients, including for continued participation if one becomes pregnant during trial and for data collection on outcomes • Facilitate practitioners' and patients' understanding of their obligation to contribute healthy and adverse outcome data • Facilitate shift from reporting adverse events to reporting healthy outcomes and benefit-risk, including promotion of discussion with patients

indication, safety, effectiveness, and necessity of each drug should be reviewed. Patients should be reassured about drug safety in most circumstances, since the majority of prescribed medications are safe in pregnancy, even in the first trimester. Only a few drugs, chemicals, infections, or radiation are proven teratogens.[10,11] Teratogenic drugs are sometimes used during pregnancy when the benefits outweigh the risks (eg, a female with mechanical cardiac valves who accepts the teratogenic risk of warfarin). To set the stage for patients to be willing to listen to and accept medication-in-pregnancy study data and conclusions, awareness efforts must address current perceptions and misperceptions about benefit-risk.

Communication is essential for engagement, for the transfer of knowledge, and for decision making in partnership. To set the stage for improved communication, stakeholders need to first fully understand the extent and importance of the issue. Most stakeholders are still unaware of the current state of pregnancy research, the reasons for the research, and how they can help to fill these critical gaps. When it comes to better decision making, a better understanding of the inherent risks of pregnancy, how drugs affect pregnancy, and how to find and interpret information is an essential requirement. Thus, communication is the essential link between research and behavior that leads to better outcomes and moves beyond the traditional means of data publications in the medical literature. To move from data to value, there is a need to add context first, then understanding, and then applicability, all of which require effective two-way communication.

Because of the importance of communication, a specific communication workstream is proposed and will focus efforts within 2 work groups: the Awareness Work Group and the Culture Transformation Work Group (Table 1). The overall goal is to provide knowledge about medication use in pregnancy to patients and their HCPs to support decision making. This will require priming the environment for understanding the knowledge gaps, the critical needs for the pregnant patient population, and the role that it plays in advancing data collection, as well as the hurdles that need to be overcome, particularly in regard to cultural issues that drive legal concerns. Even if cultural norms are unchanged, understanding the complexities of the issues is important for progress to be made as new data collection methods are considered.

Develop Awareness

Awareness can be facilitated by promoting education, research, and best practices for safe medication use during pregnancy that includes benefit-risk information for patients for on- and off-label use. Guidance makers, decision makers, regulators, payers, providers, researchers, institutional review boards (IRBs) and investigational ethics committees, patients, and the general public are all key stakeholders. Raising key stakeholders' awareness of unmet needs regarding data for treatment decision making in pregnant patients is paramount to all the workstreams (Figure 1).

A logical approach to initiating an awareness program would be to identify the top 10 chronic disease states for which pregnant women require treatment, where information can provide the greatest impact. These disease states then become the focus of initial communication campaigns. The next step would be to identify and seek to understand key considerations that drive the hesitancy and reluctance to use medications during

pregnancy. Discussion of current knowledge gaps, as well as the strengths and limitations of current data and data capture methods, will be important. Subsequent development and reporting of metrics on the topic could aid efforts in spreading the message and tracking progress over time. The ultimate goal can be to improve and apply the process for better decision making about common drugs used for common medical issues during pregnancy.

Culture Transformation

Cultural transformation can be started by addressing multiple ethical questions in concert with setting standards and spreading awareness. For example, pregnant women should not always continue to be excluded from clinical research after a drug has been approved for years and has a known safety profile. Pregnancy should not always be a standard exclusion criterion and reason for dropout from clinical trials. Starting with the end in mind, determination is needed of what information should be the norm that will be provided to regulators and payers and ultimately made available to clinicians and patients. These issues need to be addressed for studies of women being treated for chronic disease (eg, cancer and rheumatologic drugs) as well as pregnant women needing more common and more acute medications, such as a pain medication.

Adverse event self-reporting systems need improvement and expansion, and the role that clinicians have in data contribution when they prescribe medication for pregnant women should be discussed. Additionally, research efforts need to move from an individual group focus to a focus on cross-group collaboration, globalization, and harmonization. This will enable more effective data collection, outcome communication, and movement beyond data publication to patient awareness.

Once standards are identified, researchers, regulators, providers, payers, and patients, in concert with IRBs and legal departments, should work together to integrate their data collection goals and efforts, and leaders within the pregnancy research arena will have to get buy-in and advocate for research that may go against previously established paradigms. Awareness of this public health care issue must be brought to the forefront, and providers and patients need to be informed about the importance of providing data. Moreover, a shift from adverse event reporting to all outcomes reporting, including healthy outcome, is needed for pregnancy. A cultural change from a risk-driven to a benefit-risk approach should occur.

Educating stakeholders on the importance of moving to a benefit-risk analysis will set the stage for addressing additional issues associated with pregnancy research. The legal and regulatory environment needs both modification and strengthening to facilitate communication and knowledge sharing.[2] Addressing patient-perceived risk, which is often based on inaccuracies and misunderstanding, is important. Solutions to these issues are not easily found, but a shift is needed from a focus on the potential legal risk for the HCP to the prioritization of patient health. A paradigm and incentive shift is required to address collaboration, standards, and data collection efforts.

Table 2. Engagement workstream objectives.

Develop Collaboration
• Develop an innovative and collaborative consortium among stakeholder groups to join forces to create positive changes concerning unmet patient needs and foster engagement • Identify collaborators, stakeholders, and relevant organizations willing to invest time and resources; reach out to academia, industry, government, health service, guidance development, and patient advocacy groups • Develop a repository of information sources and contacts • Facilitate research and stimulate data collection; bring research group efforts together to build complementary efforts and synergy

One topic that should be debated is the potential for prospective controlled clinical trials under the right circumstances. Determination is needed on whether prospective controlled research can be done without fear of litigation, when done under consensus-based, appropriate conditions. Because legislation and regulatory changes may be necessary to effect change, this might be an unachievable goal in the current climate. However, lessons learned from pediatric study models may be useful in addressing IRB and industry legal department needs. In addition to the pediatric research incentives of the Food and Drug Administration Modernization Act, the Pediatric Research Equity Act[4] authorizes the FDA to require pediatric assessment of some approved drug products, and the Best Pharmaceuticals for Children Act[5] provides incentives for manufacturers to conduct pediatric research. Before the enactment of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, 70% of all medication use in the pediatric population was off-label. This figure has since dropped to about 50%.[12]

Engagement Workstream

Beyond awareness development and cultural transformation, engagement requires leadership in raising issues, facilitating discussion, recommending improvements, and initiating the collaborative process. A multifaceted integration of groups with different paradigms and focus is needed for a robust dialogue. Such a forum requires a proactive initiative involving all stakeholders (Table 2).

A collaborative effort across stakeholders is imperative to address all the gaps identified in current data for medication use in pregnancy.[2] Without the cooperation of industry members that develop and manufacture medications, little progress can

be made. Without vendor or contract research organization input, new data collection technologies will not be developed and integrated into research efforts. The initial focus of the engagement workstream should be the development of stakeholder collaboration.

Develop Collaboration

Objectives of the Develop Collaboration Work Group should include the identification of potential collaborators, stakeholders, and relevant organizations willing to invest time and resources in the cause. This group will be tasked with fostering stakeholder engagement to increase collaboration across groups: academic, industry, government/regulatory, patient advocacy, health service, and guidance (eg, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) (Table 2). Relationships and alliances must be forged to better focus efforts and optimize resources. Collaboration among companies is critical and feasible. Precedents include an antiviral pregnancy registry for which 22 companies currently collaborate, 17,978 patients are enrolled, and multiple research publications are attributed.[13,14] Coalition efforts in other areas of medication research are positive examples to highlight. The Coalition Against Major Disease is a precompetitive consortium of the Critical Path Institute, which was formed as part of the FDA's Critical Path Initiative. The coalition is focused on accelerating drug development for neurodegenerative diseases with workstreams that include development of standards, creation of integrated study databases, and development of study models.[15] A collaboration that may yield results for pregnancy research is the Innovative Medicines Initiative's PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium), a consortium of 29 public and private participants.[16] One of its objectives is to study modern ways of collecting data from consumers using Internet and telephone, in addition to studying new modeling approaches to integrate existing information from various data sources to facilitate and enhance the continuous monitoring of the benefit-risk of medicines.

To get the patient voice, the Develop Collaboration Work Group will also need to engage advocacy groups, such as patient support groups and government organizations. This group can join forces with other workstreams to facilitate research efforts and stimulate data collection through complementary and synergistic programs.

In the short term, this group would develop a repository of information sources and contacts. The long-term objective of this group will be to create an innovative and collaborative consortium among stakeholder groups to join forces for joint action on the common coalition cause. Suballiances could be created to tackle various workstream efforts. Without collaboration, the other workstreams cannot succeed.

Data Generation and Collection Workstream

To move from the status quo and increase our knowledge, stakeholders are encouraged to transform this research space through data integration, such as the OpenMedNet,[17] and new data capture technology, such as social network applications.[18] If controlled trials are not the answer, then new standards and mechanisms for integrating observational data are needed to fill persistent knowledge gaps. Because of the variability in the methodology used for current observational methods, researchers need to find ways to effectively bridge this gap. Less variability would greatly improve the capacity to learn across studies through data integration. In many diseases and for many medications, decades of studies based on the current methods have not resulted in resolving decision-making issues for either patients or clinicians. Whether this is due to the nature and limitations of the studies not allowing for conclusive answers or to the inadequate communication of the results does not change the predicament.

At the start, 4 work group focuses have been proposed as important for the data generation and collection workstream: compile existing data, compile existing data, develop data capture tools, and capture new data. Separation of these groups with unique objectives is important to facilitate individual project completion, but these work groups will need to be in communication and collaboration, as their efforts are interconnected (Table 3).

Develop Standards

To address the lack of standardization in pregnancy research, accepted standards for a well-documented case of pregnancy and pregnancy outcome must be created. Standards must be created for further testing of identified signals. Data capture standards are needed to enable pooling of data across different indications, manufacturers, geographies, and market authorization holders. Regulators need to develop guidance for approval of conditional medicine use by pregnant women. To enable this, researchers, HCPs, and regulators, with input from patients, must develop and agree on research (data capture, analysis, and control group), ethical, and legal standards.

Standards must be developed or adopted from existing research efforts before extensive progress can be made in regard to research facilitation and data capture during preconception, pregnancy, and postpartum periods. Standards and guidance for study design and length; measure, parameter, and outcome variables; inclusion and exclusion criteria; comparison and control groups; mother-baby linkage; data quality and accuracy; pregnancy, exposure, and outcome confirmation; confounder control; and statistical analytical approaches are all

Table 3. Data generation and collection workstream objectives.

Develop Standards	Compile Existing Data
• Define core research parameters that are harmonized; establish standards and related protocols for data collection (include women, fetus, infant) • Define what acceptable level of evidence is needed to allow for approval of using a drug in pregnancy • Define what constitutes a well-documented case of pregnancy and pregnancy outcome; define constructs for follow-up of patient and offspring • Establish guidelines for data capture in the preconception, conception, and postconception periods, including pharmacokinetics/pharmacodynamics, safety, clinical outcome, and pregnancy outcome data (standardize data collection) • Standardize data assessment methods and harmonize around accepted statistical concepts; include how to capture more subtle effects on development	• Map out data already available, noting strengths and limitations • Create comprehensive directory of ongoing efforts, and identify opportunities for collaboration • Gather, combine, and analyze existing data to build benefit-risk assessments and identify gaps • Engage existing registry owners to combine efforts; develop platform to make this work effectively • Compile existing guidance (eg, regulatory, professional association, advocacy)
Develop Data Capture Tools	**Capture New Data**
• Identify and create data capture and analysis tools for inclusion of existing and new data across data types with a focus on patient and provider usability • Develop prospective data tools that utilize health care social application technologies • Investigate alternative data collection collaborations • Apply continuous health care learning system concepts	• Develop a central public database, and pool data (existing and new) across companies and organizations • Collect and address data for subpopulations (eg, age, disease, race); engage patients and collect pharmacokinetic and effect-of-pregnancy data • As appropriate, include pregnant women in random controlled trials • Collect self-reported data from pregnant mothers

needed. Standards would reduce duplication of effort, thus speeding progress, aligning stakeholders, and aiding in communication. Established, standardized guidelines for data collection in the preconception, conception, and postconception periods—including pharmacokinetics/pharmacodynamics, safety, clinical outcome, and pregnancy outcome data—would greatly benefit future research efforts. Created standards must be meaningful to research efforts, regulatory approval, and patient awareness needs while enabling data output interpretation and reliable benefit-risk determination.

The objectives of the Develop Standards Work Group should focus on developing core research parameters that are harmonized to better enable integration of data across research efforts (Table 3). Defining what constitutes a well-documented case of pregnancy outcome is vital for fostering research integration. Defining what the acceptable level of evidence is needed to allow for approval of using a drug in pregnancy will be critical for fostering data-driven guidance. Once data capture standards are established, the next task will be to standardize data assessment and analysis methods that are harmonized around accepted statistical concepts. These standards will then need to be communicated in the form of guidelines and other resources to all members of the health and research community.

When standards have been defined to collect events that are observed, the more difficult topic of what to do with events that did not happen can be tackled. This is crucial if the effort is also to address issues such as fertility as well as childhood development milestones. In this regard, it is important to also discuss ways to address current gaps in the basic understanding of how specific maternal diseases themselves (ie, without medication) influence fertility, pregnancy, and child development. Similarly, the effect of pregnancy itself on several diseases needs to be better understood. It is very important to understand these basic interactions before the additional effect of medications can be assessed.

Compile Existing Data

To overcome the lack of integration of pregnancy data, methods linking data from multiple and disparate sources are needed. While investigation of newer technologies and data collection projects takes place, initial efforts could focus on compilation of existing database data from pregnancy registries, claims databases, and other study sources (Table 3). It is important to tap into and leverage existing initiatives that have had success.[2] For example, OpenMedNet has shown success in combining patient-sourced data with insurance, provider, pharmacy, hospital, and other data sources.[17]

The first objective of the Compile Existing Data Work Group should be to map out what data are already available and in what format, noting strengths and limitations.[2] A comprehensive directory of ongoing efforts that identifies opportunities for collaboration (eg, registries, claims databases, literature cases, and regulatory submissions) would be of value. This could be followed by actually combining existing data to build benefit-risk assessments while completing a gap analysis to aid other workstream efforts.

It is important to bring together disparate groups researching the same questions to discuss barriers to combining and sharing data. A potential early win could be to engage existing registry owners to combine efforts through the development of platforms to make this work effectively. These efforts will have to be closely linked to other work groups in the data generation and collection workstream.

In concert with the Awareness Work Group, it will be important to compile existing guidance (eg, regulatory, professional association, and advocacy) related to medication use in pregnancy research. The communication workstream could also help to address the challenges of enlisting health care professionals and patients to participate and proactively volunteer their data to registries, particularly for industry and government registries. This issue is oddly compounded by promotional regulations governing registries.[19] Integrated efforts from neutral organizations moving forward may aid in reducing limitations[2] to harness the true potential of registries and patient participation.

The data derived from the efforts to date are critical to address current gaps in communication and awareness. The examination of limitations of research efforts to date serves to identify gaps and barriers to progress in meeting patient needs.[1,2] A key to moving forward will be to integrate now separate efforts in a coalition to address the limitations of current research in pregnant populations, catalyze discussion on this issue of medication use in pregnancy, and address the gaps. Existing advocacy groups and data collection efforts are valuable starting points for integration and future research development.

Develop Data Capture Tools

The application of new data collection tools, including mobile and health care social application technologies, can help to complement traditional clinical or observational trial data collection methods. This will entail defining acceptable and technically feasible data, data collection, and data analysis tools and methods. Acceptance will be needed across regulators, researchers, providers, and patients and will need to include several dimensions, such as privacy, quality, and rigor. Given the importance and vastness of this topic, a separate Develop Data Capture Tools Work Group is proposed (Table 3).

Three parallel concepts should be developed: the creation of a central repository for data on medication use in pregnant women, the integration of existing data and data collection methods, and the use of novel prospective data capture and analysis tools for inclusion of existing and new data across data types. An important difference from traditional data collection is the very short time between data collection and resulting feedback. This opens the possibility for immediate and continuous health care learning systems that enable rapid knowledge building as new data are collected and integrated with existing information.

In regard to new paradigms, there is great potential for consumer data collection through self-tracking Internet tools. For example, 47% of consumers who are using a health-related application on their smartphones are using a pregnancy-related application.[20] The Text4baby application has reached more than 555,000 mothers since launch in 2010.[21] In the Google application store alone, there are more than 1,000 pregnancy-related applications.[18] The ability to harvest and analyze self-reported patient data will be important.

Voluntary pregnancy registries have thus far been unsuccessful in generating adequate information to guide medication use during pregnancy. The use of data currently being tracked through mobile applications and social media sites may prove more successful than voluntary registries. Providing patients access to their data and the ability to benchmark against similar patient populations may provide the incentives necessary to convince patients to share these data. It will be critical to ensure that data provided through these nontraditional channels meet the minimum standards for quality so that they can be used in labeling, medical information sharing, and clinical decision making.

One important goal may be to validate certain applications used in pregnancy with a ''quality label'' denoting ability to deliver value to the individual user as well as to society by contributing to our understanding of the issues relating to medicines and pregnancy. This could significantly enhance adoption and, thus, the generation of new data.

Capture New Data

The collection of self-reported data from pregnant mothers via new tools might be an important future source of data and knowledge, if proper standards and controls are integrated. Linked to this, the development of a public database with pooled data (existing and new) across companies and organizations is extremely important for strengthening the power of the data, which is needed in making decisions about potentially rare safety findings (Table 3). Also in the preclinical area, including chemistry and toxicology, such a public knowledge resource could help researchers and drug developers make

early informed decisions about new molecules. In the clinical stages, pooled data may also allow for the study of patient subpopulations based on demographics such as age and race and on health characteristics such as disease type. This in turn may open the avenue toward more targeted and meaningful studies about drug pharmacokinetics/pharmacodynamics in pregnant women.

While controversial with no easy solutions or guidance, discussing ideas about including pregnant women in randomized controlled trials might be another important topic for the Capture New Data Work Group.

Administration

A Coalition Core Team with responsibility for administration of the workstreams should be tasked with developing the consortium, aiding in collaborative connections, organizing groups, facilitating interaction and integration, providing transparency, communicating results, and providing administration support. This team would also be tasked with developing timely consensus statements to aid in driving workstream efforts and communicating their outputs.

Discussion

This article proposes a framework addressing the serious public health issue of a lack of medical information for decision making on medication use in pregnancy. Three fundamental areas are defined with limitations that must be addressed to make meaningful progress: communication, engagement, and data collection. It is important to work on all 3 areas in parallel and close coordination, given the impact that each area has on the others.

A change in clinical, legal, regulatory, and research culture is warranted. An emphasis on addressing legal concerns is needed, and considerations for tackling some of these issues have been provided.[2,22,23] Pregnancy needs to stop being treated as an adverse event. Ethical considerations and regulatory guidance around various research approaches need to be reopened for debate. Discussions regarding the considerations that drive the hesitancy and reluctance to medicate or not medicate during pregnancy must be undertaken. Stakeholders, including and especially patients and their HCPs, must be engaged and contribute to more data collection and sharing. These discussions and related changes are not likely to occur in a timely manner without greater cross-stakeholder engagement and collaboration.

Learning more from existing data and more effectively communicating existing knowledge could lead to meaningful, near-future results. In addition, new standards and tools are needed for future pregnancy research that satisfy scientific, statistical, data management, legal, and ethical concerns while better enabling data collection efforts. Novel data capture tools and methods need to be applied to increase both the quantity and the quality of data capture. Understanding drug effect on mother and fetus, as well as pregnancy effect on drug dynamics, is vital, and toxicologic studies utilizing novel tools and biomarkers are needed.[24] Ideally, a central public database for pooling data would be created to enhance preclinical and clinical knowledge and exchange.

The suggested workstream objectives (Tables 1-3) are not intended to be all-inclusive and may be modified by workstream leadership. For example, awareness efforts might also entail communication of data on the top 10 medicines used by pregnant patients. Facilitating patient-physician communication about self-medication with over-the-counter products, complementary/alternative medications, dietary, and/or cultural-based treatments and practices may be an important objective for awareness and transformation work groups. This lack of communication inhibits the ability to control for such confounding factors that can affect outcomes attributed to prescription medication and related research. Workstreams should emphasize plans to address patient engagement across a broad landscape of cultural, geographic, and socioeconomic status variables. Utilizing existing patient advocacy group networks organized through a central consortium may be an effective option. National or global prospective registries that encompass new data-gathering technologies are needed. For success, patient contribution is extremely important, but there are no current tools based in patient-reported outcomes that address all the identified issues and fully meet current needs for pregnancy research,[2] which emphasizes the need of the proposed collaborative workstreams.

The proposed workstreams and associated work groups will need to form, assign leadership, develop a charter, determine specific projects and associated deliverables, assign roles and responsibilities, and set timelines. The voices from all stakeholders must be represented in the work groups and include patients, HCPs, academia, regulators, industry, and the public. Patient participation is especially critical for understanding needs and developing acceptable solutions. A strong commitment is needed, and working group members must be engaged and willing to work and proactively promote the group's efforts broadly.

Work groups need to tap into existing organizations already working to address medication use in pregnant women, with the aim to learn from their successes and to identify, understand, and address limitations and gaps. To achieve this, work groups also need access to cross-functional expertise in clinical research, including clinical operations, medical safety and pharmacovigilance, epidemiology, health outcomes, regulatory, statistics, and data management.

As work groups, objectives, and projects mature, a future step may be to create a consortium to serve as a sustainable partnership effort among the many stakeholders in this cause. The consortium could aid work groups in gaining cross-group alignment and collaboration for goals, standards, and awareness and communication efforts. It could also sustain membership recruitment, data sharing, and broad education efforts, which are key components to long-term success. Partnership with other existing coalitions, such as the Council for International Organization of Medical Sciences or the International Conference on Harmonisation, can help to drive topics across regions and organizations.

Conclusion and Call to Action

There is a great need to provide meaningful answers to the many questions that exist about medication use during and around pregnancy. Existing and new knowledge must be integrated and communicated to enhance health and quality of life in this very important phase of life.

Standard clinical research solutions such as placebo-controlled randomized clinical trials, observational studies, clinical registries, claims databases, meta-analyses, and literature reviews done to date have not provided clear, consistent, and benefit-risk treatment guidance for pregnant patients. These research methodologies in many ways may be yesterday's answers to today's and tomorrow's questions. A new path is needed.

At the intersection of the information revolution and the new personalized medicine revolution, new technologies and social movements have enabled us to address key challenges of the past, such as scale, validity, and data access. Numerous new opportunities exist to collect, analyze, share, and communicate data. These opportunities need to be connected with existing initiatives in a meaningful way while maintaining appropriate research ethics and respect for patient rights. There has never been a better time to bring about meaningful improvement in the care for the pregnant.

Through the auspices of the DIA and with input from many stakeholders, a proposal is outlined with several cross-functional workstreams to investigate and tackle current research limitations and gaps (Figure 1). It is hoped that this proposal will spur to action health care researchers, providers, regulators, and patients in collaboration with lawyers, IRBs, and technical experts (data management, statistics, clinical operations, and technology development) to address current issues through communication, awareness, and collaborative research campaigns using previously successful and new technology and data capture methodologies.

This paper is meant to widen the circle of discourse and open the dialogue on the topic of medication use in pregnancy. We hope to stimulate debate, action, and the sharing of concurring as well as diverse opinions, and we invite readers to e-mail their thoughts to MedsandPregnancy@diahome.org. All interested parties are invited to contribute to the workstream efforts identified in the proposed framework, with the hope that all stakeholders will engage, collaborate, and provide expert insight, solution-oriented discussion, and appropriate challenge on issues and direction. The workstreams can be the avenue for dialogue and, most important, act as an operational system to ultimately enhance decision making about medication use and pregnancy

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